U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FY 2021 GDUFA SCIENCE AND RESEARCH REPORT

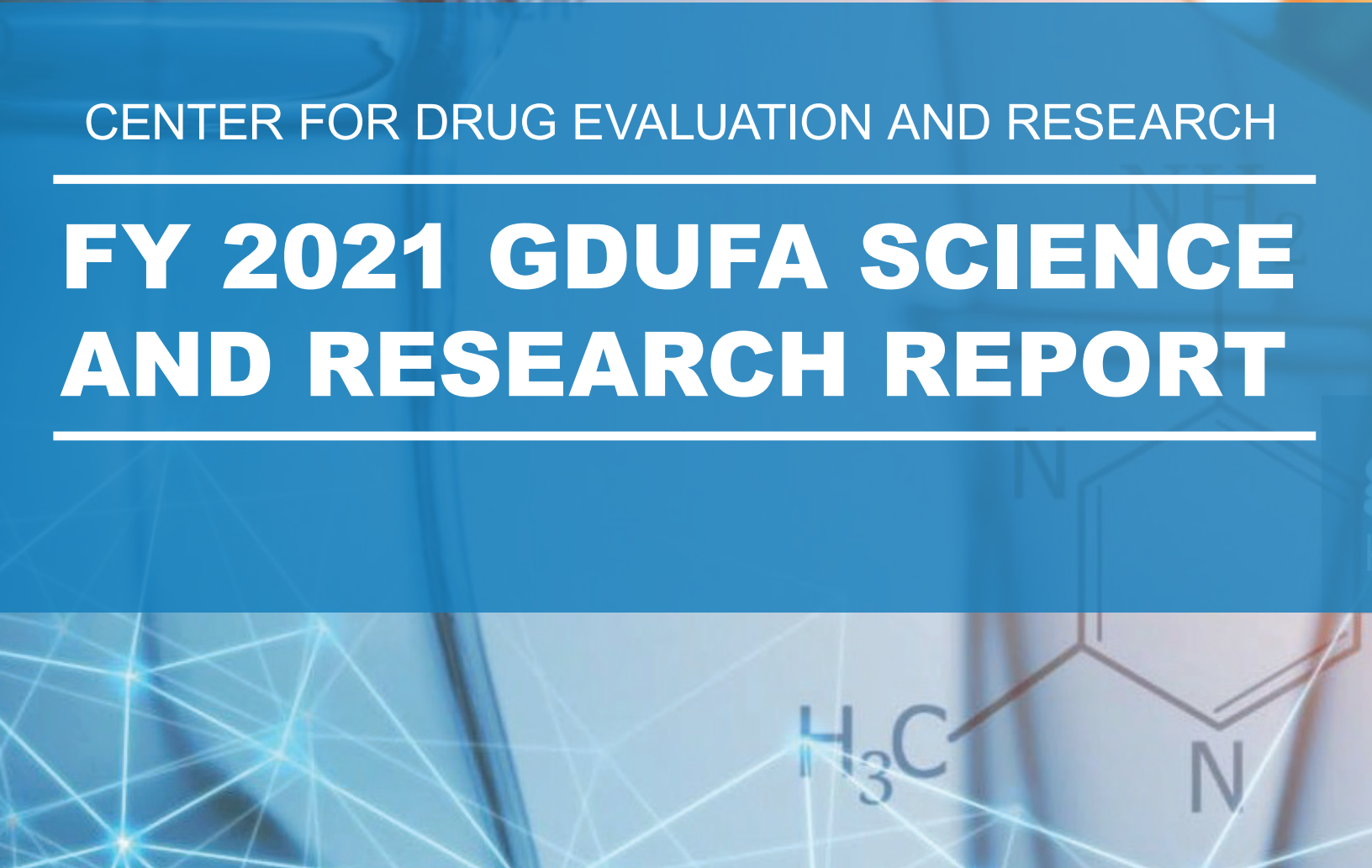

Table of Contents

Joint Directors' Message

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The Generic Drug User Fee Amendments (GDUFA) established a Science and Research Program at FDA that is implemented through extensive intramural research collaborations among FDA scientists, as well as through numerous extramural collaborations with research institutions around the world. The research focuses on overcoming scientific challenges for generic product development in the areas that generic industry stakeholders identify to be priorities for each fiscal year (FY).

This Directors' Message is a joint message from the Director of the Office of Generic Drugs (OGD) and the Director of the Office of Pharmaceutical Quality (OPQ), as both of these offices within the Center for Drug Evaluation and Research (CDER) are significantly involved in GDUFA-funded research collaborations and projects. We also acknowledge other collaborators within FDA who are closely involved with our GDUFA Science and Research Program, such as CDER's Office of Translational Sciences, FDA's Center for Devices and Radiological Health (CDRH), FDA's National Center for Toxicological Research, and FDA's Office of Regulatory Affairs.

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

To enhance patient access to complex generics, in FY 2021 FDA awarded 6 new research

contracts and 10 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 80 intramural GDUFA Science and Research projects focused on how to best use our resources to improve generic drug development and regulatory assessment. These research projects follow the FY 2021 Science and Research Priority Initiatives.

The outcomes from GDUFA-funded research expand our understanding of these 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 of complex generic products and establish the scientific basis for novel and more efficient pathways by which to develop complex generics. Bioequivalence and quality recommendations are communicated to the generic industry, such as through the continual publication of new and revised product-specific guidances (PSGs), as well as general guidances for industry.

In FY 2021, FDA issued 135 new and revised PSGs (53 were for complex products), which provided recommendations for developing generic drugs and generating the evidence supporting ANDA approval. These PSGs helped prospective generic applicants focus their product development, prepare for ANDA submission, and mitigate certain risks associated with generic drug product development. The development of these PSGs also helped FDA to expedite the assessment of ANDAs, once submitted to FDA.

In addition to informing FDA guidances, GDUFA research outcomes also allow FDA to clarify whether proposed bioequivalence approaches presented to FDA in pre-ANDA product development meetings are likely to be suitable and 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 2021, FDA facilitated 87 product development and pre-submission pre-ANDA meetings. The GDUFA research outcomes also prepared FDA to assess ANDAs referencing complex products, which ultimately improved patient access to complex generics that were presumed to be unfeasible to develop even just a few years ago.

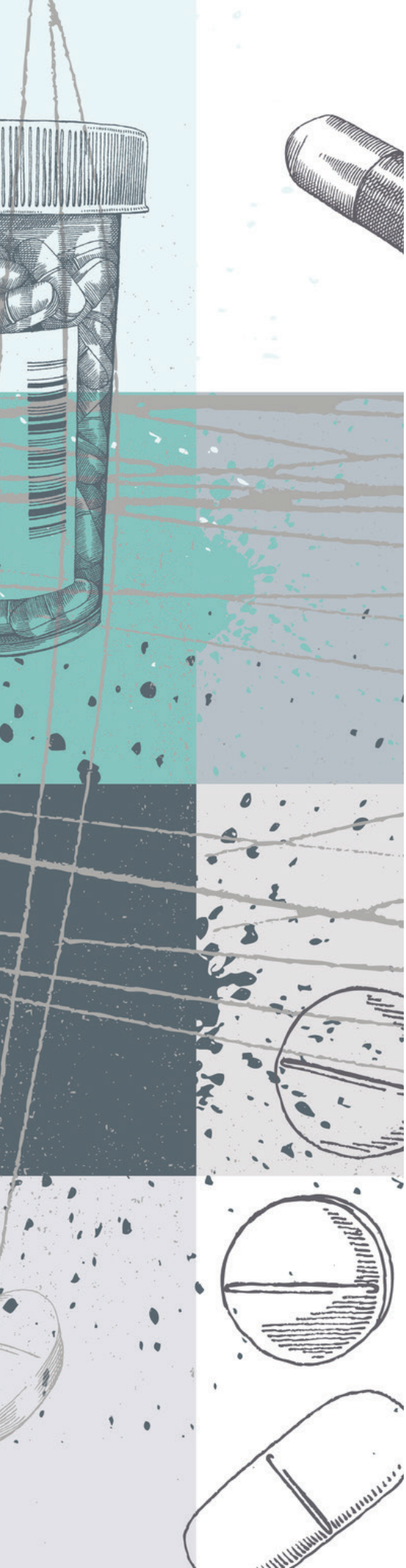
For example, on December 28, 2020, FDA approved the first generic glucagon for injection. Generic peptide products have been exceptionally difficult to develop, in part, due to challenges with demonstrating active ingredient sameness, characterizing potential differences in peptide impurity profiles, and assessing the immunogenicity of novel impurities. Generic industry stakeholders and FDA had collaboratively identified products containing complex mixtures and peptides as being a GDUFA science and research priority. The sophisticated techniques developed as part of the resulting research made it possible to characterize the physicochemical and structural properties of peptides, including their primary and secondary structures, impurities characterization and quantification, oligomers, and aggregation states, while complementary research led to the development and finalization of non-clinical assays to assess the immunogenicity risk of peptide impurities. Intensive collaboration among experts in multiple offices across OPQ and OGD ultimately led to the finalization of a general guidance for industry entitled *Submission of Abbreviated New Drug Applications for Certain Highly Purified Synthetic Peptide Drug Products* (May 2021), which applied to glucagon, and which directly supported the development, assessment and approval of the first generic glucagon in FY 2021.

As another example, on August 9, 2021 FDA approved an ANDA for the first generic difluprednate ophthalmic emulsion. Ophthalmic emulsions like this have been challenging to develop as generics because they involve a complex dosage form administered by a complex route of delivery. After generic industry stakeholders and FDA collaboratively established a research priority to develop new bioequivalence methods and pathways for locally-acting drug products, the GDUFA research program coordinated intensive collaboration among experts in multiple offices across OPQ and OGD, as well as CDRH, which resulted in numerous scientific innovations. These included the first application of asymmetric flow field flow fractionation to measure emulsion globule size distribution, the first biphasic diffusion method to quantify the rate and extent of drug transfer across different phases in emulsions, the first non-invasive nuclear magnetic resonance method to assess drug distribution in the dosage form, and the first physiologically relevant (and highly discriminatory) in vitro drug release testing method based on adaptive perfusion. Along with several other scientific breakthroughs, these GDUFA research outcomes established the scientific foundation for bioequivalence recommendations in a PSG for difluprednate ophthalmic emulsion that directly facilitated the development, assessment, and approval of the first generic difluprednate ophthalmic emulsion in FY 2021.

As part of FDA's commitment to expanding its collaboration and communication with industry, during FY 2021, the Center for Research on Complex Generics (CRCG) was established to enhance how generic industry stakeholders and the FDA work together to overcome challenges impacting patient access to high quality, safe and effective generic products. In addition to ensuring that GDUFA science and research initiatives are focused on the most pressing scientific challenges, the CRCG is committed to helping generic industry stakeholders efficiently access and effectively utilize the scientific insights, technical methods, study designs, data analyses, and other GDUFA Science and Research outcomes to successfully develop complex generics.

During FY 2021, the CRCG solicited and received feedback from a wide range of generic industry stakeholders that provided more detailed insights into specific challenges related to the development and assessment of complex generics and helped identify actionable outcomes that can address these challenges. To help generic industry stakeholders implement scientific insights from GDUFA research outcomes in a manner consistent with the FDA's regulatory expectations, the CRCG hosted two scientific workshops. The CRCG also played a central role in coordinating and enhancing generic industry engagement in the FY 2021 GDUFA Science and Research Initiatives Public Workshop, which helped to inform the ongoing priority areas for the GDUFA Science and Research Program.

We are deeply grateful to all of our collaborators within FDA and at institutions around the world, and our stakeholders throughout the global generic drug industry. There remain numerous challenges to face, and we look forward with optimism and we remain confident that our collaborations to advance the GDUFA Science and Research Program are the most effective way to address scientific challenges for complex generics, and to enhance patient access to high quality, safe, and effective medicines.



Abuse-Deterrent Opioid Products

Summary of FY 2021 Activities

In FY 2021, intramural and extramural research projects focused on enhancing regulatory assessments for abuse-deterrent formulations (ADF) of opioid drug products. Extramural research included three ongoing projects on abuse deterrence (AD) assessment of various routes of abuse through chewing, nasal insufflation, and vaping or smoking.

To investigate the AD performance against chewing, an extended-release ADF of hydrocodone bitartrate with a different resistance to chewing than the approved product (Hysingla, NDA 0206627) is being developed (Grant 3U01FD004275-07S1). Pharmacokinetic (PK) characteristics of the drug product chewed for various lengths of time will be investigated (Contract HHSF223201610004I-75F40119F19004). The results will be used to help determine critical study design parameters for chewing PK studies. Additionally, the results will be used to evaluate the in vitro chewing method in combination with physiologically based PK (PBPK) modeling and simulation for predicting in vivo PK following chewing of an ADF opioid product.

A nasal insufflation study (Contract HHSF223201610004I-HHSF22301002T) is being conducted that investigates an oxycodone drug product designed to also contain an opioid antagonist (naloxone) to deter abuse. This project evaluates the PK and pharmacodynamics following nasal insufflation of milled drug products of different particle size ranges. Similarly, the results will be used to verify an in silico model developed by FDA to further develop in vitro tools for predicting in vivo AD behavior.

In another study (Contract 75F40119C10112), the factors that affect the measurement of smoking and vaping will be determined with a focus towards standardization and validation of smoking and vaping methods and apparatus. This study will assess the smoking and vaping potential of various opioid drug substances and drug products under a range of temperatures, vaping fluids, and environmental conditions.

Internal FDA research initiatives on ADF are focused in three areas. First, in vitro testing and in silico models to predict in vivo AD performance were developed and integrated to aid in study design and to minimize the reliance on costly in vivo studies. For example, work related to the nasal route of abuse involved use of hybrid computational fluid dynamics and PBPK modeling, and has identified useful dissolution testing methods as well as the need for developing an in vitro tool to evaluate the effect of formulation differences on mucoadhesion. Separately, a PBPK modeling initiative focused on ADF products containing both an opioid agonist and an antagonist has revealed that the impact of the particle size distribution in the manipulated product on the PK characteristics of the agonist and the antagonist could differ greatly. Second, a testing method and a mathematical model to predict the syringeability and injectability for ADFs was developed for further testing that could aid in future ADF assessments. The viscosity of the testing sample was found to be a critical material attribute and can serve as a useful surrogate for injectability assessment. The relationships between injection force, viscosity, and testing conditions were elucidated using a mathematical model. Third, research initiatives have enhanced the safety assessment of ADFs abused by non-intended routes of use (see **Research Highlight**).

In 2017, Opana ER was withdrawn from the market due to concerns that the risks outweighed the drug's therapeutic benefits. One major concern was the thrombotic thrombocytopenic purpura (TTP)-like syndrome associated with abuse via the intravenous route, which was later mechanistically linked to systemic exposure to a high molecular weight polyethylene oxide (PEO), an excipient in the oral drug product. However, it was not known how differing PEO preparations might alter this response in vivo. A study was designed to understand the impact of PEO molecular weight on thrombotic microangiopathy-related hemolytic uremic syndrome (TMA-HUS) in a guinea pig model of acute repeat PEO (1, 4, and 7 MDa) dosing. Results from this study suggested that repeated dosing of PEO with 4 or 7 MDa molecular weights, but not 1 MDa, induced a marked intravascular hemolysis with schistocytes (**Figure 1**), mild anemia, thrombocytopenia, hemoglobinuria, and kidney injury, consistent with observations of a TMA-HUS-like syndrome.

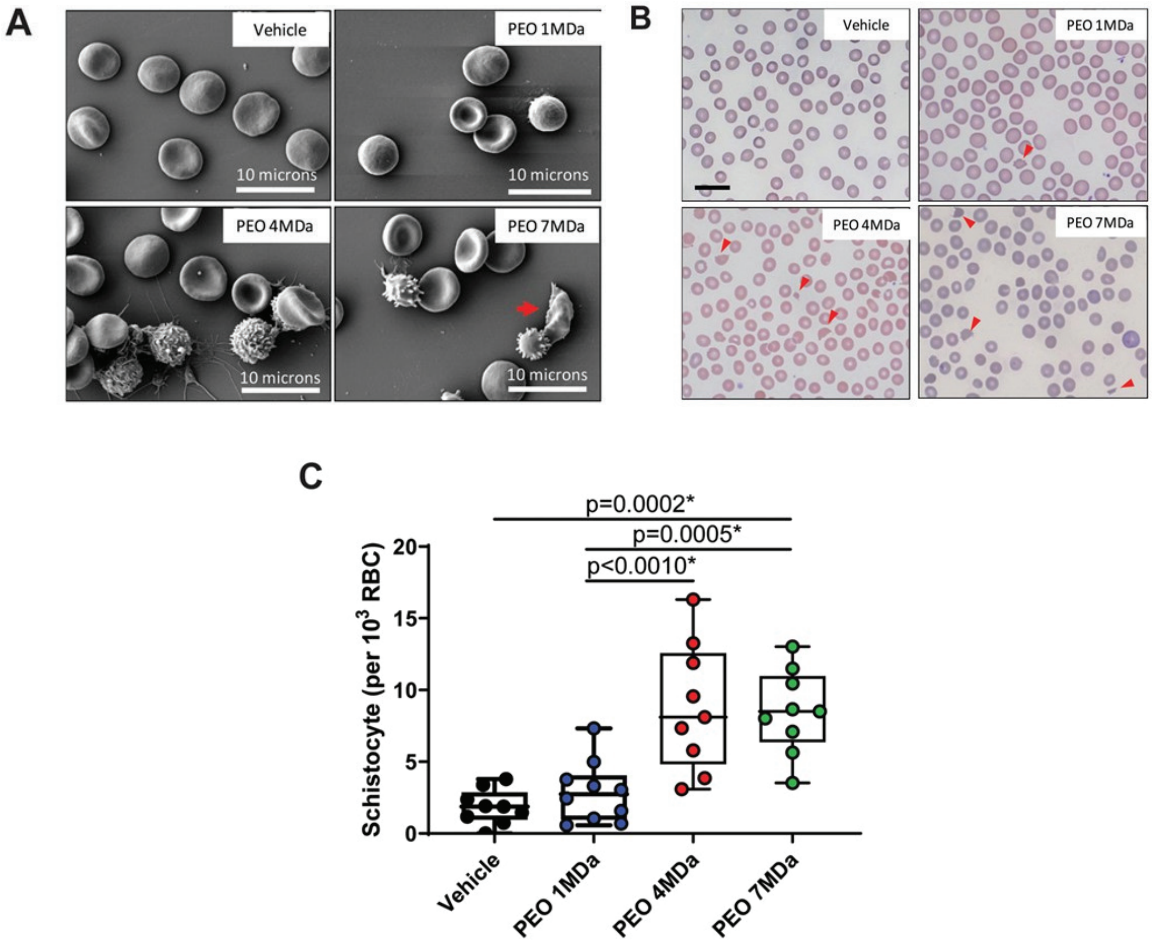


Figure 1: Red blood cell (RBC) morphology and appearance of schistocytes in blood smears prepared from PEO-dosed guinea pigs. (A) Electron microscopy gross morphologic features of guinea pig RBCs 24 h post infusions, (B) Appearance and quantitation of schistocytes (arrowheads) in blood smear in the peripheral blood 24 h post-injection, and (C) Quantitation of schistocytes presented as number per 1000 RBCs in box and whisker plots. Analyses were performed using a one-way ANOVA with a multiple comparisons test and a post hoc Tukey's correction using GraphPad Prism, version 8.

However, observations of tissue microthrombi, complement or altered von Willebrand factor involvement were not observed, which would be consistent with a definitive TMA. Further, only 7 MDa PEO dosing was associated with marked renal hypoxia. Taken together, this study observed renal injury risk with PEO formulations >1 MDa that is driven by a robust intravascular hemolysis and, potentially, tissue hypoxia.

To develop a simple and reproducible in vitro tool for evaluating such safety concerns, two test methods (i.e., a needle model and a microfluidic model; **Figure 2**) are under development and evaluation. In preliminary testing, the microfluidic model generated comparable levels of PEO-induced hematotoxicity relative to the needle model but provided additional value on interactions between PEO and blood components in a dynamic environment. The results from the in vitro models will be correlated with the data from the guinea pig studies.

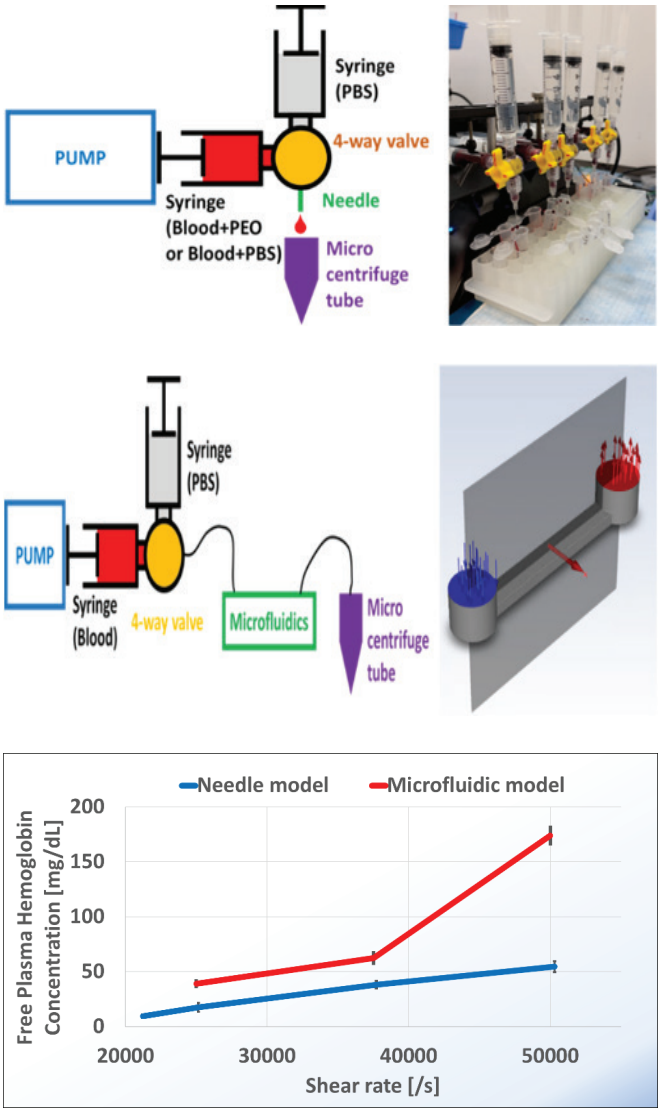


Figure 2: The needle model and microfluidic model schematics and experimental setups, and the testing results showing the greater shear rate dependency of PEO hematotoxicity in the microfluidic model compared to the needle model.

Continuing Grant(s) and Contract(s)

- Grant (3U01FD004275-07S1) *Formulation of Hydrocodone Bitartrate Opioid Tablet* with Mansoor A. Khan at 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 Steven R. Byrn at National Institute for Pharmaceutical Technology & Education (NIPTE).
- Contract (HHSF223201610004I-HHSF22301002T) *Nasal Pharmacokinetic(PK)/ Pharmacodynamic(PD) Studies of Oral Combination Products Containing Opioid Agonists and Antagonists* with Artan Markollari at Biopharma Services USA Inc.
- Contract (HHSF223201610004I-75F40119F19004) *Pharmacokinetic (PK) Study of Opioid Drug Products Following Oral Ingestion of Chewed Products* with Artan Markollari at Biopharma Services USA Inc.

Completed Grant(s) and Contract(s)

- Contract (HHSF223201510138C) *Pharmacokinetics Study of Opioid Drug Product Following Insufflation of Milled Drug Products* with Debra Kelsh at Vince & Associates Clinical Research.

Active FDA Research

- *Development of a Standardized Method and a Predictive Model for Syringeability and Injectability Assessment for Abuse-Deterrent Formulations (ADF)*
- *Development of In Vitro Methods for Nasal Abuse-Deterrent Formulation (ADF) OpioidsCFD Models of Soft Mist Inhalers*
- *In Vivo Nasal Bioequivalence (BE) Study to Evaluate Abuse Deterrence of Agonist-Antagonist Combination Products (Embeda)*
- *Evaluate the Emerging Safety Concerns Associated with the Abuse of Abuse-Deterrent Oral Formulations of Opioids Via the Intravenous (IV) Route and Develop In Vitro Predictive Models to Assess the Safety of Oral Excipients Through Non-Intended Routes of Delivery*
- *Utilize PBPK Model to Understand the Effect of Particle Size of Injectable Suspensions on Their Systemic Exposure*

Product-Specific Guidance(s) (PSG)

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

- *New Draft Guidance for Naloxone Hydrochloride; Oxycodone Hydrochloride Tablet, Extended Release.* (November 2020) Link to Posting.

Article(s)

- Raofi S, Kinjo M, Sun D, Li Z, Boyce H, Natarajan K, Frost M, Zhao L, Luke M, Lionberger R, Kelsh D, and Kim M. *Particle Size Affects Pharmacokinetics of Milled Oxycodone Hydrochloride Tablet Products Following Nasal Insufflation in Nondependent, Recreational Opioid Users*. Clinical and Translational Science. (2021) 14(5): 1977-1987. doi: https://doi.org/10.1111/cts.13053. PMID: 33982418.
- Zhao L, Li Z, Fang L, Kim M-J, Nallani S, Sahajwalla C, Calderon S, Roca R, Feng K, Zineh I, and Lionberger R. *Association of Partial Systemic Exposure and Abuse Potential for Opioid Analgesics with Abuse Deterrence Labeling Claims Supporting Product-Specific Guidance*. EClinicalMedicine. (2021) 41: Article 101135. doi: https://doi.org/10.1016/j.eclinm.2021.101135. PMID: 34585126.

Poster(s)

- Chopski S, Walenga R, Boyce H, Babiskin A, and Kim M. *Physiologically-Based Pharmacokinetic Model to Describe the Pharmacokinetics of Crushed Morphine Sulfate and Naltrexone Hydrochloride Extended-Release Capsules with Abuse Deterrent Properties*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Kim D, Natu R, Malinauskas R, Herbertson L, Baek J, Feng X, Qu H, and Xu X. *Development of In Vitro Predictive Models for Abuse-Deterrent Opioid Safety Assessment*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Sun W, Boyce H, Tang F, Hollenbeck R, Ibrahim A, Hoag S, and Kim M. *Physical Manipulation of an Opioid Drug Product Containing Combination of Opioid Agonist and Antagonist*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Walenga R, Boyce H, Feng X, Zidan A, Kamal N, Xu X, Babiskin A, Kim M, and Zhao L. *Hybrid CFD-PBPK Model for Prediction of Systemic PK Following Nasal Insufflation of Milled Oxycodone Hydrochloride Extended-Release Tablets*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.

Presentation(s)

- Al-Ghabeish M. *Advancement in the In-Vitro Evaluation of Abuse-Deterrent Formulations for Opioid Analgesics: Research and Assessment Perspectives*. Presentation at the 2021 Small Business & Industry Association (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Boyce H. *Pharmacokinetics of Milled Oxycodone Hydrochloride Tablet Products Following Nasal Insufflation in Nondependent, Recreational Opioid Users*. Presentation at the National Institute for Pharmaceutical Technology and Education (NIPTE) Annual Scientific Conference. Virtual Meeting, December 9, 2020.
- Raofi, S. *Nasal Pharmacokinetic Study of Abuse-Deterrent Oxycodone HCl ER Products Following Insufflation of Physically Manipulated Products*. Presentation at the 2021 Small Business & Industry Association (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.

Complex Injectables, Formulations, and Nanomaterials

Summary of FY 2021 Activities

In FY 2021, research efforts for complex injectables, formulations, and nanomaterials focused on the following aspects: (1) development of novel in vitro drug release test (IVRT) methods, (2) evaluation of new analytical methods for characterizing complex injectables, (3) use of in silico multi-scale model to evaluate target site bioequivalence and critical quality attributes of injectable nanomaterials, and (4) investigate the relationships between physicochemical features of amphotericin B liposomes and product toxicity (detailed in **Research Highlight**).

Development of a fit-for-purpose and robust IVRT method for a complex drug products containing nanomaterials, such as liposomes and nano-emulsions, can be challenging. Accordingly, new IVRT methods were developed through internal collaborations to assist with the evaluation of these complex formulations. For example, FDA developed a novel IVRT method based on the principle of tangential flow filtration. This method is free from the constraints of rate-limiting factors of some IVRT methods (e.g., diffusion through dialysis membrane). This method is capable of differentiating drug release profiles from solutions, micelles, and nano-emulsions of different globule sizes. In addition, FDA scientists developed an electroanalytical method for the continuous and direct qualification of drug released from liposomes, based on the redox-active feature of the drug substance (**Figure 1**). The tangential flow method eliminates the need of additional lengthy separation steps that may cause inaccurate qualification

due to liposome rupture. This method may be further applied in other liposomal formulations containing redox-active drug substances. Furthermore, an IVRT method was developed for a verteporfin liposome formulation to better mimic in vivo conditions. Overall, these new methods may serve as useful tools to support a demonstration of bioequivalence for generic drugs or for quality control purposes.

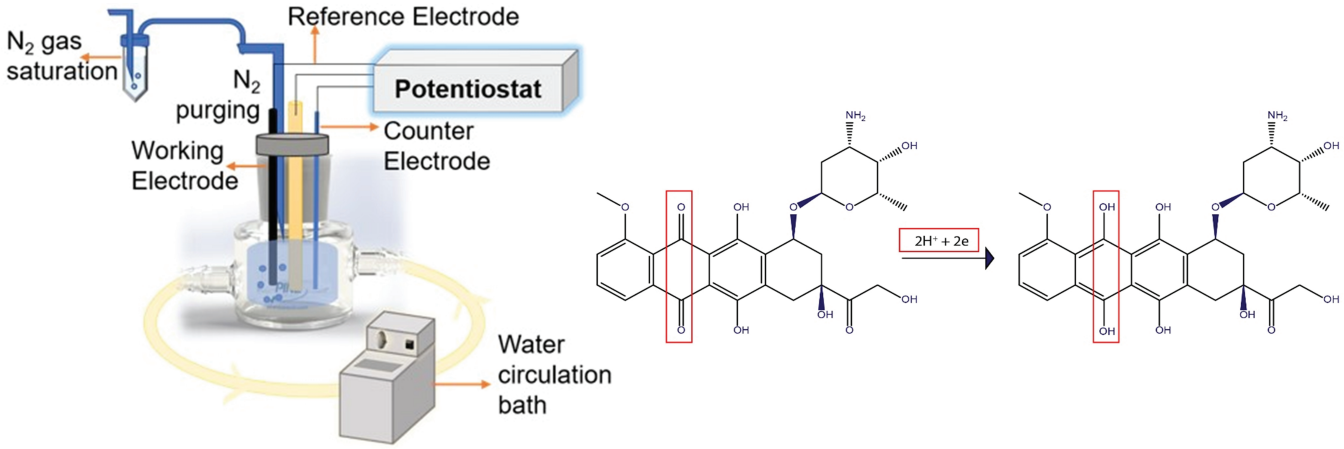


Figure 1: Illustration of the in-vitro drug release/dissolution set up and quinone group redox reaction.

FDA continued efforts to evaluate new analytical methods for characterizing complex injectables and for developing standards. Three liposome test method standards were developed by FDA scientists and are currently under ballot at the American Society for Testing and Materials (ASTM) International, E56 Sub-Committee on Nanotechnology. In a grant (U01FD005946) awarded to the University of Maryland, a new method based on hyperspectral interferometric scattering microscopy is being developed to characterize physicochemical properties of nanoparticle-based therapeutics. In addition, FDA examined a nuclear magnetic resonance-based in vitro method to characterize the initial aggregation of degarelix in a complex injectable product. This method was demonstrated to quickly differentiate lot-to-lot differences in degarelix aggregation kinetics, and to reveal the effects of degarelix concentration, pH, salt, and temperature on the kinetics.

FDA continued its contract (75F40119C10139) with the Institute of Quantitative Systems Pharmacology (IQSP) for evaluating target site bioequivalence of injectable drug products that incorporate nanomaterials (e.g., liposomal doxorubicin) through in silico system-based multi-scale modeling. The model intends to capture various biological and physicochemical events that affect the transport and residence of nanoparticles and nanoparticles' cargo active ingredient. The outcome of this contract would provide a link between certain nanoparticle attributes and target site bioavailability.

Liposomal amphotericin B is a lipid formulation of amphotericin B for systemic treatment of fungal infections, where amphotericin B is intercalated into the liposomal membrane. Research conducted in a previous BAA contract (HHSF223201610093C) discovered that amphotericin B could exist as either a loose or a tight aggregate in the lipid bilayer, and heat treatment (curing) during the liposome manufacturing process can alter the aggregation status of amphotericin B. However, the precise mechanistic relationship between aggregation and toxicity is not well understood. In the current contract (75F40120C00055), the rate of drug release from the variant liposomal formulations of amphotericin B with loose and tight aggregates were measured to evaluate correlations among drug aggregation state, drug release, and in vitro toxicity. The data demonstrated that as the curing of the drug product progressed, amphotericin B aggregation state within the liposomal bilayer transitioned from loose to tight, as confirmed by the blue shift of λmax and by the decreased pool ratio derived from the kinetic model. Tight aggregates released the free drug slower than loose aggregates. In vitro toxicity decreased with curing, as indicated by an increase in concentrations causing half maximal potassium release (TC_{50}). This study demonstrated the relationship between amphotericin B aggregation status within the lipid bilayer and drug release, providing a mechanistic link between aggregation status and in vitro toxicity in the liposomal formulations.

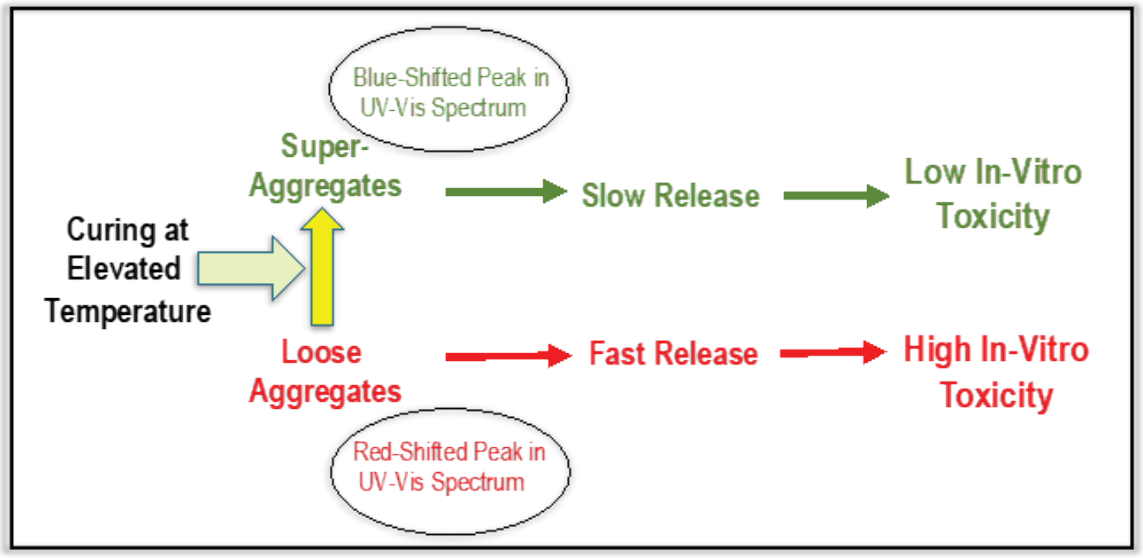


Figure 2: A model showing how curing changes the aggregation status of amphotericin B, drug release, and toxicity of liposomal amphotericin B.

New Grant(s) and Contract(s)

- Grant (1U01FD007363) *Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex-Ferric Derisomaltose* with Sarah L. Michel at University of Maryland Baltimore.
- 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 (75F40121C00189) Characterization of Car*boxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes* with Eric J. Munson at Purdue University.

Continuing Grant(s) and Contract(s)

- Grant (5U01FD005946-04) *Hyperspectral Interferometric Scattering Microscopy for Characterizing Nanoparticle-Based Therapeutics* with William E. Bentley, James E. Polli at University of Maryland (Baltimore).
- Contract (75F40119S30028) *Nanofluidic Slit Devices for Measuring Nan-Particle Drug Concentration to Improve Complex Drug Regulation* with Samuel Stavis at the NIST Center for Nanoscale Science and Technology.

Completed Grant(s) and Contract(s)

- Contract (75F40120C00055) *Evaluation of Critical Process Parameters for the Preparation of Amphotericin B that Influence Toxicity* with Nelson Landrau at Landrau Scientific Innovations, LLC.
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie L.S. Au at Institute of Quantitative Systems Pharmacology (IQSP).

Active FDA Research

- *Assessing New Analytical Methods for Characterizing Characterization of Complex Nanotechnology Drug Products*
- *Assessing Qualitative Sameness of Polyoxly Castor Oil in Phytonadione Injectable Generics*
- *Bupivacaine Multivehicle Liposomes*
- *In Vitro Performance Characterizations of Sucroferric Oxyhydroxide to Establish Bioequivalence Methods*
- *In Vivo Biodistribution Evaluation of Liposome Drug Products*
- *In Vivo Gel or Depot Formation*

Product-Specific Guidance(s) (PSG)

There were four new and two revised PSGs published in FY 2021 related to complex injectables, formulations, and nanomaterials. These PSGs were directly impacted by GDUFA-funded research in this area:

- *New Draft Guidance for Degarelix Acetate Powder Subcutaneous.* (March 2021) Link to Posting.
- *Revised Draft Guidance for Ferric Oxyhydroxide Injectable.* (September 2021) Link to Posting.
- *Revised Draft Guidance for Ferric Oxyhydroxide Chewable Tablet.* (September 2021) Link to Posting.
- *New Draft Guidance for Meloxicam Solution.* (May 2021) Link to Posting.
- *New Draft Guidance for Octreotide Acetate Solution.* (March 2021) Link to Posting.
- *New Draft Guidance for Penicillin G Benzathine Injectable.* (March 2021) Link to Posting.

Article(s)

- Brandis J, Kihn K, Taraban M, Schnorr J, Confer A, Batelu S, Sun D, Rodriguez J, Jiang W, Goldberg D, Langguth P, Stemmler T, Yu Y, Kane M, Polli J, and Michel S. *Evaluation of the Physicochemical Properties of the Iron Nanoparticle Drug Products: Brand and Generic Sodium Ferric Gluconate*. Molecular Pharmaceutics. (2021) 18(4): 1544-1557. doi: https://doi.org/10.1021/acs.molpharmaceut.0c00922. PMID: 33621099.
- Patel D, Zhang Y, Dong Y, Qu H, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: An In Vitro Release Test (IVRT) for Complex Drug Products*. Journal of Controlled Release. (2021) 333: 65-75. doi: https://doi.org/10.1016/j.jconrel.2021.03.024. PMID: 33766693.
- Patil S, Qin B, Wang Y, Ahmed S, Yilmaz H, Jiang X, Keire D, and Chen K. *Real-Time NMR Based In Vitro Aggregation Kinetics Analysis of Degarelix Drug Product*. AAPS PharmSciTech. (2021) 22(2): Article 73. doi: https://doi.org/10.1208/s12249-021-01948-5. PMID: 33586081.
- Smith W, Bae J, Zhang Y, Qin B, Wang Y, Kozak D, Ashraf M, and Xu X. *Impact of Flocculation on the Dissolution and Bioavailability of Injectable Suspensions*. International Journal of Pharmaceutics (2021) 604: Article 120767. doi: https://doi.org/10.1016/j.ijpharm.2021.120767. PMID: 34087414.

Poster(s)

- Bae J, Patel M, Manna S, Smith W, Vo A, Wang Y, Choi S, Kozak D, Zheng J, and Xu X. *Impact of Manufacturing Process on Critical Quality Attributes of Multivesicular Liposomes*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) PharmSci 360. Virtual Meeting, October 26, 2020.
- Naik S, Palui G, Majumdar S, Raghavendra A, Sharmah A, Koonce N, Zheng J, Paredes A, Jiang W, and Patri A. *Comprehensive Physico-Chemical Characterization of Liposomal Doxorubicin*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Siriwardane D, Jiang W, and Mudalige T. *Profiling In-Vitro Release of Verteporfin from VISUDYNE Liposomal Formulation and Investigating the Kinetics of Human Serum Albumin (HSA)-Verteporfin Complex Formation*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Smith W, Bae J, Zhang Y, Wang Y, Qin B, Kozak D, Ashraf M, and Xu X. *Clinical Performance of Injectable Suspensions: Interplay between Particle Flocculation and Dissolution*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Yurtsever F, Siriwardane D, Jiang W, and Mudalige T. *Exploring an Electroanalytical Method to Determine Drug Release from Liposomal Doxorubicin HCl*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: An In Vitro Drug Release Testing Method for Complex Drug Products*. Poster Presentation at the FDA Science Forum, May 26, 2021.
- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: An In Vitro Drug Release Testing Method for Complex Drug Products*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.

Presentation(s)

- Jiang W. *Complex Drug Products Containing Nanomaterials*. Presentation at the 12th European Foundation for Clinical Nanomedicine Annual Summit. Virtual Meeting, October 27, 2020.
- Jiang W. *Liposome Guidance*. Presentation at the Nanotechnology Task Force NanoDay Virtual Research Symposium. Virtual Meeting, October 9, 2020.
- Jiang W. *Advances in Iron Colloid Products: Product-Specific Guidance Discussion*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Kozak D. *Advanced Analytical Methods in Generic Drug Development and Approval*. Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Li Y. *Advances in Iron Colloid Products: Quality Considerations When Conducting Comparability Studies*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Qin B. *Injectable Suspensions: Tools and Methods Bridging the In Vivo and In Vitro Gap*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Xu X. *Understanding Drug Release from Multivesicular Liposomes.* Presentation at the Nanotechnology Task Force NanoDay Virtual Research Symposium. Virtual Meeting, October 9, 2020.
- Xu X. *Supporting the Development of Drug Products Containing Nanomaterials: Trends, Guidances, and Voluntary Consensus Standards*. Presentation at the U.S. Pharmacopeia (USP) Nanomaterial Working Group Meeting. Virtual Meeting, October 16, 2020.
- Xu X. *Supporting the Development of Drug Products Containing Nanomaterials: Guidance, Trends and Research*. Presentation at the National Institute for Pharmaceutical Technology & Education (NIPTE) Annual Conference. Virtual Meeting, December 8, 2020.
- Xu X. *Connecting the Dots: Particle Size, Drug Distribution and Drug Release in Nanoemulsions*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Webinar. Virtual Meeting, May 7, 2021.
- Xu X. *Supporting the Development of Drug Products Containing Nanomaterials: Guidance, Trends, and Research*. Presentation at the Workshop on Advancing Measurement Technologies and Standards for Nano-Enabled Therapeutics and Vaccines. Virtual Meeting, June 15, 2021.

Complex Mixtures and Peptide Products

Summary of FY 2021 Activities

In FY 2021, research efforts continued in the development of advanced analytical methods for the evaluation and characterization of complex active pharmaceutical ingredients (APIs) including complex mixtures, oligonucleotides, peptides, and synthetic polymers. Characterization of complex APIs using advanced methods is essential for supporting a demonstration of pharmaceutical equivalence and linking product attributes to safety, quality, and clinical performance, thereby facilitating the generic drug development and approval process.

Internal FDA research focused on the development of new analytical methods for the characterization of complex APIs, addressing analytical challenges with oligonucleotide characterization (detailed in **Research Highlight**). These complex macromolecular therapeutics present unique scientific and regulatory challenges, as efficacy and safety are highly dependent on a specific sequence structure and potential sequence impurities. To address these challenges, FDA is developing a liquid chromatography-high resolution mass spectrometry (LC-HRMS)-based multi-attribute method workflow for characterization and impurity profiling of synthetic oligonucleotides. In addition, FDA developed a product-independent ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) method to quantify impurities of peptide drug products. Research into the characterization of therapeutic peptide impurities, such as those in teriparatide, using UHPLC-MS/MS and

RapidFire mass spectrometry continues (detailed in **Research Highlight**). A concomitant challenge of using advanced methods is the analysis of multivariate data from multi-component mixtures. FDA is developing a statistical approach to conduct quantitative assessments of API sameness for complex drug products.

While the immunogenicity risk of synthetic generic peptides is not expected to be high in comparison to their respective reference listed drugs (RLDs), peptide-related impurities may induce unwanted immune responses. In January 2021, FDA hosted the inaugural workshop titled "Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling" where leading experts from FDA and industry discussed utilizing nonclinical methods to assess the potential immune response of generic peptides. To further explore this topic, FDA collaborated with external research partners, including EpiVax and the National Cancer Institute (NCI). EpiVax has developed in silico tools that are adept at identifying putative T cell epitopes but may also be able to distinguish immunogenic and tolerogenic ones. In addition, research is being conducted to understand the immunogenicity risk of the impurities prior to product development. In collaboration with EpiVax, a novel algorithm called the "What If Machine" (WhIM) was created to generate a list of potential impurities based on known failures in the synthesis process and assess their immunogenic potential. These research efforts provide useful insights and recommendations on the use of non-clinical methods to evaluate the immunogenicity risk of these complex generics.

Oligonucleotides

Oligonucleotide therapeutics present unique scientific and regulatory challenges because the efficacy and safety of these products are highly dependent on the sequence of the oligonucleotides, and impacted by structurally related impurities. Synthetic oligonucleotides are specifically excluded from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for impurities (Q3A and Q3B) and specifications (Q6A) designed for typical small molecules. To address these challenges, FDA is developing a LC-HRMS method for characterization and impurity profiling of synthetic oligonucleotides. The method was developed, optimized, and evaluated for sequence characterization, impurity identification, and quantification using custom synthesized oligonucleotides of likely sequences, modifications, and impurities of Nusinersen API (**Figure 1**). This research will support the development of product-specific guidances (PSGs) for oligonucleotides and facilitate the development and approval of generics in this evolving class of therapeutics.

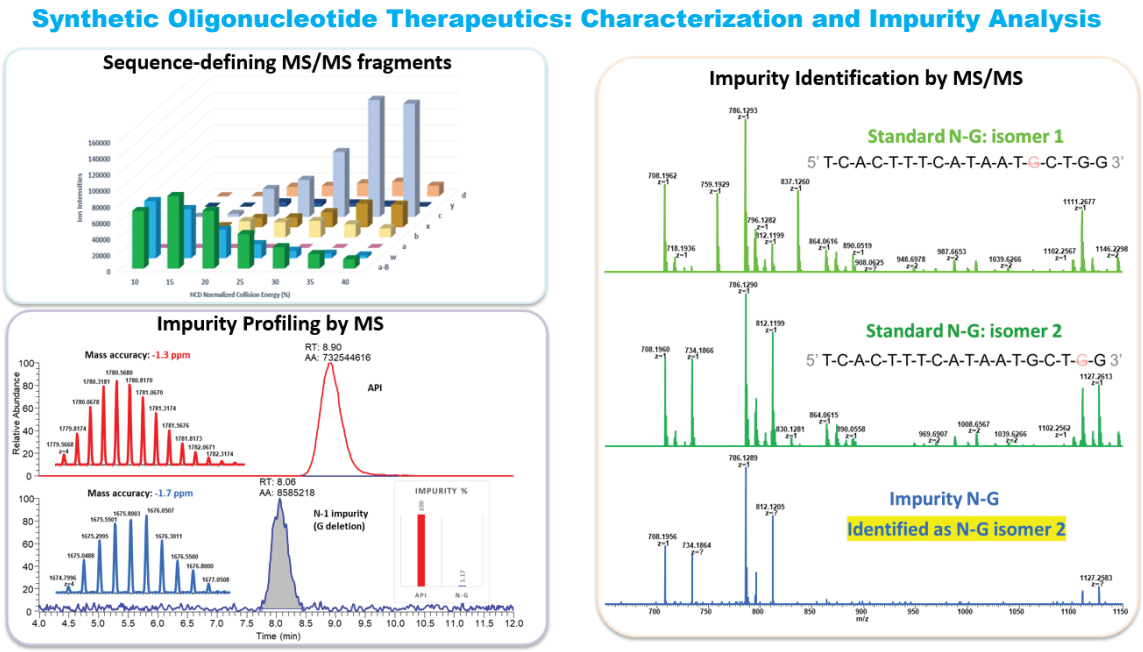


Figure 1: Sequence characterization and impurity analysis of synthetic oligonucleotides and product-related impurities by LC-HRMS and MS/MS.

Peptides

Although potentially immunogenic impurities can be assessed following generic peptide product development through non-clinical assays, it may be advantageous to understand which impurities have the potential for immunogenicity prior to product development. This assessment could enable the reduction, elimination, and detection of highly immunogenic peptide impurities during process development. A pilot version of WhIM was developed in collaboration with EpiVax, which identified potential impurities that could be produced during the synthesis of teriparatide. Several theoretical impurities with modifications to the T-cell epitope region make the impurities appear more foreign to the immune system. When evaluated with in vitro assays using human peripheral blood mononuclear cells, a considerable increase was observed compared to the native teriparatide peptide in the T cell response to these impurities (**Table** and **Figure 2**).

Test Article	EpiMatrix Score (Epitope Content)	JanusMatrix Score (Human Homology)	Percent Donor Response
Forteo®	***16.03***	***4.47***	***20%***
WhIM_ENDO-Leu11	36.3	3.52	45%
WhIM_Des-Gly12	46.63	1.19	45%

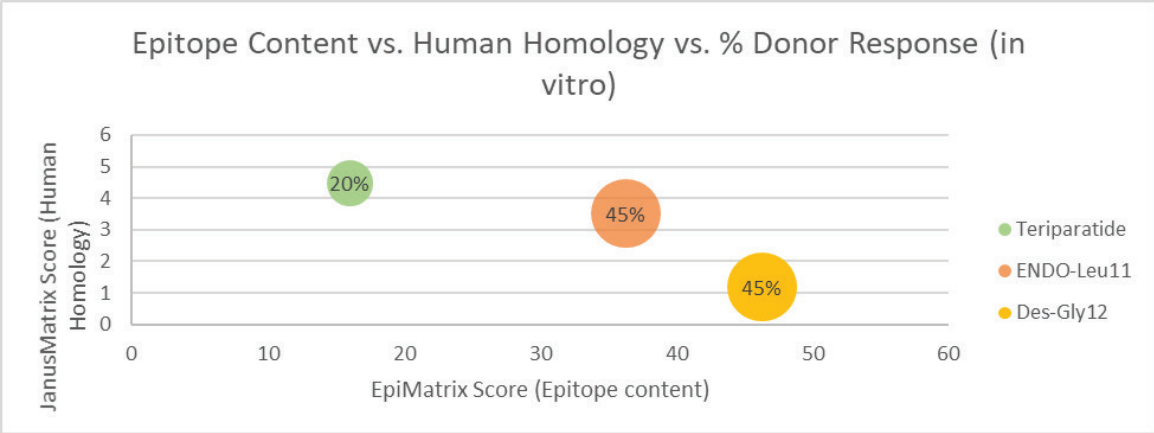


Figure 2: Two theoretical impurities (Endo-Leu11 and Des-Gly12) predicted to have high immunogenicity potential by WhIM (when assessed with epitope content and human homology) have been shown to have increased responses with in vitro assessment (donor responses).

Continuing Grant(s) and Contract(s)

- 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.

Completed Grant(s) and Contract(s)

- Grant (5U01FD004275) *Solid State NMR Analysis (NIPTE)* with Vadim J. Gurvich at National Institute for Pharmaceutical Technology and Education (NIPTE).
- Contract (IAA-224-19-3008S) *Evaluating Innate Immune Response of Generic Peptide Drugs and Impurities* with Marina Dobrovolskaia at National Cancer Institute (NCI).

Active FDA Research

- *Characterization of Patiromer Drug Products*
- *Characterization of Synthetic Oligonucleotides to Support Generic Drug Equivalence*
- *Development of Quantitative Approaches to Facilitate Active Pharmaceutical Ingredient (API) Sameness Assessment*

General Guidance(s)

- *Guidance for Industry: ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin*. (May 2021) Link to Posting.

Product-Specific Guidance(s) (PSG)

There were two new PSGs published in FY 2021 related to complex mixtures and peptide products. These PSGs were directly impacted by GDUFA-funded research in this area:

- *New Draft Guidance for Crofelemer Oral Tablet, Delayed Release.* (November 2020) Link to Posting.
- *New Draft Guidance for Semaglutide Tablet.* (August 2021) Link to Posting.

Article(s)

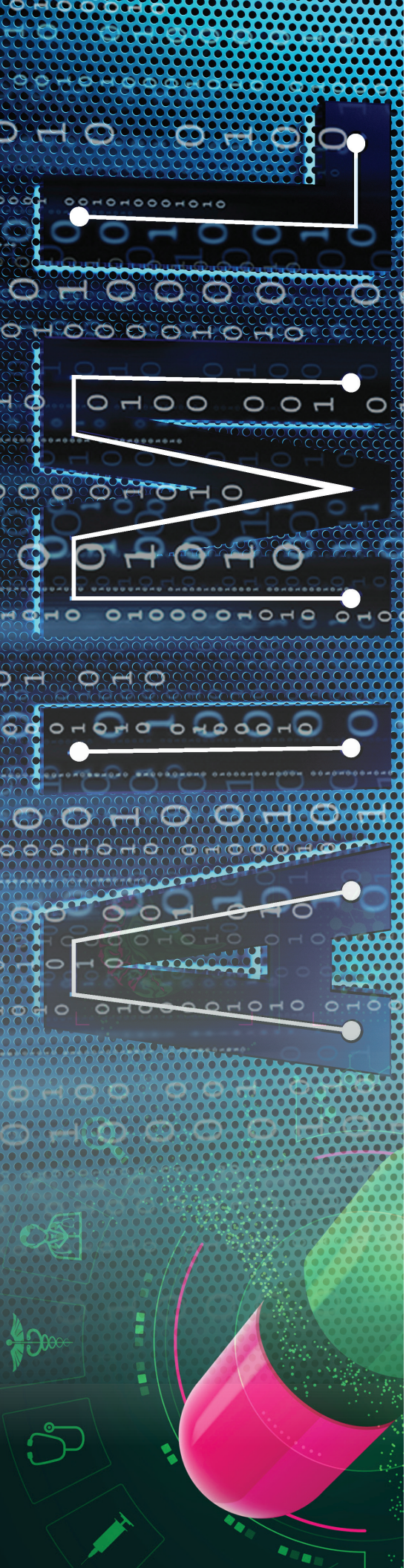
- Korang-Yeboah M, Ketcham S, Shih M, Ako-Adounvo AM, Zhang JH, Bandaranayake BM, Abbey-Berko Y, Faustino P, Ashraf M. *Effect of Formulation and Peptide Folding on the Fibrillar Aggregation, Gelation, and Oxidation of a Therapeutic Peptide*. International Journal of Pharmaceutics. (2021) 604: Article 120677. doi: https://doi.org/10.1016/j.ijpharm.2021.120677. PMID: 33961953.

Poster(s)

- Sung J, Becker R, Knapton A, Pang E, and Howard K. *A Humanized Mouse Model to Predict Immunogenicity of Impurities in Generic Peptide Drugs*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Zhang D, Li S, Jarrells T, Munson E, Kozak D, and Jiang X. *Solid State 13C NMR Analysis of Patiromer*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.

Presentation(s)

- Kozak D. *Advanced Analytical Methods in Generic Drug Development and Approval*. Presentation at The Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Lionberger R. *Introductory Remarks*. Presentation at the Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling. Virtual Meeting, January 26, 2021.
- Pang E and Vertheryi D. *Overview: Non-clinical Immunogenicity Assessment of Generic Peptide Products*. Presentation at the Non-clinical Immunogenicity Assessment of Generic Peptide Products: Development, Validation, and Sampling. Virtual Meeting, January 26, 2021.
- Weng Y, Hu M, Zhao L, Wang C, Shen M, and Gong X. *Developing a Statistical Approach to Facilitate Sameness Assessment of Complex Heterogenous Active Pharmaceutical Ingredients*. Presentation at The 2021 Joint Statistical Meetings. Virtual Meeting, August 08, 2021.
- Yang K, Abdullah AM, Sommers C, and Rodriguez J. *Resolving Impurity Isomers in Synthetic Oligonucleotides by High Resolution Mass Spectrometry*. Presentation at the International Foundation Process Analytical Chemistry (IFPAC) 2021 Annual Meeting. Virtual Meeting, February 28, 2021.
- Zhang D. *Considerations in Submitting Abbreviated New Drug Application of Generic Peptide Drug Products*. Presentation at The TIDES USA 2021 Workshop #5: FDA Guidance on ANDA Submission for Peptides. Virtual Meeting, September 20, 2021.



Data Analytics

Summary of FY 2021 Activities

In FY 2021, FDA's research efforts continued in the development of data analytics capacities. Regarding the use of artificial intelligence (AI), FDA developed a user-friendly bioequivalence (BE) assessment assist tool - BE Assessment Mate (BEAM) - to support efficient and high-quality BE assessment by streamlining labor-intensive work (e.g., table filling) to save time in the BE assessment process. The BEAM development team is further improving the tool with a more intelligent BEAM version by integrating natural language processing (NLP) techniques. As the broad agency announcement (BAA) contract (#75F40119C10106) for developing data analytics tools to facilitate the product-specific guidance (PSG) development entered its second year, an NLP-based pipeline was established to automatically retrieve supportive information from drug labeling to facilitate efficient PSG development (see **Research Highlight**). Other ongoing efforts have included 1) the machine learning (ML)-based Abbreviated New Drug Application (ANDA) workload prediction (e.g., forecasting ANDA submissions), and 2) heterogeneous treatment effect analysis that can be used to optimize a treatment strategy. In addition, ML methods have been applied to investigate generic availability for oncology drug products, including identifying critical factors that impact generic competition for oncology products.

To support regulatory assessments, a data imputation method based on Gibbs sampling (a general framework for sampling from a large set of variables especially when the joint distribution is not known explicitly or is difficult to sample from, directly) is being developed and tested. This method can be used to impute data for missing values at random and/or not at random by left or right censoring. The results of current simulations show that the developed method outperforms several

mainstream methods of data imputation and can be a promising tool for generating model-based evidence to support BE assessment. In addition, FDA is working to develop a multivariate statistical approach to facilitate active pharmaceutical ingredient (API) sameness assessment, which often involves analytical methods that generate complex multi-dimensional data for assessment. The usefulness of a Bayesian estimation-based BE statistical method is also being explored to handle complex pharmacokinetics (PK) BE data (e.g., with extreme values). Furthermore, research on data analytics facilitated to develop improved methods for assessing BE. For example, dose-scale analysis was developed to overcome the complexities of curvilinear responses associated with pharmacodynamic endpoints. The research on data analytics helped improve the implementation of the dose-scale analysis method, which supported recommendations for dose-scale analysis to estimate relative bioavailability in the PSG for orlistat oral capsules.

PSGs represent FDA's current thinking on the optimal approaches to demonstrate BE between a test product and its corresponding reference listed drug. Under the Generic Drug User Fee Amendments II, FDA is committed to issuing PSGs for 90% of non-complex new chemical entity products approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date. This commitment, in addition to the demands of developing PSGs for complex drug products, calls for an enhanced PSG development process. To address this challenge, one of the solutions is to automate the portions of tasks which are labor-intensive during PSG development.

Under BAA contract #75F40119C10106, the time-cost analysis of PSG development process shows that FDA assessors usually expend extensive efforts on retrieving supportive information (e.g., pharmacokinetics, food effect, and potential safety concerns) about the drug products of interest from the drug labeling. As a staged outcome of this contract, an NLP pipeline was developed to extract supportive drug product information from the labeling with minimal human intervention. To facilitate accurate information extraction, an ML-model, the pretrained Bidirectional Encoder Representations from Transformers (BERT) model, was employed to achieve automatic paragraph locating. A case study for locating food effect paragraphs from drug labeling (**Figure 1**) was conducted to illustrate the usefulness of the developed NLP pipeline, especially for scenarios where keyword detection and regular expression are not applicable. The results showed that the pre-trained BERT model can outperform the traditional ML techniques (e.g., random forest and logistic regression) in addressing the challenge for locating food effect paragraphs in labeling due to potential inconsistencies in labeling formats (**Table 1**). These established techniques can be adapted to other drug labeling sections or data sources and have built a solid foundation for the future development of automated tools to facilitate efficient and high-quality PSG development.

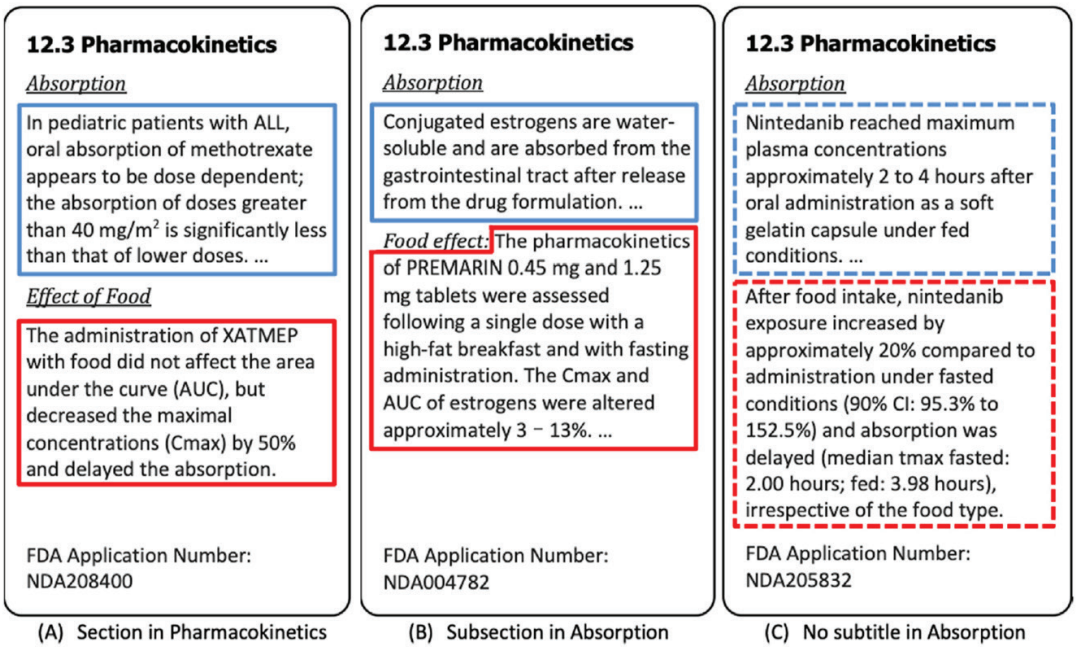


Figure 1: Three examples of food effect paragraphs from drug labeling; "Non-Food Effect" and "Food Effect" are indicated with the blue and red border, respectively. In (A) and (B), "Food effect" can be found as a section in Pharmacokinetics. In (C), no "Food effect" sub-title is present and keyword detection is not applicable for its detection.

Table 1: Performance comparison between different methods for locating food effect paragraphs from drug labeling. The best model performance is indicated in bold.

	Precision	Recall	F1*
Rule-based method 1	0.6429	0.2348	0.3439
Rule-based method 2	0.5000	0.6522	0.5660
Logistic regression	0.9091	0.8696	0.8889
Linear SVC	0.8966	0.9043	0.9004
Random forest	0.9386	0.9304	0.9345
BERT	0.9316	0.9478	0.9397
RoBERTa	0.9469	0.9304	0.9386
DistiBERT	**0.9649**	**0.9565**	**0.9607**

* F1 is a model performance metric based on true positives, false positive, and false negatives.

Reference:
Shi YW, Ren P, Zhang Y, Gong XJ, Hu M, and Liang HL. *Information Extraction from FDA Drug Labeling to Enhance Product-Specific Guidance Assessment Using Natural Language Processing*. Frontiers in Research Metrics and Analytics. (2021) 6: Article 670006. doi: https://doi.org/10.3389/frma.2021.670006. PMID: 34179681.

New Grant(s) and Contract(s)

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

Continuing Grant(s) and Contract(s)

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

Completed Grant(s) and Contract(s)

- Grant (1U01FD005978-P1) *Chemoinformatic Tools to Predict the Effects of Excipients in Generic Drugs* with Brian Shoichet at University of California, San Francisco.
- Contract (75F40120F80605) *Software Development Services for Bioequivalence Review Assistance Tool* with Yvonne Zhou at FUTREND Technology Inc.

Active FDA Research

- *Develop a Machine Learning (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 (ML) to Enhance Product-Specific Guidance (PSG) Review Efficiency*
- *Development and Analysis of a Complex Product Database*
- *Development of a Pharmacokinetic (PK) Data Warehouse for Bioequivalence (BE) Analysis*
- *Development of Quantitative Approaches to Facilitate Active Pharmaceutical Ingredient (API) Sameness Assessment*
- *Machine Learning (ML) for Generic Drug Analysis*
- *Postmarketing Surveillance of Generic Drug Using Sentinel*

Product-Specific Guidance(s) (PSG)

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

- *Revised Draft Guidance for Orlistat Capsule, Oral.* (August 2021) Link to Posting.

Article(s)

- Shi Y, Ren P, Zhang Y, Gong X, Hu M and Liang H. *Information Extraction from FDA Drug Labeling to Enhance Product-Specific Guidance Assessment Using Natural Language Processing*. Frontiers in Research Metrics and Analytics. (2021) 6: Article 670006. doi: https://doi.org/10.3389/frma.2021.670006. PMID: 34179681.

Poster(s)

- Gong X, and Hu M. *Heterogeneous Treatment Effect Analysis Based on Machine Learning Methodology*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, February 14, 2021.

Presentation(s)

- Hu M. *Development of a Data/Text Analytics Tool to Enhance Quality and Efficiency of Bioequivalence Assessment*. Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Hu M. *Utility of Artificial Intelligence to Facilitate the Development and Regulatory Assessment of Complex Generic Drugs*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Weng Y, Hu M, Zhao L, Wang C, Shen M, and Gong X. *Developing a Statistical Approach to Facilitate Sameness Assessment of Complex Heterogenous Active Pharmaceutical Ingredients*. Presentation at the 2021 Joint Statistical Meetings. Virtual Meeting, August 8, 2021.

Drug-Device Combination Products

Summary of FY 2021 Activities

In FY 2021, FDA continued to perform research related to the impact of identified user interface differences on the therapeutic equivalence of complex generic drug-device combination products (DDCPs) and their reference listed drugs (RLDs). As one of FDA's key research initiatives[1], this research included two ongoing contracts, an FDA laboratory project, and two newly awarded grants.

Contract HHSF223201810113C, with the Research Triangle Institute (RTI) International, aims to advance the understanding of patient and caregiver attitudes toward generic substitution of DDCPs through focus groups with asthma and chronic obstructive pulmonary disease (COPD) patients who use a dry powder inhaler (DPI) and focus groups with patients and caregivers who use an epinephrine auto-injector (AI). For FY 2021, RTI International completed ten in-person focus groups. The **Research Highlight** below describes key outcomes from the DPI focus groups. During FY 2022, RTI International plans to complete epinephrine AI focus groups using four virtual sessions due to impacts of COVID-19.

Contract HHSF22320171007C, with the Imperial College of Science Technology & Medicine, aims to develop a standardized questionnaire to quantitatively evaluate a patient's perception of airflow resistance through a DPI, which may provide insights into how

1. U.S. Food and Drug Administration (FDA). *GDUFA Regulatory Science Priority Initiatives for Fiscal Year 2021*. Link: https://www.fda.gov/media/144140/download.

much consideration should be given to differences in airflow resistance between proposed generic and RLD DPIs during generic drug development. In FY 2021, investigators completed an in vitro assessment of airflow resistance across a range of DPI products and several focus groups with asthma and COPD patients to identify critical themes for inclusion in the questionnaire.

In FY 2021, FDA initiated a laboratory research project to evaluate the electronic componentry and mobile application software in three FDA-approved metered dose inhalers. The goals of this project are (1) to understand the impact of the electronic components and software functionality on patient usability and device performance and (2) to use this understanding to inform future guidance for generic drug development and anticipate therapeutic equivalence and generic substitutability challenges.

FDA also awarded two FY 2021 Grants, 1U01FD007359 and 1U01FD007360 to Battelle Memorial Institute and University of Detroit Mercy, respectively. Both grants aim to develop methods for evaluating the impact of differences in user interface designs between generic DDCPs and their RLDs. The research will inform methods and criteria for categorization of user interface differences and approaches (in vitro and/or in vivo methods) to assessing "other design differences" between generic and RLD DDCPs. The outcomes of these two grants will help improve our understanding of how certain types of user interface design differences may impact substitutability of a generic DDCP for its RLD for intended end-user groups.

The outcomes of these projects are expected to provide significant insights into device performance, patient use, patient perceptions, and the assessment of user interface differences of generic DDCPs as compared to their branded counterparts.

Another FY 2021[2] GDUFA Science and Research Priority initiative for complex DDCPs was the development of device performance comparison criteria using in vitro methods to eliminate the need for additional in vivo studies. Through external grant 1U01FD004955, in vitro tools were developed that can be utilized to compare changes in active ingredient bioavailability from transdermal delivery systems (TDS) following heat application between a prospective test product and its reference product. Over the last several years, OGD oversaw completion of multiple in vitro and/or in vivo (clinical) studies with TDS products containing nicotine, fentanyl, buprenorphine, and lidocaine. During FY 2021, research studies with TDS products containing oxybutynin and rivastigmine were completed. Data from these research studies supported the development of guidance recommendations related to the assessment of heat effects on generic TDS products. The outcomes from these studies provided new insights related to product design and in vitro tools that can enhance complex generic DDCP development, inform guidance development (new and revised guidances), and contribute to the FDA's abbreviated new drug application (ANDA) reviews for such products.

2. U.S. Food and Drug Administration (FDA). *Draft Guidance for Industry, Transdermal and Topical Delivery Systems - Product Development and Quality Considerations.* (November 2019). Link: https://www.fda.gov/media/132674/download.

The three key objectives of Contract # HHSF223201810113C are: (1) to examine the behavioral implications of substituting a generic DDCP for the brand name (reference) product; (2) to assess how the design and functionality of generic DDCPs affect patient perceptions of product quality, efficacy, and usability; and (3) to explore participants' views on how generic and branded DDCPs compare. In FY 2021, RTI International completed six focus groups with asthma and COPD patients – five with adults (n= 36) and one with adolescents (n=4). Key results obtained from these patient focus groups are:

- The pre-focus group questionnaire revealed that 75% of adolescents and 81% of adults were somewhat or very satisfied with their current DPI, and half of adult and adolescent participants received training from a healthcare provider when first prescribed their DPI.
- Adolescents were unfamiliar with the term "generic" as it related to generic drugs and needed a brief introduction to the concept.
- All groups mentioned the positive financial impacts of lower cost generic medicines and discussed the role of health insurance companies in dispensing generic vs. brand name products.
- Participants had different beliefs about the safety, efficacy, and quality of a generic DPI compared to the brand name product. Some participants stated that a generic has the same active ingredients, quality, and outcomes/effectiveness as the brand name product; other participants expressed concerns that a generic may not work as well or as fast, and the manufacturing and quality are not monitored as well when compared with the brand name product.
- Participant reactions to unexpectedly receiving a generic DPI were mixed. Members of all groups expressed positive feelings about having a less expensive DPI medicine option but anticipated feelings of confusion about why they received a different product than expected and the subsequent implications of the substitution. Participants in half of the focus groups expressed disappointment, anger, or frustration on not being consulted about the switch and distrust/skepticism toward the involved parties. In four of six focus groups, participants described feelings of doubt or anxiety related to their ability to use the generic device effectively.
- When asked about anticipated challenges in making the brand to generic switch, participant discussion focused on usability, efficacy, and cost. Patients are interested in cost savings with use of generic DDCPs but want to be informed about changes to their medicines, including generic substitution. Participant uncertainty about how generic drug products differ from brand name products and how to navigate a new device caused anticipatory anxiety and frustration.

These outcomes provided insights on current patient perceptions about generic DPIs and will help inform FDA's ongoing efforts to enhance scientific methods for identifying and characterizing DDCP user interface differences and evaluating how differences affect risk of user medication errors at the time of a generic switch. This study also revealed opportunities for FDA and its partners to improve generic drug literacy among adults, adolescents, and healthcare providers.

New Grant(s) and Contract(s)

- 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 University of Detroit Mercy.

Continuing Grant(s) and Contract(s)

- Contract (HHSF223201810113C) *Formative Research Study to Understand the Impact of Generic Substitutes for Various Patient and Caregiver Populations* with Vanessa Boudewyns at Research Triangle Institute (RTI) International.
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London.

Completed Grant(s) and Contract(s)

- Grant (1U01FD004955) *Heat Effect on Generic Transdermal Drug Delivery Systems* with Audra L Stinchcomb at University of Maryland.

Active FDA Research

- *Development of New Bioequivalence (BE) Methods for Transdermal Adhesion*
- *Development of New Bioequivalence (BE) Methods for Transdermal Irritation and Sensitization*
- *Evaluation and Comparison of Electronic Components of Three Approved New Drug/Device Combination Inhaler Products Indicated for Treatment of Bronchospasm or Asthma and Implications for Development of Future Generic Versions of Combination Drug/Device Products*

Product-Specific Guidance(s) (PSG)

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

- *New Draft Guidance for Ethinyl Estradiol; Levonorgestrel System.* (August 2021) Link to Posting.

Presentation(s)

- Ballard B. *Device Considerations from User Interface Perspective: Comparative Analyses*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Bielski E. *The Impact of Actuator Device Design on Metered Dose Inhaler (MDI) In Vitro Performance*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Chang R. *Quality Considerations for Injectable Drug-Device Combination Products in Abbreviated New Drug Applications (ANDAs)*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Conti D. *Device Considerations for Pre-ANDA Meeting and Case Scenario Setup: Device Constituent of Hypothetical BREATHEATOL Drug Product*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Conti D. *Device Considerations for Pre-ANDA Meeting Requests for Complex Drug-Device Combination Products*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Conti D. *Introduction to Session 4: Device Considerations for Complex Drug-Device Combination Products*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Kelchen M. *An FDA Perspective on the Comparative Analyses of Critical Material, Quality, and Design Attributes for Topical, Transdermal, Rectal, and Vaginal Drug-Device Combination Products*. Presentation at the Drug Information Association (DIA)/FDA Complex Generic Drug-Device Combination Products Conference 2020. Virtual Meeting, October 20, 2020.
- Walenga R. *Computational Fluid Dynamics (CFD) Modeling for Optimization of Device Design and Understanding of Product Performance*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.

- Witzmann K. *Complex Generic Drug-Device Inhalation Products and User Interface Sameness: Successful Outcomes*. Presentation at the Drug Information Association (DIA)/FDA Complex Generic Drug-Device Combination Products Conference 2020. Virtual Meeting, October 19, 2020.

Inhalation and Nasal Products

Summary of FY 2021 Activities

FY 2021 research supported the first product-specific guidances (PSGs) for inhalation spray drug products containing tiotropium bromide alone or in combination with olodaterol hydrochloride. These two PSGs included new in vitro bioequivalence (BE) studies for spray velocity and duration, which were supported by internal research exploring optimized methods for particle image velocimetry (PIV) and assessment of the impact of environmental conditions. Two additional PSGs for solution-based metered dose inhalers (MDIs) for ipratropium bromide and ciclesonide were posted that included recommendations for alternative BE approaches to conducting comparative clinical endpoint BE studies. These PSGs were supported by research into dissolution methods (Grants# 1U01FD004953, 1U01FD004950, and 1U01FD004941)[1, 2], more predictive aerodynamic particle size distribution (APSD) using anatomical mouth-throat (MT) models (Grant# 1U01FD005231)[3, 4], and in silico methods for assessing

1. Sakagami M, Li H, and Venitz J. *In Vivo-Relevant Transwell Dish-Based Dissolution Testing for Orally Inhaled Corticosteroid Products*. Pharmaceutical Research. (2019) 36(7): Aticle 95. doi: https://doi.org/10.1007/s11095-019-2635-2. PMID: 31073686.
2. Price R, Shur J, Ganley W, Farias G, Fotaki N, Conti D, Delvadia R, Absar M, Saluja B, and Lee S. *Development of an Aerosol Dose Collection Apparatus for In Vitro Dissolution Measurements of Orally Inhaled Drug Products*. The AAPS Journal. (2020) 22(2): Article 47. doi: https://doi.org/10.1208/s12248-020-0422-y. PMID: 32060670.
3. Wei X, Hindle M, Kaviratna A, Huynh BK, Delvadia RR, Sandell D, and Byron PR. *In Vitro Tests for Aerosol Deposition. VI: Realistic Testing with Different Mouth-Throat Models and In Vitro-In Vivo Correlations for a Dry Powder Inhaler, Metered Dose Inhaler, and Soft Mist Inhaler*. Journal of Aerosol Medicine and Pulmonary Drug Delivery. (2018) 31(6): 358-371. doi: https://doi.org/10.1089/jamp.2018.1454. PMID: 29878859.
4. Kaviratna A, Tian G, Liu X, Delvadia R, Lee S, and Guo C. *Evaluation of Bio-Relevant Mouth-Throat Models for Characterization of Metered Dose Inhalers*. AAPS PharmSciTech. (2019) 20(3): Article 130. doi: https://doi.org/10.1208/s12249-019-1339-6. PMID: 30815748.

the impact of product- and patient-related factors on lung regional drug deposition (Grants# 1U01FD004570, 1U01FD005837, and 1U01FD005214).

To potentially improve efficiency of BE recommendations for suspension-based MDIs and dry powder inhalers (DPIs) via alternative approaches, an internal research project explored more clinically relevant in vitro dissolution methods using abbreviated cascade impactors, realistic MT models, and breathing profiles to collect DPI respirable aerosol particles (**Figure 1**). DPI particle agglomeration factors are being explored by Princeton University (Grant #1U01FD006514) using a novel computational fluid dynamics and discrete element method (CFD-DEM) model that better captures fluid motion and particle interactions[5], and another CFD-DEM model is in development by the University of Sydney (Grant #1U01FD006525). CFD is also being used to better approximate whole lung regional deposition through research by CFD Research corporation (Contract #HHSF223201810182C)[6] and Virginia Commonwealth University (Grant #1U01FD007353).

Through a pair of publications[7, 8] resulting from internal FDA collaborations and external research projects (Contract #HHSF223201710163C), FDA has communicated findings on Morphology Directed Raman Spectroscopy (MDRS) with nasal suspension products, including suggestions for proper analytical method development. Virginia Commonwealth University explored how in vitro nasal models derived from computed tomography scan data of adult (Contract #HHSF223201810144C) and pediatric (Contract #75F40120C00172) rhinitis patients can support nasal deposition predictions and BE assessment. Using the adult in vitro nasal models, posterior nasal deposition measurements from two nasal spray products varied between 22-92%[9]. CFD predictions were also used to predict posterior nasal deposition, where including the effects of cloud motion and two-way momentum coupling improved accuracy[10]. North Carolina State University (Grant #1U01FD006537) has also demonstrated how a three-dimensional CFD model of the nasal mucus layer can provide improved predictions of local nasal absorption by incorporating predictions from mucociliary clearance, dissolution, and absorption of deposited particles[11].

5. Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Particle-Based Coarse-Grained Approach for Simulating Dry Powder Inhaler*. International Journal of Pharmaceutics. (2021) 606: Article 120821. doi: https://doi.org/10.1016/j.ijpharm.2021.120821. PMID: 34171427.

6. Kannan R, Singh N, Przekwas A, Zhou XA, Walenga R, and Babiskin A. *A Quasi-3D Model of the Whole Lung: Airway Extension to the Tracheobronchial Limit Using the Constrained Constructive Optimization and Alveolar Modeling, Using a Sac-Trumpet Model*. Journal of Computational Design and Engineering. (2021) 8(2): 691-704. doi: https://doi.org/10.1093/jcde/qwab008. PMID: 34046370.

7. Thomas B, Absar M, Delvadia R, Conti D, Witzmann K, and Guo C. *Analytical Method Development for Characterizing Ingredient-Specific Particle Size Distributions of Nasal Spray Suspension Products*. J Pharm Sci. (2021) 110(7): 2778-2788. doi: https://doi.org/10.1016/j.xphs.2021.03.005. PMID: 33713688.

8. Farias G, Shur J, Price R, Bielski E, and Newman B. *A Systematic Approach in the Development of the Morphology-Directed Raman Spectroscopy Methodology for Characterizing Nasal Suspension Drug Products*. AAPS Journal. (2021) 23(4): Article 73. doi: https://doi.org/10.1208/s12248-021-00605-w. PMID: 34008082.

9. Manniello MD, Hosseini S, Alfaifi A, Esmaeili AR, Kolanjiyil AV, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, and Hindle M. *In Vitro Evaluation of Regional Nasal Drug Delivery Using Multiple Anatomical Nasal Replicas of Adult Human Subjects and Two Nasal Sprays*. International Journal of Pharmaceutics. (2021) 593: Article 120103. doi: https://doi.org/10.1016/j.ijpharm.2020.120103. PMID: 33242586.

10. Kolanjiyil AV, Hosseini S, Alfaifi A, Hindle M, Golshahi L, and Longest PW. *Importance of Cloud Motion and Two-way Momentum Coupling in the Transport of Pharmaceutical Nasal Sprays*. Journal of Aerosol Science. (2021) 156: Article 105770. doi: https://doi.org/10.1016/j.jaerosci.2021.105770.

11. Chari S, Sridhar K, Walenga R, and Kleinstreuer C. *Computational Analysis of a 3D Mucociliary Clearance Model Predicting Nasal Drug Uptake*. Journal of Aerosol Science. (2021) 155: Article 105757. doi: https://doi.org/10.1016/j.jaerosci.2021.105757.

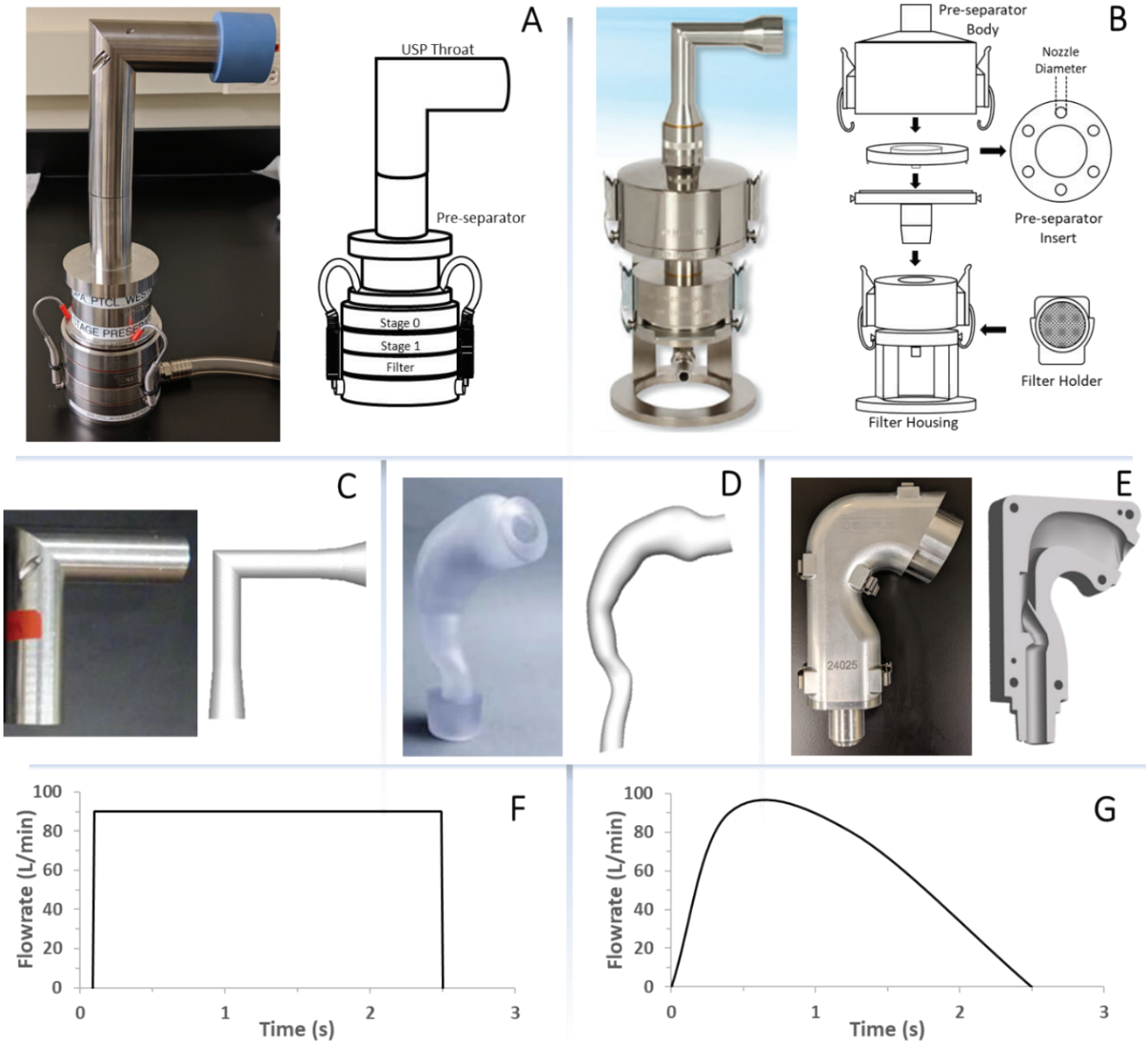
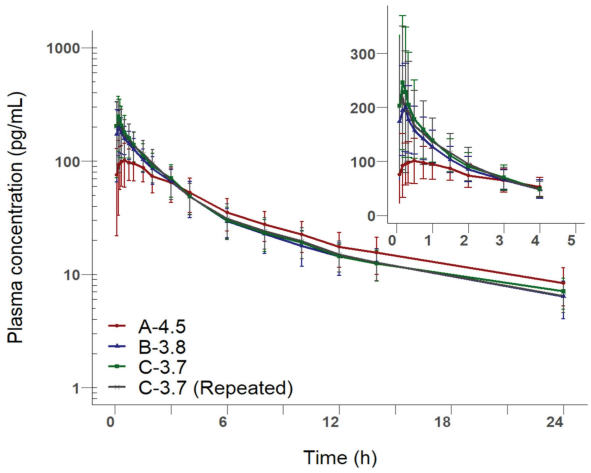


Figure 1: Images and schematics of (A) Fast Screening Andersen (FSA) and (B) Fast Screening Impactor (FSI) abbreviated impactors used to test biorelevant flow rates with (C) United States Pharmacopeia (USP) Throat, (D) Virginia Commonwealth University Realistic Throat (VCU-RT), and (E) Alberta Idealized Throat (AIT). Graphical representations of an idealized fixed flowrate-fixed volume inhalation profile (F) and a realistic inhalation profile (G) are also shown.

For many orally inhaled drug products, FDA recommends conducting in vivo pharmacokinetic (PK) BE studies for establishing equivalence in systemic exposure between test and reference products. Since PK studies measure the drug after it has moved away from the site of action in the lungs, there is uncertainty about whether these studies can also assess where the drug deposits regionally throughout the lungs. Through several research grants and contracts led by the University of Florida (1U01FD004950, HHSF223201110117A, HHSF223201610099C) and Virginia Commonwealth University (1U01FD005231), three fluticasone propionate (FP) DPI formulations were designed to deposit in different lung regions, and were tested in a single dose, four-way crossover PK study to evaluate PK sensitivity in detecting exposure differences.

A After Dose Normalization



B Before Dose Normalization

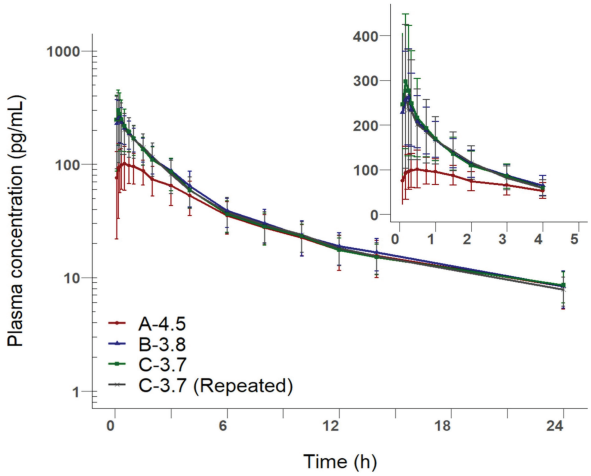


Figure 2: Plasma concentrations (mean ± SD) following administration of fluticasone propionate containing DPI formulations A, B, and C, with MMADs of 4.5 µm, 3.8 µm, and 3.7 µm, respectively. The plasma concentrations are represented (A) after dose normalization, and (B) before dose normalization, using the average in vitro total lung dose. The inserts represent the data on a linear scale up to the first 4 hours following administration. Reprinted with permission of Springer Nature. Copyright© 2021 Springer Nature.

For these formulations, different amounts of fine lactose particles were used to change the mass median aerodynamic diameter (MMAD) without changing the API particle size distribution (Formulation A, B, and C MMADs were 4.5, 3.8, and 3.7 µm, respectively). In vitro characterization of the three formulations found that Formulation A had a slower dissolution and a lower average in vitro total lung dose (12.8 µg) as compared to the dissolution of Formulations B and C and their average in vitro total lung dose (16.7 µg and 15.2 µg, respectively). To control for potential differences in delivered dose in vivo, the PK data were normalized using the ratio of the in vitro lung dose between formulations, with Formulation A serving as the reference. After normalization, Formulation A showed a significantly lower Cmax compared with the other formulations, indicating slower absorption, and suggesting that Cmax may also reflect differences in regional lung deposition (**Figure 2**). Formulation A also showed a lower, albeit not significant, AUC compared with the other formulations, indicating that PK sensitivity to regional deposition differences may vary between parameters for FP containing DPIs.

Reference:
Hochhaus G, Chen M, Kurumaddali A, Schilling U, Jiao Y, Drescher S, Amini E, Kandala B, Tabulov C, Shao J, Seay B, Abu-Hasan M, Baumstein S, Winner L, Shur J, Price R, Hindle M, Wei X, Carrasco C, Sandell D, Oguntimein O, Kinjo M, Delvadia R, Saluja B, Lee S, Conti D, and Bulitta J. *Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate?*. AAPS Journal. (2021) 23(3): Article 48. doi: https://doi.org/10.1208/s12248-021-00569-x. PMID: 33768368.

New Grant(s) and Contract(s)

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Richard Esther at University of North Carolina Chapel Hill.
- Grant (1U01FD007353-01) *Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers* with Longest, P. Worth at Virginia Commonwealth University.
- Grant (1U01FD007348) *Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics* with Jill Barber at University of Manchester.

Continuing Grant(s) and Contract(s)

- Grant (1U01FD005837) *A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways* with Ching-Long Lin at 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 Raleigh.
- Contract (HHSF223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation.
- Contract (HHSF223201810169C) *Evaluating Batch to Batch Variability and Its Origins in Dry Powder Inhalers* with Hugh D.C. Smyth at University of Texas at Austin.
- 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 (HHSF223201710163C) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Robert Price and Jag Shur (presently at Nanopharm Ltd.) previously at University of Bath, UK.
- Contract (HHSF223201710116C) *Investigating the Microstructure of Dry Powder Inhalers Using Orthogonal Analytical Approaches* with Robert Price (PI) and Jag Shur (CI) at University of Bath, UK.
- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Predication of Nasal Corticosteroid Deposition, Absorption and Bioavailability* with Jeffry Schroeter at Applied Research Associates.

- Contract (75F40119C10154) *Systematic Evaluation of the Ex-Throat Plume Properties of MDI Formulations* with Guenther Hochhaus at University of Florida and S5 Consulting.

Completed Grant(s) and Contract(s)

- Grant (1U01FD006525) *Development of Computational Models to Predict Delivery of Inhalation Drug Powders: from Deagglomeration in Devices to Deposition in Airways* with Kim Chan at University of Sydney.
- Contract (HHSF223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition In Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University.
- Contract (75F40120C00036) *Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations* with Jag Shur at Nanopharm.
- Contract (HHSF223201710072C) *New Patient's Perception of Dry Powder Inhaler Airflow Resistance* with Omar Usmani at Imperial College of Science and Technology, London.

Active FDA Research

- *Computational Fluid Dynamics (CFD) Models of Droplet Formulation from Metered Dose Inhaler (MDI)*
- *Computational Fluid Dynamics (CFD) Models of Soft Mist Inhalers*
- *Develop Clinically Relevant In Vitro Dissolution Methods for Orally Inhaled Products (OIPs)*
- *Development of In Vitro Methods for Nasal Abuse Deterrent Formulation (ADF) Opioids*
- *Evaluation of the Staccato Drug Delivery System*
- *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*

Product-Specific Guidance(s) (PSG)

There were ten new and two revised PSGs published in FY 2021 related to inhalation and nasal products. These PSGs were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Albuterol Sulfate; Ipratropium Bromide Spray, Metered.* (August 2021) Link to Posting.
- *Revised Draft Guidance for Ciclesonide Aerosol, Metered.* (March 2021) Link to Posting.
- *New Draft Guidance for Diazepam Spray.* (November 2020) Link to Posting.
- *New Draft Guidance for Epinephrine Aerosol, Metered.* (November 2020) Link to Posting.
- *New Draft Guidance for Fluticasone Furoate; Umeclidinium Bromide; Vilanterol Trifenatate Powder.* (May 2021) Link to Posting.
- *Revised Draft Guidance for Ipratropium Bromide Aerosol, Metered.* (March 2021) Link to Posting.
- *New Draft Guidance for Ipratropium Bromide Spray, Metered.* (August 2021) Link to Posting.
- *New Draft Guidance for Metoclopramide Hydrochloride Spray, Metered.* (May 2021) Link to Posting.
- *New Draft Guidance for Midazolam Spray.* (May 2021) Link to Posting.
- *New Draft Guidance for Olodaterol Hydrochloride Spray, Metered.* (August 2021) Link to Posting.
- *New Draft Guidance for Olodaterol Hydrochloride; Tiotropium Bromide Spray, Metered.* (July 2021) Link to Posting.
- *New Draft Guidance for Tiotropium Bromide Spray, Metered.* (November 2020) Link to Posting.

Article(s)

- Amini E, Kurumaddali A, Bhagwat S, Berger S, and Hochhaus G. *Optimization of the Transwell® System for Assessing the Dissolution Behavior of Orally Inhaled Drug Products through In Vitro and In Silico Approaches*. Pharmaceutics. (2021) 13(8): Article 1109. doi: https://doi.org/10.3390/pharmaceutics13081109. PMID: 34452069.
- Chari S, Sridhar K, Walenga R, and Kleinstreuer C. *Computational Analysis of a 3D Mucociliary Clearance Model Predicting Nasal Drug Uptake*. Journal of Aerosol Science. (2021) 155: Article 105757. doi: https://doi.org/10.1016/j.jaerosci.2021.105757.
- Dhapare S, Newman B, Svensson M, Elfman P, Sandell D, Winner L, Bulitta J, and Hochhaus G. *Factors Influencing Plume Characteristics of Metered Dose Inhalers (MDIs) Following Passage Through Bio-relevant Mouth-Throat Models*. Respiratory Drug Delivery. (2021) 1: 301-306.

- Farias G, Shur J, Price R, Bielski E, and Newman B. *A Systematic Approach in the Development of the Morphology-Directed Raman Spectroscopy Methodology for Characterizing Nasal Suspension Drug Products*. AAPS Journal. (2021) 23(4): Article 73. doi: https://doi.org/10.1208/s12248-021-00605-w. PMID: 34008082.
- Hochhaus G, Chen M, Kurumaddali A, Schilling U, Jiao Y, Drescher S, Amini E, Kandala B, Tabulov C, Shao J, Seay B, Abu-Hasan M, Baumstein S, Winner L, Shur J, Price R, Hindle M, Wei X, Carrasco C, Sandell D, Oguntimein O, Kinjo M, Delvadia R, Saluja B, Lee S, Conti D, and Bulitta J. *Can Pharmacokinetic Studies Assess the Pulmonary Fate of Dry Powder Inhaler Formulations of Fluticasone Propionate?*. AAPS Journal. (2021) 23(3): Article 48. doi: https://doi.org/10.1208/s12248-021-00569-x. PMID: 33768368.
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- Kolanjiyil AV, Hosseini S, Alfaifi A, Hindle M, Golshahi L, and Longest PW. *Importance of Cloud Motion and Two-Way Momentum Coupling in the Transport of Pharmaceutical Nasal Sprays*. Journal of Aerosol Science. (2021) 156: Article 105770. doi: https://doi.org/10.1016/j.jaerosci.2021.105770.
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- Manniello M, Hosseini S, Alfaifi A, Esmaeili A, Kolanjiyil A, Walenga R, Babiskin A, Sandell D, Mohammadi R, Schuman T, Hindle M, and Golshahi L. *In Vitro Evaluation of Regional Nasal Drug Delivery Using Multiple Anatomical Nasal Replicas of Adult Human Subjects and Two Nasal Sprays*. International Journal of Pharmaceutics. (2021) 593: Article 120103. doi: https://doi.org/10.1016/j.ijpharm.2020.120103. PMID: 33242586.
- Singh G, Lowe A, Azeem A, Cheng S, Chan H, Walenga R, and Kourmatzis A. *Effect of Inflow Conditioning for Dry Powder Inhalers*. International Journal of Pharmaceutics. (2021) 608: Article 121085. doi: https://doi.org/10.1016/j.ijpharm.2021.121085. PMID: 34508843.
- Thomas B, Absar M, Delvadia R, Conti D, Witzmann K, and Guo C. *Analytical Method Development for Characterizing Ingredient-Specific Particle Size Distributions of Nasal Spray Suspension Products*. Journal of Pharmaceutical Sciences. (2021) 110(7): 2778-2788. doi: https://doi.org/10.1016/j.xphs.2021.03.005. PMID: 33713688.

- Walenga R, Dhapare S, Newman B, Babiskin A, and Zhao L. In Silico and Experimental Methods to Support Generic Nasal Drug Product (NDP) Development. Respiratory Drug Delivery (RDD) 2021. (2021) 1: 141-150.

Poster(s)

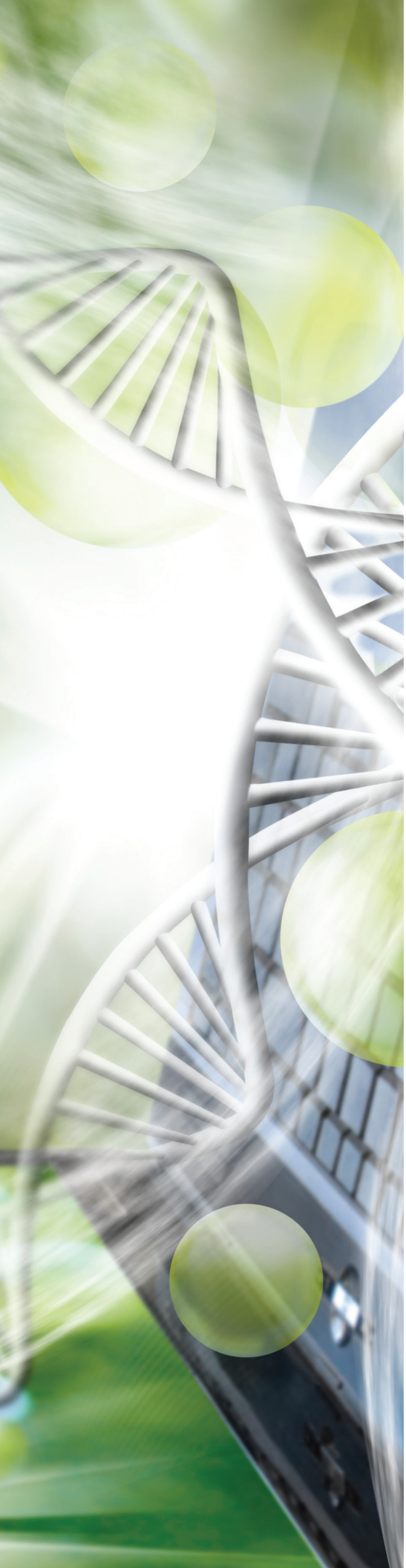
- Bielski E, Conti D, Oguntimein O, Sheth P, Hallinger M, Svensson M, Sandell D, Bulitta J, and Hochhaus G. *The Effects of Formulation Factors and Actuator Design on Mometasone Furoate Metered Dose Inhaler In Vitro Aerosolization Performance*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Dhapare S, Bielski E, Conti D, Oguntimein O, Sheth P, Svensson M, Sandell D, Bulitta J, and Hochhaus G. *Effects of Formulation and Actuator Design on Spray Pattern and Plume Geometry of Mometasone Furoate Metered Dose Inhalers (MDIs)*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Dhapare S, Newman B, Svensson M, Elfman P, Sandell D, Winner L, Bulitta J, and Hochhaus G. *Factors Influencing Plume Characteristics of Metered Dose Inhalers (MDIs) Following Passage through Bio-relevant Mouth-Throat Models*. Poster Presentation at the Respiratory Drug Delivery (RDD) 2021 Virtual Conference. Virtual Meeting, May 7, 2021.
- Kaisar MA, Dhapare S, Newman B, Svensson M, Sandell D, Bulitta J, and Hochhaus G. *Factors Influencing Plume Characteristics of Flovent® HFA Following Passage Through Bio-relevant Mouth-Throat Models*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Kolanjiyil A, Hosseini S, Alfaifi A, Golshahi L, Hindle M, and Longest W. *How Spray Metric Variability Impacts the Initial Deposition of Nasal Sprays*. Poster Presentation at the Respiratory Drug Delivery (RDD) 2021 Virtual Conference. Virtual Meeting, May 7, 2021.
- Schroeter J, Rose M, Kimbell J, Chopski S, and Walenga R. *Effect of Polydispersity on PBPK Model Simulations of Intranasal Corticosteroid Sprays*. Poster Presentation at the International Society for Aerosols in Medicine (ISAM) 2021. Virtual Meeting, May 22, 2021.

Presentation(s)

- Boc S. *Product-Specific Considerations for Alternative Bioequivalence (BE) Approaches to Comparative Clinical Endpoint BE Studies*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Conti D. *Emerging Concepts and New Technologies for Bioequivalence of Orally Inhaled and Nasal Drug Products*. Presentation at the American Thoracic Society (ATS) International Conference. Virtual Meeting, May 14, 2021.
- Dhapare S, Newman B, Svensson M, Elfman P, Sandell D, Winner L, Bulitta J, and Hochhaus G. *Factors Influencing Plume Characteristics of Metered Dose Inhalers (MDIs) Following Passage through Bio-relevant Mouth-Throat Models*. Presentation at the Respiratory Drug Delivery (RDD) 2021 Virtual Conference. Virtual Meeting, May 4, 2021.
- Dhapare S. *Demonstrating Bioequivalence with Inhalation Spray Drug Products*. Presentation at the 2021 Small Business & Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Hochhaus G, and Bulitta J. *Pharmacokinetic Comparison of Locally Acting Nasal Suspension Spray Products*. Presentation at the Drug Information Association (DIA)/ FDA Complex Generic Drug-Device Combination Products Conference 2020. Virtual Meeting, October 19, 2020.
- Hochhaus G. *Dissolution Methodologies*. Presentation at the 2021 International Society for Aerosols in Medicine (ISAM) Conference. Virtual Meeting, May 25, 2021.
- Jiang W. *Global Bioequivalence Requirements for Orally Inhaled Drug Products (OIDPs)*. Presentation at the Development of Inhalation Therapeutics Symposium Jointly Organized by the American Association of Pharmaceutical Scientists – Bay Area Discussion Group & Pharmaceutical & BioScience Society (AAPS-BADG&PBSS). Virtual Meeting, July 29, 2021.
- Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Modeling Complex Particle Interactions in Dry Powder Inhaler*. Presentation at the 2020 Virtual American Institute of Chemical Engineers (AIChE) Meeting. Virtual Meeting, November 20, 2020.
- Longest W. *Case Study: Predicting Regional Lung Deposition of Pharmaceutical Aerosols with CFD*. 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, September 30, 2021.
- Newman B. *Overview of Complex Generic Inhalation and Nasal Drug-Device Combination Products*. Presentation at the Drug Information Association (DIA)/FDA Complex Generic Drug-Device

Combination Products Conference 2020. Virtual Meeting, October 19, 2020.

- Newman B. *Overview of Complex Generic Orally Inhaled Drug 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, September 30, 2021.
- Sulaiman M, Liu X, Kolehmainen J, Ozel A, and Sundaresan S. *Powder Fluidization in Dry Powder Inhalers*. Presentation at the 2020 Virtual American Institute of Chemical Engineers (AIChE) Meeting. Virtual Meeting, November 20, 2020.
- Walenga R. *In Silico and Experimental Methods to Support Generic Nasal Drug Product (NDP) Development*. Presentation at the Respiratory Drug Delivery (RDD) 2021 Virtual Conference. Virtual Meeting, May 7, 2021.
- Walenga R. *Abbreviated New Drug Application (ANDA) and Pre-ANDA Experience with Orally Inhaled Drug Product (OIDP) Modeling*. 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, September 30, 2021.



Locally-Acting Physiologically-Based Pharmacokinetic Modeling

Summary of FY 2021 Activities

Locally-acting mechanistic models, such as physiologically-based pharmacokinetic (PBPK) models, have the potential to open new avenues for establishing bioequivalence (BE) between complex generic drugs and their reference listed drugs. One such approval for a dermatological topical product was highlighted in the FY 2019 Generic Drug User Fee Amendments (GDUFA) Science and Research Report (https://www.fda.gov/media/135187/download#page=35). Regularly, through interactions with external experts, regulatory assessments, and internal research projects, FDA gauges the current state-of-art for these models and specifically identifies opportunity gaps to be addressed in extramural research projects (i.e., contracts and grants). In FY 2021, 23 contracts and grants were active or completed, which includes 6 new grants:

- In the oral inhalation area
  - Regional deposition predictions in a whole lung geometry following administration of a solution-based metered dose inhaler will be produced as part of a new grant with Virginia Commonwealth University (VCU) (1U01FD007353), which will be validated with in vivo data. The results of this grant are expected to help clarify the process

to establish model credibility for computational fluid dynamics (CFD) models of orally inhaled drug product regional deposition for all interested stakeholders.
    - A comprehensive assessment of the drug metabolizing enzymes and transporters in airway epithelia is planned in a new grant awarded to the University of North Carolina at Chapel Hill (1U01FD007338). Quantitative targeted absolute proteomic (QTAP) methods will be utilized to measure the protein levels in human airway epithelia representing a wide range of demographic features, anatomic locations, and inflammatory states. Ultimately, the obtained data will be utilized to enhance PBPK model predictability to support the development and approval of generic inhaled drugs.
- In the dermal area
    - Enhanced mechanistic PBPK models that allow the description of absorption through the skin of active ingredients applied as topical dermatological drug products will be developed under two new grants awarded to Certara UK, LTD (1U01FD007323) and Simulations Plus, Inc. (1U01FD007320). The developed models will be utilized to inform decisions on generic dermatological product development and to perform virtual BE assessments in support of regulatory decisions.
    - A comprehensive assessment of the drug metabolizing enzymes and transporters in skin tissues is planned in a new grant awarded to the University of Manchester (1U01FD007348). Liquid chromatography-mass spectrometry proteomics methods will be utilized to provide a full proteomics map for diverse human skin tissues and the data obtained will be used to enhance the predictability of skin PBPK models in support of the development and approval of generic dermatological drug products.
- In the complex injectable area, one new contract (75F40121C00133) was awarded that aims to increase our understanding on the in vivo behavior of long-acting injectable suspension drug products by identifying formulation critical quality attributes, establishing physiologically based (mechanistic) in vitro-in vivo correlation (IVIVC) model and narrowing our knowledge gap to the observed discrepancy between the IVIVCs with animal model and human subjects.

For the ongoing and completed contracts and grants, some noteworthy and published accomplishments in addition to the **Research Highlight** (below) include:

- Princeton University developed a new CFD model as part of an ongoing grant (1U01FD006514) that pairs fluid continuum predictions with discrete element method (DEM) modeling predictions of particle transport and inter-particle interactions for prediction of dry powder inhaler behavior[1]. As shown in **Figure 1**, this new CFD-DEM model is capable of understanding agglomeration and deagglomeration processes that occur during fluidization of dry powders in the device and dynamic changes of particle size distribution during inhalation.
- A nasal CFD model was developed as part of a contract with VCU (HHSF223201810144C) that explored the effects of two-way momentum coupling and cloud motion on regional deposition predictions after administration of nasal suspension sprays, which demonstrated that validation with in vitro data was improved when including these effects in the model[2].

1. Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Particle-Based Coarse-Grained Approach for Simulating Dry Powder Inhaler*. International Journal of Pharmaceutics. 2021:120821. (2021) 606: Article 120821. doi: https://doi.org/10.1016/j.ijpharm.2021.120821. PMID: 34171427.

2. Kolanjiyil AV, Hosseini S, Alfaifi A, Hindle M, Golshahi L, and Longest PW. *Importance of Cloud Motion and Two-Way Momentum Coupling in the Transport of Pharmaceutical Nasal Sprays*. Journal of Aerosol Science. (2021) 156: Article 105770. doi: https://doi.org/10.1016/j.jaerosci.2021.105770.

- Another nasal CFD model was developed in support of Grant 1U01FD006537 with North Carolina State University that modeled mucociliary clearance in the nasal mucus layer to simultaneously predict particle transit, dissolution, and absorption for deposited particles, which facilitates more accurate predictions of local absorption[3].
- Developed versions of dermal (https://github.com/Open-Systems-Pharmacology/Skin-permeation-model) and inhalation (https://github.com/Open-Systems-Pharmacology/Inhalation-model) PBPK models are now available within the Open Systems Pharmacology suite. Their development and validation have been supported in part by Grant 1U01FD006549.
- Ophthalmic ointment rabbit models were developed for dexamethasone and fluorometholone as part of a completed contract with Simulations Plus (HHSF223201810255P) that added the capability of simulating ophthalmic ointment formulation. The sensitivity analysis on application surface area, application time and the Higuchi release constant was performed in the published models[4].

3. Chari S, Sridhar K, Walenga R, and Kleinstreuer C. *Computational Analysis of a 3D Mucociliary Clearance Model Predicting Nasal Drug Uptake*. Journal of Aerosol Science. (2021) 155: Article 105757. doi: https://doi.org/10.1016/j.jaerosci.2021.105757.

4. Le Merdy M, Spires J, Lukacova V, Tan ML, Babiskin A, Xu X, Zhao L, and Bolger MB. *Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations*. Pharm Res. (2020) 37(12): Article 245. doi: https://doi.org/10.1007/s11095-020-02965-y. PMID: 33215336.

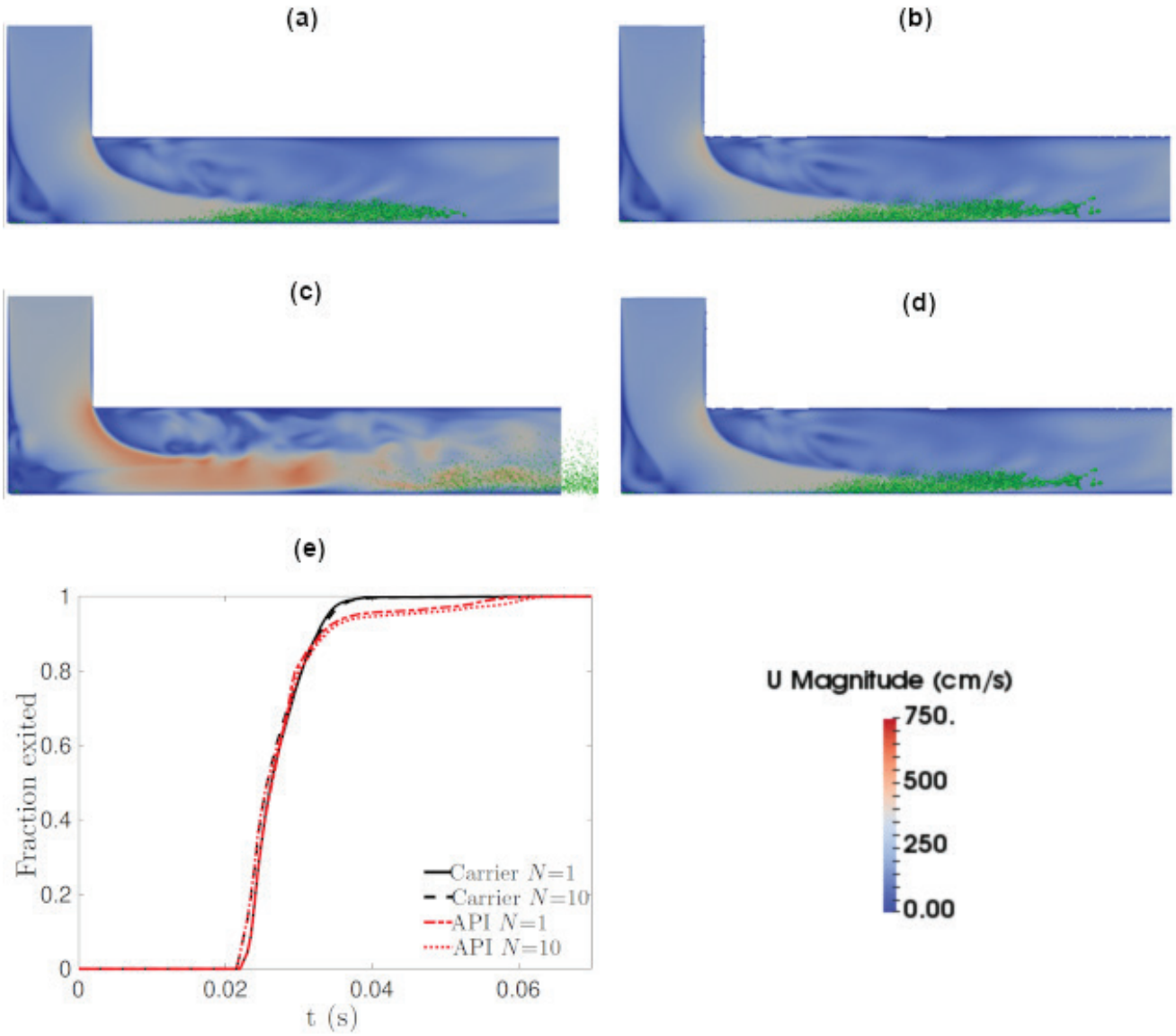


Figure 1: CFD-DEM predictions of fluid and particle motion for 3.5 mg of powder with 70 µm carrier particles and 5 µm active ingredient particles (Hamaker constant of 1 x 10-19 J) showing (a) all particles represented (N = 1) after 0.01 s, (b) one-tenth of original active ingredient particles represented (N = 10) after 0.01 s, (c) N = 1 after 0.02 s, (d) N = 10 after 0.02 s, and (e) the fraction of particles exited. The figure is reproduced by permission of Elsevier[5].

5. Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Particle-Based Coarse-Grained Approach for Simulating Dry Powder Inhaler*. International Journal of Pharmaceutics. 2021:120821. (2021) 606: Article 120821. doi: https://doi.org/10.1016/j.ijpharm.2021.120821. PMID: 34171427.

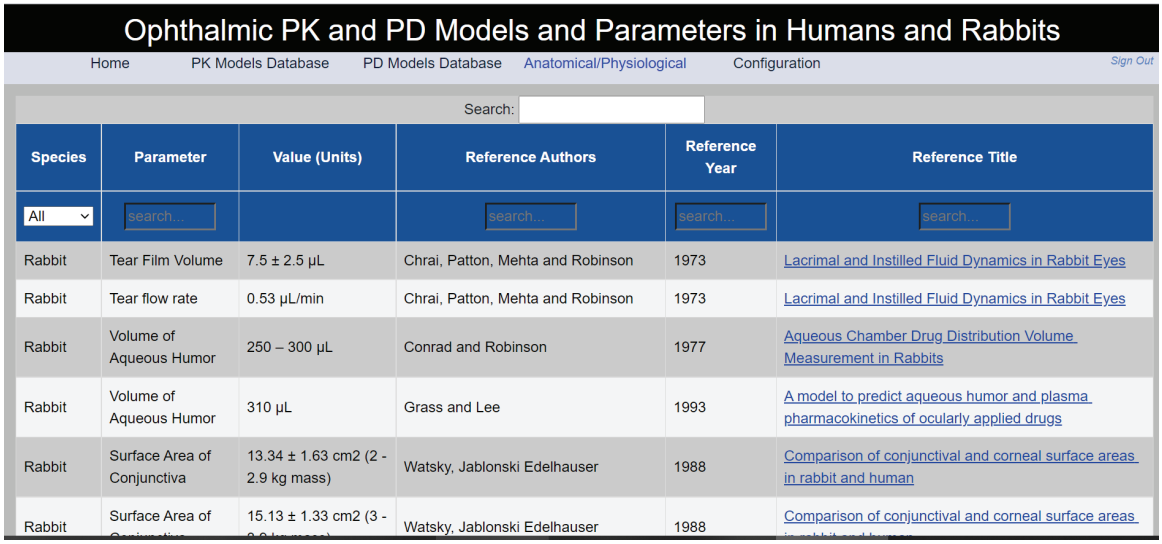
FDA authored two publications about dermal PBPK illustrating how these tools can be leveraged for regulatory and product development decision-making. One publication describes the scientific considerations on the development, verification and validation (V&V), and application of dermal PBPK models within the context of a virtual BE assessment for topical dermatological drug products[6]. The authors detailed a multi-level model V&V approach involving validation for the model of the drug product of interest coupled with the overall assessment of the modeling platform in use, while leveraging in vitro and in vivo data related to local and systemic bioavailability. These considerations were implemented in a published report on FDA approval of a generic diclofenac sodium topical gel[7]. FDA collaborated with the Center for Research on Complex Generics (CRCG) to hold a 2-day workshop titled "Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches" on September 30 and October 1, 2021 (https://www.fda.gov/drugs/news-events-human-drugs/fda-and-center-research-complex-generics-co-hosted-workshop-regulatory-utility-mechanistic-modeling). The first day of the workshop was dedicated to locally-acting products and included sessions on orally inhaled and dermal products followed by a general session to capture other locally-acting areas. The second day of the workshop was dedicated to oral products (please refer to "FY 2021 GDUFA Science and Research Report: Oral Absorption Models and Bioequivalence" for more details) and included a symposium on model sharing. Workshop panelists and presenters in these sessions included representatives of FDA, generic industry, academia, research organizations, and software/model developers to give a broad depiction of the state of modeling in each area and opportunities for regulatory decision-making. The workshop materials can be found here: http://www.complexgenerics.org/PBPK2021/.

6. Tsakalozou E, Alam K, Babiskin A, and Zhao L. *Physiologically-Based Pharmacokinetic Modeling to Support Determination of Bioequivalence for Dermatological Drug Products: Scientific and Regulatory Considerations*. Clinical Pharmacology & Therapeutics. (2021) July 7. Online ahead of Print. doi: https://doi.org/10.1002/cpt.2356. PMID: 34231211.

7. Tsakalozou E, Babiskin A, and Zhao L. *Physiologically-Based Pharmacokinetic Modeling to Support Bioequivalence and Approval of Generic Products: A Case for Diclofenac Sodium Topical Gel, 1%*. CPT: Pharmacometrics & Systems Pharmacology. (2021) 10(5): 399-411. doi: https://doi.org/10.1002/psp4.12600. PMID: 33547863.

Two research grants (1U01FD006927 and 1U01FD006929) have been awarded to support research relevant to ophthalmic drug products that will predict human ocular pharmacokinetics (PK) and pharmacodynamics (PD) through interspecies extrapolation by PBPK modeling. The focus is on understanding the differences in anatomy and physiology between species, current existing knowledge gaps and potential solutions of human model scale-up from animal models.

Extensive literature search has been performed to collect the rabbit and human anatomy and physiology data, existing PK and PD models. Subsequently, several ophthalmic PBPK/PD models have been under investigation for both rabbit and human using platforms such as the OCATTM (1U01FD006927) and CoBi (1U01FD006929) with updated anatomy and physiology data as aforementioned. As one of the aims for the research project 1U01FD006929, an open-source ophthalmic model database has been created and it is currently available publicly (https://eye.health-map.net/). This database contains the rabbit and human eye anatomical and physiological data, ophthalmic PK and PD models available (**Figure 2**), which have been collected through a comprehensive literature search. The database is searchable and sortable, and further development/ improvement is under way.



Species	Parameter	Value (Units)	Reference Authors	Reference Year	Reference Title
All	search...		search...	search...	search...
Rabbit	Tear Film Volume	7.5 ± 2.5 µL	Chrai, Patton, Mehta and Robinson	1973	Lacrimal and Instilled Fluid Dynamics in Rabbit Eyes
Rabbit	Tear flow rate	0.53 µL/min	Chrai, Patton, Mehta and Robinson	1973	Lacrimal and Instilled Fluid Dynamics in Rabbit Eyes
Rabbit	Volume of Aqueous Humor	250 – 300 µL	Conrad and Robinson	1977	Aqueous Chamber Drug Distribution Volume Measurement in Rabbits
Rabbit	Volume of Aqueous Humor	310 µL	Grass and Lee	1993	A model to predict aqueous humor and plasma pharmacokinetics of ocularly applied drugs
Rabbit	Surface Area of Conjunctiva	13.34 ± 1.63 cm2 (2 - 2.9 kg mass)	Watsky, Jablonski Edelhauser	1988	Comparison of conjunctival and corneal surface areas in rabbit and human
Rabbit	Surface Area of	15.13 ± 1.33 cm2 (3 -	Watsky, Jablonski Edelhauser	1988	Comparison of conjunctival and corneal surface areas

Figure 2: A snapshot of Anatomical/Physiological tab in the database https://eye.health-map.net/.

New Grant(s) and Contract(s)

- Grant (1U01FD007338) *A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia* with Charles Esther at University of North Carolina at Chapel Hill.
- Grant (1U01FD007353-01) *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 MAM and PBPK Simulation* with Jessica Spires at Simulations Plus, Inc.
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterization, Release and Permeation Data to the Next Level-PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK, LTD.
- Grant (1U01FD007348) *Quantitative Expression and Inter-Individual Variability of Skin Proteins Involved in Drug and Excipient Metabolism and Transporters Using Targeted and Label Free LC MS/MS Proteomics* with Jill Barber at University of Manchester.
- Contract (75F40121C00133) *Enhancement and Validation of In Vitro-In Vivo Correlation Method for Long-Acting Injectable Drug Products to Accelerate Their Generic Development* with Diane J. Burgess at University of Connecticut.

Continuing Grant(s) and Contract(s)

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

- 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.
- 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 (223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation Of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation.
- Contract (223201810182C) *A Multiscale Computational Framework for Bioequivalence of Orally Inhaled Drugs* with Narender Singh at CFD Research Corporation.
- Contract (75F40120C00172) *Evaluation of Current Approaches Used to Establish Bioequivalence of Nasal Sprays for Local Action in Children* with Laleh Golshahi at Virginia Commonwealth University.
- Contract (75F40119C10139) *MIDD Approach to Identify Critical Quality Attributes and Specifications for Generic Nanotechnology Products* with Jessie L.S. Au at Institute of Quantitative Systems Pharmacology (IQSP).
- Contract (75F40119C10079) *Modifications and Improvements to Hybrid CFD-PBPK Models for Predications of Nasal Corticosteroid Deposition, Absorption And Bioavailability* with Jeffry Schroeter at Applied Research Associates, Inc.
- Contract (223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Robert Bies at State University of New York at Buffalo.

Completed Grant(s) and Contract(s)

- Grant (1U01FD006526) *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations* with Jessica Spires at Simulations Plus, Inc.
- Grant (1U01FD006525) *Development of Computational Models to Predict Delivery of Inhalation Drug Powders: from Deagglomeration in Devices to Deposition in Airways* with Kim Chan at University of Sydney.

- Grant (1U01FD006522) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems* with Michael Roberts at University of Queensland.
- Contract (223201810144C) *Evaluating Relationships Between In Vitro Nasal Spray Characterization Test Metrics for Bioequivalence and Nasal Deposition in Silico and In Vitro* with Laleh Golshahi at Virginia Commonwealth University.

Active FDA Research

- *Computational Fluid Dynamics (CFD) Analysis of Spreadability of Topical Formulation*
- *Computational Fluid Dynamics (CFD) Models of Droplet Formulation from Metered Dose Inhaler (MDI)*
- *Computational Fluid Dynamics (CFD) Models of Soft Mist Inhalers*
- *Development of In Vitro Methods for Nasal Abuse-Deterrent Formulation (ADF) Opioids*
- *Development of Ophthalmic Physiological Based Pharmacokinetic (PBPK) Modeling Platform*
- *In Vivo Nasal Bioequivalence (BE) Study to Evaluate Abuse Deterrence of Agonist-Antagonist Combination Products*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

Product-Specific Guidance(s) (PSG)

There were two new PSGs published in FY 2021 related to locally-acting physiologically-based pharmacokinetic modeling. These PSGs were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Albuterol Sulfate; Ipratropium Bromide Spray, Metered.* (August 2021) Link to Posting.
- *New Draft Guidance for Olodaterol Hydrochloride Spray, Metered.* (August 2021) Link to Posting.

Article(s)

- Chari S, Sridhar K, Walenga R, and Kleinstreuer C. *Computational Analysis of a 3D Mucociliary Clearance Model Predicting Nasal Drug Uptake*. Journal of Aerosol Science. (2021) 155: Article 105757. doi: https://doi.org/10.1016/j.jaerosci.2021.105757.
- 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(S2): S26-S33. doi: https://doi.org/10.1002/jcph.1760. PMID: 33274513.
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- Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Particle-Based Coarse-Grained Approach for Simulating Dry Powder Inhaler*. International Journal of Pharmaceutics. (2021) 606: Article 120821. doi: https://doi.org/10.1016/j.ijpharm.2021.120821. PMID: 34171427.
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Women in the United States. The Journal of Clinical Pharmacology. (2020) 60(S2): S34-S38. doi: https://doi.org/10.1002/jcph.1710. PMID: 33274507.

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Poster(s)

- Arora S, Polak S, Jamei M, Tsakalozou E, Ghosh P, Alam K, Liu X, Namjoshi S, Grice J, Mohammed Y, and Roberts M. *Integrating Drug Product Quality Attributes in a Bottom-up Physiologically Based Pharmacokinetic (PBPK) Model to Simulate In Vitro Skin Permeation of Acyclovir Commercial Formulations*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Bois F, Hsieh N, Gao W, Chiu W, and Reisfeld B. *Well-Tempered MCMC Simulations for Population Pharmacokinetic Models*. Poster Presentation at the American Conference on Pharmacometrics (ACoP) 11. Virtual Meeting, November 9, 2020.
- Hsieh N, Bois F, Tsakalozou E, Yoon M, Reisfeld B, and Chiu W. *A Bayesian Population Compartmental Absorption and Transit Modeling Approach to Support Generic Drug Development and Regulation-Application to Bupropion*. Poster Presentation at the American Conference on Pharmacometrics (ACoP) 11. Virtual Meeting, November 9, 2020.
- Kolanjiyil A, Hosseini S, Alfaifi A, Golshahi L, Hindle M, and Longest W. *How Spray Metric Variability Impacts the Initial Deposition of Nasal Sprays*. Poster Presentation at the Respiratory Drug Delivery

(RDD) 2021 Virtual Conference. Virtual Meeting, May 7, 2021.

- Schroeter J, Rose M, Kimbell J, Chopski S, and Walenga R. *Effect of Polydispersity on PBPK Model Simulations of Intranasal Corticosteroid Sprays*. Poster Presentation at the International Society for Aerosols in Medicine (ISAM) 2021. Virtual Meeting, May 22, 2021.
- Tsakalozou E, Alam K, Babiskin A, Fang L, and Zhao L. *Development of a Dermal PBPK Modeling for an Ethinyl Estradiol-Containing Transdermal Delivery System*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 12, 2021.
- Tsakalozou E, Alam K, Babiskin A, and Zhao L. *PBPK Modeling of Percutaneous Pharmacokinetics for Tazarotene and Tretinoin Creams: Applicability and Challenges*. Poster Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, September 29, 2021.

Presentation(s)

- Alam K. *Research Overview and Regulatory Experience on Mechanistic Modeling for Generic Dermatological Drug 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, September 30, 2021.
- Alam K, and Tsakalozou E. *Challenges and Considerations with Model-Based Virtual Bioequivalence Assessments for Generic Dermatological Products, Part 2*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Arora S. *Integrating Topical Drug Product Quality Attributes Within Physiologically-Based Pharmacokinetic Models*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) PharmSci 360 Webinar. Virtual Meeting, October 24, 2020.
- Arora S. *Modeling Dermal Drug Absorption from Complex Semisolid Formulations: Insights from Multi-Phase, Multi-Layer MechDermA Model*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Community. Virtual Webinar Series, February 26, 2021.

- Babiskin A. *Regulatory Perspective: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use*. 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, September 30, 2021.
- Dhapare S. *Demonstrating Bioequivalence with Inhalation Spray Drug Products*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Ince I, and Dallmann A. *Predictive Performance of PBPK Dose Estimates for Pediatric Trials*. Presentation at the Center of Excellence in Regulatory Science and Innovation (M-CERSI) "Pediatric Dose Selection" Virtual Conference. Virtual Meeting, October 22, 2020.
- Liu X, Sulaiman M, Kolehmainen J, Ozel A, and Sundaresan S. *Modeling Complex Particle Interactions in Dry Powder Inhaler*. Presentation at the 2020 Virtual American Institute of Chemical Engineers (AIChE) Meeting. Virtual Meeting, November 20, 2020.
- Longest W. *Case Study: Predicting Regional Lung Deposition of Pharmaceutical Aerosols with CFD*. 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, September 30, 2021.
- Spires J. *PBPK Modeling of Dermal Penetration from Topical Formulations*. 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, September 30, 2021.
- Sulaiman M, Liu X, Kolehmainen J, Ozel A, and Sundaresan S. *Powder Fluidization in Dry Powder Inhalers*. Presentation at the 2020 Virtual American Institute of Chemical Engineers (AIChE) Meeting. Virtual Meeting, November 20, 2020.
- Tan M. *Physiologically-Based Pharmacokinetic Modeling to Support Generic Ophthalmic Product Development and Regulatory Decision Making*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Tan M. *GDUFA Research Update on Mechanistic Modeling Approaches for Generic Ophthalmic, Nasal, Implant and Injectable Drug 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, September 30, 2021.
- Tsakalozou E, and Alam K. *Challenges and Considerations with Model-Based Virtual Bioequivalence Assessments for Generic Dermatological Products, Part 1*. Presentation at the

2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.

- Tsakalozou E. *Scientific and Regulatory Considerations on Dermal PBPK Modeling for Virtual BE Assessments and Decision-Making*. 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, September 30, 2021.
- Walenga R. *ANDA and Pre-ANDA Experience with OIDP Modeling*. 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, September 30, 2021.
- Walenga R. *In Silico and Experimental Methods to Support Generic Nasal Drug Product (NDP) Development*. Presentation at the Respiratory Drug Delivery (RDD) 2021 Virtual Conference. Virtual Meeting, May 7, 2021.
- Zhao L. *Regulatory Perspective: What Can Be a Model Master File and How to Share It?*. 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, September 30, 2021.

Long-Acting Injectable and Implant Products

Summary of FY 2021 Activities

In FY 2021, research projects on long-acting injectable and implant products aimed to: 1) develop new tools for characterizing complex polymeric excipients; 2) better understand the impact of variation in raw materials on formulation physicochemical characteristics and drug release; 3) explore new in vitro drug release testing (IVRT) methods that have better clinical relevance; 4) investigate advanced imaging tools to explore correlations between formulation characteristics and in vitro/in vivo drug release; and 5) develop new modeling tools to support the development of alternative bioequivalence (BE) approaches. Summaries in each area appear below.

New characterization tools including 1) 3D laser scanning microscopy, 2) focused ion beam scanning electron microscopy (FIB-SEM), and 3) X-ray microtomography have been used to characterize poly (lactide-co-glycolide) (PLGA)-based microspheres and in situ forming implants. In addition to PLGA microparticles, the FIB-SEM was also used to characterize polydimethylsiloxane levonorgestrel intrauterine systems (LNG-IUSs). The image data were analyzed to obtain information about the morphology, porosity, and drug distribution within the polymer matrix and the impact on drug release kinetics.

Impact of variations in raw materials on formulation physicochemical characteristics and drug release was determined through 1) characterizing customized PLGA polymers and 2) evaluating PLGA formulations prepared

using same/similar PLGA polymers from different vendors. The study results showed that physicochemical properties (e.g., particle size, porosity, and average pore diameter) and in vitro release characteristics of microspheres are sensitive to the source of the polymers.

In the area of IVRT, efforts continued to develop methods for LNG-IUSs, PLGA-based formulations, and suspensions of drug substance particles. A novel non-sink, discriminatory IVRT method was developed, which combined in situ fiber optic ultraviolet (UV) spectroscopy with laser diffraction to simultaneously monitor the dissolution and changing particle size distributions (PSD) of the suspension. The simultaneously measured dissolution and PSD data showed that flocculated and deflocculated particles followed different dissolution pathways (see **Research Highlight** below for more information).

As described in detail in the section of this FY 2021 GDUFA Science and Research Report titled “Quantitative Clinical Pharmacology”, modeling projects have continued to develop computational tools to facilitate alternative in vivo BE study designs and provide a mechanistic understanding of in vivo drug release.

Injectable suspensions have been observed to exhibit variations in dissolution and bioavailability, which may impact the clinical outcome(s) of the drug product and present challenges to in vivo BE studies. The observed variability of in vitro/in vivo drug release may be related to fluctuations in particle size resulting from formulation design (i.e., flocculation) and injection procedure. To test this hypothesis, particle size distribution (PSD) and in vitro drug release testing (IVRT) were conducted using triamcinolone acetonide (TA) injectable suspension as the model product. In vitro particle size analysis results indicated that TA suspensions contained primary particles of approximately 2 µm and secondary flocculates of tens of microns. The conversion between flocculated and deflocculated particles was rapid, reversible, and highly shear dependent. As such, changing shear rates during laser diffraction (LD) measurements including stirring rate, sonication, and sample introduction method (micropipette vs 25-gauge needle) may result in high variability in PSD. Furthermore, a novel non-sink, discriminatory IVRT method was developed, which combined in situ fiber optic (IFO) UV with LD to simultaneously monitor the dissolution and changing PSD of the suspension. The simultaneously measured dissolution and PSD data showed that flocculated and deflocculated particles followed different dissolution pathways. Importantly, deflocculated particles dissolved up to six times faster than the flocculated particles. Similar shear-induced changes during injection are highly likely in a clinical setting, which may have implications for bioavailability.

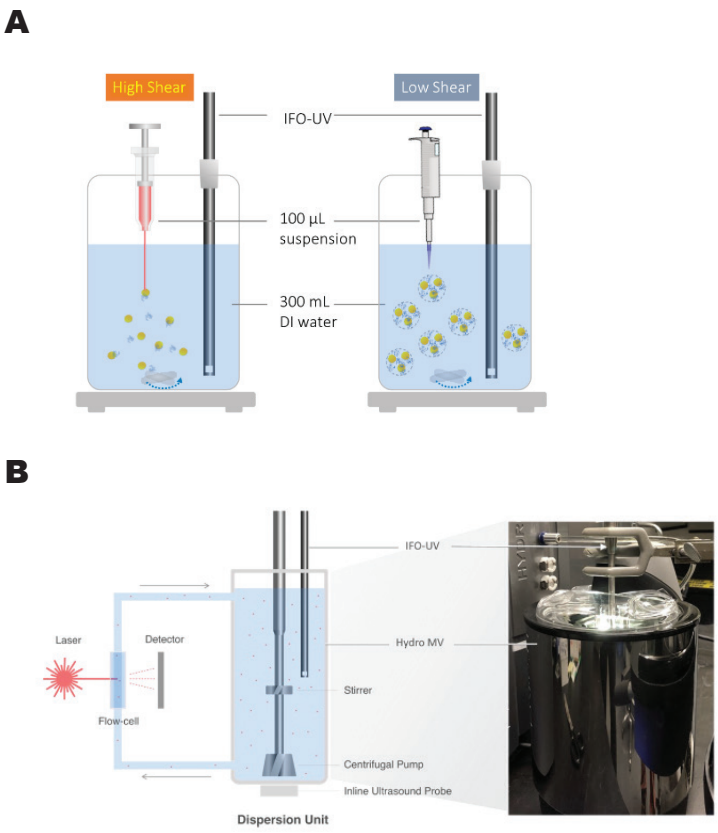

Figure 1: (A): Non-sink dissolution setup with continuous IFO UV monitoring: effect of shear on suspension dissolution. (B): View of internal flow path between laser diffraction flow cell and dispersion unit with IFO UV probe, for simultameous dissolution and particle size determination.

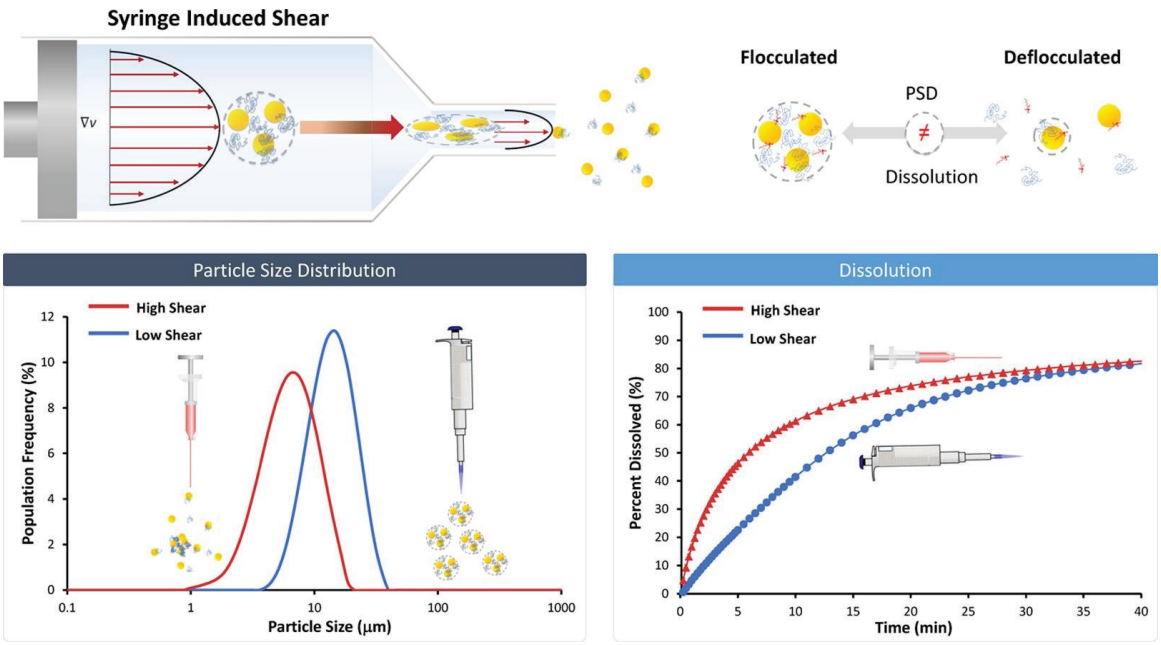

Figure 2: Visualizing the impact of shear during needle injection on particle flocculation (top) and subsequent effect on PSD (bottom left) and dissolution (bottom right).

New Grant(s) and Contract(s)

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

Continuing Grant(s) and Contract(s)

- Grant (1U01FD005443) *Development of Real-Time and Accelerated Dissolution Methods for a Long-Acting Levonorgestrel Intrauterine System* with Diane Jane Burgess at University of Connecticut.
- Contract (75F40120C00136) *Assessing Long-Acting Injectable Formulations Using in Vivo Imaging* with Xiuling Lu at University of Connecticut.
- Contract (75F40120C00198) *Effect of Repeat Unit Ordering on the Properties of Melt-Extruded, Poly(Lactide-co-Glycolide)-Based, Long-Acting Implants* at University of Texas at Austin.
- Contract (75F40120C00021) *Impact of Polymer Attributes on the Performance of in Situ Forming Implants Improve Scientific Approaches to Evaluate Generic Drugs* with Diane Burgess at University of Connecticut.
- Contract (75F40119C10157) *Microstructure Characterization with Micro-Imaging and Image-Based Analytics: A New Tool to Characterize Complex Polymer-Based Long-Acting Drug Products* with Shawn Zhang at DigiM Solutions, LLC.
- Contract (HHSF223201810188C) *Physiologically-Based Model of the Female Reproductive Tract: Vaginal and Intrauterine Delivery Components* with Chen Beatrice at University at Buffalo.

Completed Grant(s) and Contract(s)

- Contract (75F40119C10096) *New Analytical Methods for Complex Sameness of Injectable, Long-Acting PLGA Formulations* with Haesun Park at Akina, Inc.

Active FDA Research

- *Characterization of Exparel, Understanding of Critical Manufacturing Process Parameters and Characterization of Drug Release Mechanisms In Vitro and In Vivo*
- *Developing In Vitro Release Testing (IVRT) Methods and In Vitro In Vivo Correlations (IVIVC) of Long-Acting Drug Products*
- *In-Silico and In-Vitro Methods for Evaluating Generic Peptide Drug Immunogenicity*
- *Development of Real-Time and Accelerated Dissolution Methods for Long-Acting Intrauterine Systems*

Product-Specific Guidance(s) (PSG)

There were four new PSGs published in FY 2021 related to long-acting injectable and implant products. These PSGs were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Degarelix Acetate Subcutaneous Powder*. (March 2021) Link to Posting.
- *New Draft Guidance for Leuprolide Acetate Subcutaneous Powder*. (August 2021) Link to Posting.
- *New Draft Guidance for Paliperidone Palmitate Extended-Release Suspension for Intramuscular Injection*. (August 2021) Link to Posting.
- *New Draft Guidance for Penicillin G Benzathine injection*. (March 2021) Link to Posting.

Article(s)

- Bao Q, Zou Y, Wang Y, Choi S, and Burgess D. *Impact of Formulation Parameters on In Vitro Release from Long-Acting Injectable Suspensions*. AAPS Journal. (2021) 23(2): Article 42. doi: https://doi.org/10.1208/s12248-021-00566-0. PMID: 33709196.
- Beig A, Feng L, Walker J, Ackermann R, Hong J, Li T, Wang Y, and Schwendeman S. *Development and Characterization of Composition-Equivalent Formulations to the Sandostatin LAR by the Solvent Evaporation Method*. Drug Delivery and Translational Research. (2021) July 3. Online ahead of Print. doi: https://doi.org/10.1007/s13346-021-01013-5. PMID: 34215997.
- 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(S2): S26-S33. doi: https://doi.org/10.1002/jcph.1760. PMID: 33274513.
- Garner J, Skidmore S, Hadar J, Park H, Park K, Jhon Y, Qin B, and Wang Y. *Analysis of Semi-Solvent Effects for PLGA Polymers*. International Journal of Pharmaceutics. (2021) 602: Article 120627. doi: https://doi.org/10.1016/j.ijpharm.2021.120627. PMID: 33915188.
- Gu J, Wang J, Krishna A, Xu L, Stewart S, Wang Y, Faustino P, and Shakleya D. *Simultaneous Quantification of Dexamethasone and 6β-Hydroxydexamethasone in Rabbit Plasma, Aqueous and Vitreous Humor, and Retina by UHPLC-MS/MS*. Bioanalysis. (2021) 13(13): 1051-1062. doi: https://doi.org/10.4155/bio-2021-0088. PMID: 34100308.
- Li T, Chandrashekar A, Beig A, Walker J, Hong K, Benet A, Kang J, Ackermann R, Wang Y, Qin B, Schwendeman A, and Schwendeman S. *Characterization of Attributes and In Vitro Performance of Exenatide-Loaded PLGA Long-Acting Release*

Microspheres. European Journal of Pharmaceutics and Biopharmaceutics. (2021) 158: 401-409. doi: https://doi.org/10.1016/j.ejpb.2020.10.008. PMID: 33122118.

- O'Brien M, Jiang W, Wang Y, and Loffredo D. *Challenges and Opportunities in the Development of Complex Generic Long-Acting Injectable Drug Products*. Journal of Controlled Release. (2021) 336: 144-158. doi: https://doi.org/10.1016/j.jconrel.2021.06.017. PMID: 34126170.
- Park K, Otte A, Sharifi F, Garner J, Skidmore S, Park H, Jhon Y, Qin B, and Wang Y. *Formulation Composition, Manufacturing Process, and Characterization of Poly(Lactide-co-Glycolide) Microparticles*. Journal of Controlled Release. (2021) 329: 1150-1161. doi: https://doi.org/10.1016/j.jconrel.2020.10.044. PMID: 33148404.
- Park K, Otte A, Sharifi F, Garner J, Skidmore S, Park H, Jhon Y, Qin B, and Wang Y. *Potential Roles of the Glass Transition Temperature of PLGA Particles in Drug Release Kinetics*. Molecular Pharmaceutics. (2021) 18(1): 18-32. doi: https://doi.org/10.1021/acs.molpharmaceut.0c01089. PMID: 33331774.
- Patel S, Greene A, Desai S, Rothstein S, Basha I, Macpherson J, Wang Y, Zou Y, Shehabeldbin M, Sfeir C, Little S, and Rohan L. *Biorelevant and Screening Dissolution Methods for Minocycline Hydrochloride Microparticles Intended for Periodontal Administration*. International Journal of Pharmaceutics. (2021) 596: Article 120261. doi: https://doi.org/10.1016/j.ijpharm.2021.120261. PMID: 33486044.
- Patil S, Qin B, Wang Y, Ahmed S, Yilmaz H, Jiang X, Keire D, and Chen K. *A Real-Time NMR Method for Measurement of In Vitro Aggregation Kinetics of Degarelix Drug Products*. AAPS PharmaSciTech. (2021) 22(2): Article 73. doi: https://doi.org/10.1208/s12249-021-01948-5. PMID: 33586081.
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- Wan B, Andhariya J, Bao Q, Wang Y, Zou Y, and Burgess D. *Effect of Polymer Source on In Vitro Drug Release from PLGA Microspheres*. International Journal of Pharmaceutics. (2021) 607: Article 120907. doi: https://doi.org/10.1016/j.ijpharm.2021.120907. PMID: 34332059.
- Wang Y, Choi S, Xia G, and Qin B. *FDA's Poly (Lactic-co-Glycolic Acid) Research Program and Regulatory Outcomes*. AAPS

Journal. (2021) 23(4): Article 92. doi: https://doi.org/10.1208/s12248-021-00611-y. PMID: 34189655.

Poster(s)

- Bae J, Patel M, Manna S, Smith W, Vo A, Want Y, Choi S, Kozak D, Zhang J, and Xu X. *Impact of Manufacturing Process on Critical Quality Attributes of Multivesicular Liposomes*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020 Pharmsci 360. Virtual Meeting, October 26, 2020.
- Fanse S, Bao Q, Zou Y, Wang Y, and Burgess D. *Influence of Polymer Crosslinking on the Mechanical Properties of Polydimethylsiloxane Based Intrauterine Systems*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Jhon Y, Qin B, and Wang Y. *Effect of Reaction Temperature on PLGA Properties and Semi-Solvent Interactions*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Jhon Y, Qin B, and Wang Y. *Effect of Solvent Molar Volume on Its Ability to Solubilize PLGAs and Potential Implications for Understanding Polymer Structure*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Jhon Y, Qin B, and Wang Y. *Scanning Analysis of Semi-Solvent Impact (SASSI) Assays of Naltrexone Microparticles Prepared by Different Manufacturing Solvents and Conditions*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Ma Y, Liang J, Zheng J, Wang Y, Ashraf M, and Srinivasan C. *Significance of Cryogenic Broad Ion Beam Milling in Evaluating Microstructures of PLGA-Based Drug Products*. Poster Presentation at the Microscopy Microanalysis (MM) 2021 Annual Meeting. Virtual Meeting, August 2, 2021.
- Qin B, Garner J, Hadar J, Skidmore S, Jessmon F, Park H, Park K, Wang Y, and Jhon Y. *Effect of Solvent Isomeric Structures on the Dissolution of PLGAs with Different Lactide:Glycolide (L:G) Ratios*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Qin Y, Bao Q, Wang Y, Zhu A, Burgess D, Zhou L, and Shawn Z. *Drug Particle Characterization Inside Long-Acting Intrauterine Systems with 3D Imaging Analytics*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020 Pharmsci 360. Virtual Meeting, October 26, 2020.

- Shen M, Wang Y, Zhang S, Qin B, Wang R, Bao Q, and Burgess D. *PLGA Microsphere Stability Characterization Using Image-Based Key Performance Attributes and Release Prediction*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Wan B, Andhariya J, Bao Q, Wang Y, Choi S, Zou Y, and Burgess D. *Effect of Polymer Source Variation on Physicochemical Properties of Risperidone Microspheres*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Wang R, Bao Q, Wang Y, Choi S, Zhou L, Zhang S, and Burgess D. *Formulation Optimization of PLGA Microspheres Prepared Using a Coacervation Method*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Zhang Q, Qin B, Wang Y, Li Q, and Kozak D. *Scientific Gap Analysis of Polymeric In Situ Forming Depot Products for the Development of GDUFA Research Projects*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.

Presentation(s)

- Kozak D. *Advanced Analytical Methods in Generic Drug Development and Approval*. Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Qin B. *Injectable Suspensions: Tools and Methods Bridging the In Vivo and In Vitro Gap*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Wang Y. *Bioequivalence of Intravaginal Rings and Intrauterine Systems: Current Perspective and Future Directions*. Presentation at the Drug Information Association (DIA)/FDA Complex Generic Drug-Device Combination Products Conference 2020. Virtual Meeting, October 20, 2020.
- Wang Y. *Advanced Imaging and Data Analysis to Support Structure Similarity of Polymeric Formulations*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Qin B. *Injectable Suspensions: Tools and Methods Bridging the In Vivo and In Vitro Gap*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.

Ophthalmic Products

Summary of FY 2021 Activities

In FY 2021, research efforts continued to address challenges in three areas: 1) development of novel in vitro release test (IVRT) methods that more closely resemble in vivo physiological conditions; 2) identification and characterization of critical physicochemical properties of complex ophthalmic products in vitro, ex vivo, and in animals; and 3) advancement of in silico modeling to investigate the impact of formulation properties on ocular pharmacokinetics (PK) and/or pharmacodynamics (PD).

A new IVRT method, called adaptive perfusion, was developed through internal collaborative research and employs the principle of tangential flow filtration (TFF). Difluprednate was used as the model drug. Nanoemulsion formulations with known variations were prepared in house for method development and validation. The drug release profile obtained using the adaptive perfusion method was significantly faster (e.g., minutes rather than hours) and higher (e.g., >60%) than the release obtained using the conventional methods with USP Dissolution Apparatus II. In addition, the adaptive perfusion method achieved size-based separation of the particulates with simultaneous analysis of the released drug as well as remaining drug (refer to the **Research Highlight** section below for more information).

Cyclosporine ophthalmic emulsion formulations with different globule size distributions (GSDs) and viscosities were evaluated in rabbits. The central tear film thickness and tear menisci area of the rabbit eye were evaluated. The results suggested that GSD and viscosity are critical quality attributes (CQAs) of

cyclosporine ophthalmic emulsion that affect tear film properties. In addition, the PK/PD profiles of brinzolamide ophthalmic suspension with different GSDs and viscosities have been characterized in normotensive intraocular pressure rabbits. Bioanalytical methods for measuring brinzolamide distribution in aqueous humor, tears, and ocular tissues have been developed and validated. These results will be used to validate PK/PD models developed internally at FDA.

In vitro-in vivo correlation of tobramycin and dexamethasone ophthalmic ointments was explored in collaboration with the University of Connecticut and Virginia Commonwealth University (HHSF223201810114C). In vitro and ex vivo (rabbit corneal) release of both drugs has been determined and the results showed a good rank order.

In the area of in silico modeling, three research projects were awarded to focus on developing ocular physiologically based pharmacokinetic (PBPK) in silico models to predict the effect of formulation properties on ocular PK in rabbits and PBPK/PD model scale-up from animal species to humans.

With the support of GDUFA research related to complex ophthalmic products, the first ANDA for difluprednate ophthalmic emulsion, ANDA 211526, was approved in FY 2021.

Drug release is a major determinant of the drug's safety and efficacy and, hence, an integral part of product quality and equivalence evaluation. Often, the development of drug release tests for complex drug products containing particulates (e.g., emulsions, micelles, suspensions, liposomes, drug-protein complexes, microspheres) can be challenging, in part due to the inherent complexity of a drug product and the route of drug delivery. An ideal in vitro drug release test should be optimally discriminatory to detect the effects of changes in the formulation and manufacturing process on the quality and drug release of complex products containing particulates. To meet this need, a new IVRT method called adaptive perfusion was developed that employed the principle of tangential flow filtration. Notably, this method achieved size-based separation of the particulates with simultaneous analysis of the released drug as well as the remaining drug. Furthermore, discriminatory drug release profiles of the drug in various phases were obtained, such as in solution, in micelles, and in nanoemulsions of small, medium, and large size globules. Overall, the adaptive perfusion method is a new approach to study IVRT from complex formulations and provided a tool to control and monitor the rate and extent of drug release depending on the type of drug product. This new method gives a deeper insight into drug release of complex formulations and has the potential to support a demonstration of bioequivalence and a product quality assessment for generic drugs. This work has been published in the Journal of Controlled Release (https://doi.org/10.1016/j.jconrel.2021.03.024).

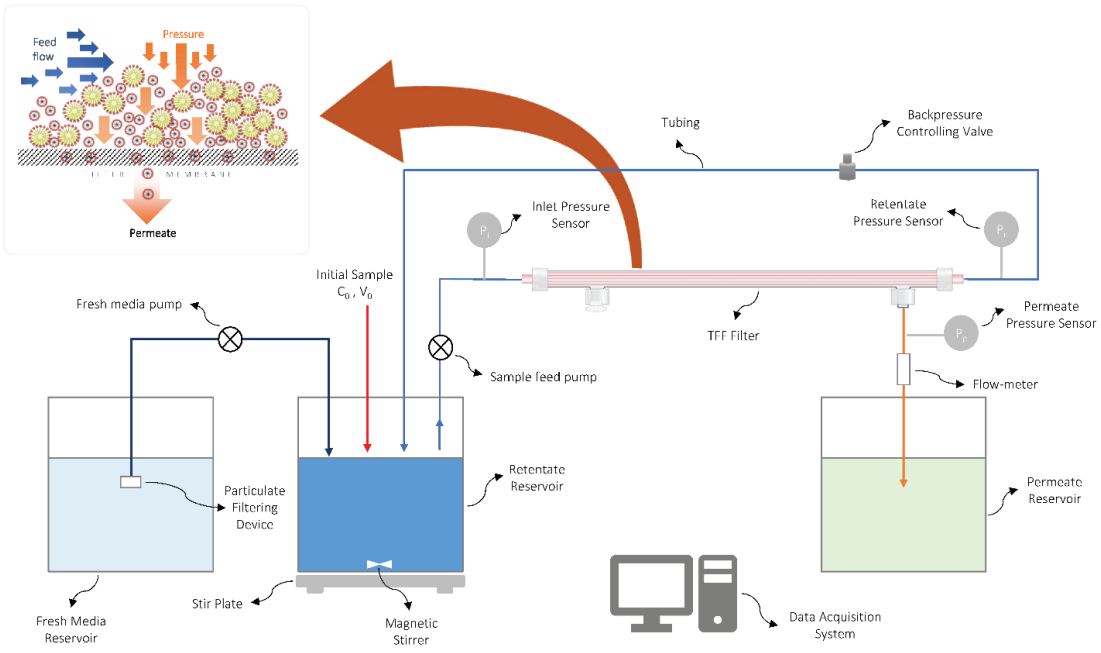

Figure 1: Schematic representation of an adaptive perfusion method using a hollow fiber TFF filter and the principle of size-based separation.

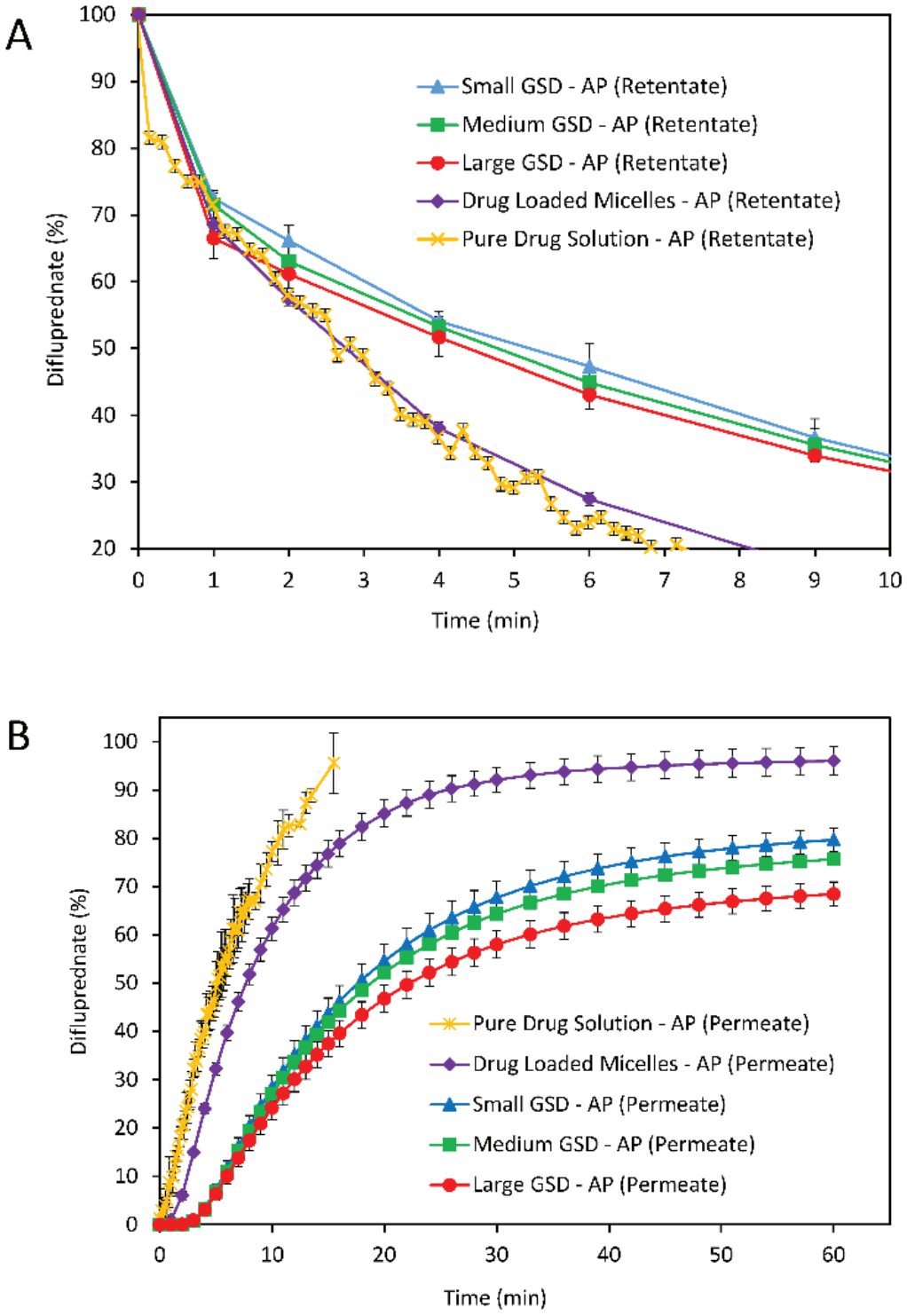

Figure 2: (A) Initial rate of drug removal and the decline of drug concentration in the retentate reservoir for small, medium, and large globule size nanoemulsions, drug loaded micelles, and pure drug solution tested using an adaptive perfusion method (Mean ± SD, 3 tests each using a new filter); (B) Extent of in vitro drug release in the permeate reservoir for a pure drug solution, drug loaded micelles, as well as small, medium, and large globule size nanoemulsions, all tested using an adaptive perfusion method (Mean ± SD, 3 tests each using a new filter).

Continuing Grant(s) and Contract(s)

- 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 (HHSF223201810151C) *An Integrated Multiscale-Multiphysics Modeling Framework for Evaluation Of Generic Ophthalmic Drug Products* with Andrzej Przekwas at CFD Research Corporation.
- Contract (HHSF223201810114C) *In Vitro and In Vivo Assessment of Ophthalmic Ointments for Generic Product Equivalence* with Xiulin Lu at University of Connecticut.
- Contract (75F40119F19002) *PK/PD Of Topically Administered Ophthalmic IOP Drug Formulations in Rabbits* with Vatsala Naageshwaran at Absorption Systems.

Completed Grant(s) and Contract(s)

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

Active FDA Research

- *Development of an Ophthalmic Physiologically Based Pharmacokinetic (PBPK) Modeling Platform*
- *Ophthalmic Antimicrobial Kill Rate Study*
- *Prediction of Tear Film Breakup Times for Ophthalmic Formulations*

Product-Specific Guidance(s) (PSG)

There were two new PSGs published in FY 2021 related to ophthalmic products. These PSGs were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Acyclovir Ointment*. (August 2021) Link to Posting.
- *New Draft Guidance for Loteprednol Etabonate Gel*. (August 2021) Link to Posting.

Article(s)

- Lemerdy M, Spires J, Lukacova V, Tan M, Babiskin A, Xu X, Zhao L, and Bolger M. *Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations*. Pharmaceutical Research. (2020) 37(12): Article 245. doi: https://doi.org/10.1007/s11095-020-02965-y. PMID: 33215336.
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- Mekjaruskul C, Beringhs A, Luo W, Xu Q, Halquist M, Qin B, Wang Y, and Lu X. *Impact of Membranes on In Vitro Release Assessment: A Case Study Using Dexamethasone*. AAPS PharmSciTech. (2021) 22(1): Article 42. doi: https://doi.org/10.1208/s12249-020-01874-y. PMID: 33426616.
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Poster(s)

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- Smith W, Vo A, Bae J, Wang Y, Qin B, and Xu X. *Influence of Polymeric Excipients on the Precision of Particle Size Distribution Measurements of Suspensions Using Laser Diffraction*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 30, 2020.
- Smith W, Bae J, Zhang Y, Wang Y, Qin B, Kozak D, and Xu X. *Interplay Between Particle Flocculation and Dissolution Leading to Variation in Bioavailability and Clinical Performance of Injectable Suspensions*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: An In Vitro Drug Release Testing Method for Complex Drug Products*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Zhang Y, Patel D, Zhu D, Dong Y, Kozak D, Ashraf M, and Xu X. *Adaptive Perfusion: An In Vitro Drug Release Testing Method for Complex Drug Products*. Poster Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.

Presentation(s)

- Chopra, P. *Challenges in the Approval of Complex Otic & Ophthalmic Generic Products: Quality Perspectives*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Kozak, D. *Ophthalmic Generic Drug Development and Approval: Challenges and Recent Research*. Presentation at the FDA Webinar on Complex Ophthalmic Formulations Hosted by Pharmaceutical Technology. Virtual Meeting, August 5, 2021.
- Tan ML. *Physiologically-Based Pharmacokinetic Modeling to Support Generic Ophthalmic Drug Product Development and Regulatory Decision Making*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Tan ML. *GDUFA Research Update on Mechanistic Modeling Approaches for Generic Ophthalmic, Nasal, Implant and Injectable Drug 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, September 30, 2021.
- Xu X. *Connecting the Dots: Particle Size, Drug Distribution and Drug Release in Nanoemulsions*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Webinar. Virtual Meeting, May 7, 2021.
- Zhao, C. *Challenges in the Approval of Complex Otic and Ophthalmic Generic Products: Bioequivalence Perspectives*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.

Oral Absorption Models and Bioequivalence

Summary of FY 2021 Activities

Oral physiologically-based pharmacokinetic (PBPK) modeling has been increasingly used for the assessment of bioequivalence (BE) approaches and standards for product-specific guidance (PSG) development and global harmonization. The extramural and intramural projects in FY 2021 related to oral absorption models and bioequivalence encompassed scientific areas including (1) potential expansion of biowaivers for Biopharmaceutical Classification System (BCS) Class III Drugs, (2) enhancement of physiologically-based pharmacokinetic (PBPK) modeling capabilities, and (3) utility of in vitro biopredictive testing and PBPK modeling to evaluate BE under fed condition.

Three extramural projects aim to study the impact of excipients on drug absorption and potentially expand eligibility for biowaivers beyond Q1/Q2 products. Grant #1U01FD005978-P2 project (completed) screened in vitro interactions of excipients with intestinal drug transporters. Of 136 excipients under investigation, 24 excipients were identified as organic anionic transporter protein 2B1 (OATP2B1) inhibitors. According to the findings of this study, some excipients such as sodium lauryl sulfate (SLS) (inhibition constant, K_i = 1.98 µM) may have a potential influence on the oral bioavailability of drugs that are OATP2B1 substrates. Following these intriguing findings, Grant #3U01FD005978 (ongoing) was awarded in FY 2020 to determine how the in vitro findings translate into clinical significance. Under this grant, an exploratory clinical study is being conducted to evaluate whether 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” (ongoing) explored the impact of individual excipients on the permeability of BCS Class III drugs. Fifteen excipients, such as povidone, hypromellose, SLS, PEG 400, and mannitol, were selected to determine their effects on permeability of five model drugs-acyclovir, atenolol, cimetidine, minoxidil, and ranitidine, using in vitro dissolution absorption system (IDAS) system. This research project is also testing the effects of different combinations of excipients on drug permeability using test capsules based on published literature and different formulations of generic drug products, including rasagiline tablets, hydroxychloroquine tablets, and acyclovir tablets. The results will be used to support evaluations of how excipients might impact BE assessments.

In this research area of enhancement of PBPK modeling capabilities, two guidances involving PBPK modeling were published in FY 2021, i.e., the draft guidance for industry titled “The Use of Physiologically-Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls” (September 2020) and the draft guidance for industry titled “Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications” (November 2020). An ongoing contract HHSF223201810112C summarized the risk factors associated with the substitution of generic products in pediatric populations when the BE studies had been conducted in adults, and published the results in the AAPS Journal in 2021. The contract also continues to explore the biorelevant dissolution methods of four Narrow Therapeutic Index (NTI) drugs and integrate the generated dissolution profiles into PBPK modelling software to determine whether these methods provide discriminatory tools to better predict risks of bio-inequivalence in pediatric patients. In addition, a contract #75F40120C00150 intends to develop a predictive in silico modeling and simulation platform for drug products delivered via the oral cavity (i.e., 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 GI tract. The initial permeability measurements will be used to develop a machine learning model to mathematically correlate atomic and molecular descriptors of the active pharmaceutical ingredient (API) with experimental permeability data to improve the predictive ability of the existing GastroPlus model for use when performing virtual BE simulations. Another contract #75F40120C00200 aims to develop biopredictive methods for setting patient centric quality specifications in 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 gastrointestinal (GI) tract regions and the GI physiological parameters will be measured. The data from the proposed study will elucidate how in vitro differences may be associated with variable absorption in vivo. In addition, FDA collaborated with the Center for Research on Complex Generics (CRCG) to hold a 2-day workshop titled “Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches” on September 30 and October 1, 2021. The first day of the workshop was dedicated to PBPK modeling for locally acting products, and are discussed in the section of this FY 2021 GDUFA Science and Research Report titled “Locally-Acting Physiologically-Based Pharmacokinetic Modeling”. The second day was dedicated to PBPK modeling for oral products, followed by a general session focused on model acceptance and model sharing for regulatory use. Workshop panelists and presenters in these sessions included representatives from the FDA, generic industry, academia, research organizations, and software/model developers to give a broad range of

perspectives on the state of modeling in each area and to provide greater opportunities for informing regulatory decision-making. The workshop materials can be found here: https://www.fda.gov/drugs/news-events-human-drugs/fda-and-center-research-complex-generics-co-hosted-workshop-regulatory-utility-mechanistic-modeling.

In FY 2021, research has been conducted to demonstrate the predictability of BE in the fed state and the potential utility of PBPK modeling as an alternative approach to evaluate BE under fed condition. For the immediate release (IR) products, other than FDA, most regulatory agencies including the European Medicines Agency (EMA), Health Canada, and others, recommend that a BE study under a fasting condition only is sufficient in most cases. The FDA internal research project involves a systemic analysis of BE approaches, formulation compositions, and excipient effects of FDA approved IR drug products (both new drug applications (NDAs) and abbreviated new drug applications (ANDAs)) in conjunction with PBPK modeling and lab testing to develop a scientifically justified framework that could indicate when a fed BE study should be recommended for IR products. An FDA internal project has been conducted using PBPK modeling and showed promising results. Scientific evidence generated in this project will directly support the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) M13 guideline development (ICH M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms). Two extramural research projects are also granted in FY 2021 in this area. Grant #1U01FD007352-01 is focusing on the 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. Contract #75F40121C00020 is focusing on the disintegration and dissolution of solid dosage forms and influence of food induced viscosity on its kinetics, tools and methodologies for bioequivalence and substitutability evaluation. These two projects will help better understanding and practicing of using in vitro biopredictive testing and oral PBPK modeling to assess BE under fed condition.

A GDUFA-funded contract HHSF223201810112C focused on understanding the risks associated with the substitution of generic products in pediatric populations when bioequivalence (BE) studies were conducted in adults. Literature data were used to generate a database of BE studies, and this database was reviewed to highlight some of the common putative risk factors associated with differences in relative bioavailability (DRBA) in pediatric populations, including age-related absorption effects, high inter-individual variability, and poor study design (see **Figure 1** and publication Pawar et al, AAPS Journal, 2021, doi: https://doi.org/10.1208/s12248-021-00592-y). The findings indicated that particular care is needed for BCS Class II (2) drugs and narrow therapeutic index (NTI) drugs when assessing BE in pediatrics. Four compounds (carbamazepine, phenytoin, tacrolimus, cyclosporine) where BE data were reported in both adult and pediatric populations were used as model drugs to explore their biorelevant dissolution methods. These generated dissolution profiles are being integrated into PBPK modelling software to determine whether these methods provide discriminatory tools to better predict risks of BE.

In addition, an FDA internal project explored the possibility of using PBPK modeling and conducting virtual BE simulations for oseltamivir phosphate (OP) in pediatrics to support setting the dissolution safe space for pediatric products and to mitigate the risk of bio-inequivalence (see **Figure 2** and publication Miao et al, AAPS Journal, 2020, doi: https://doi.org/10.1208/s12248-020-00493-6).

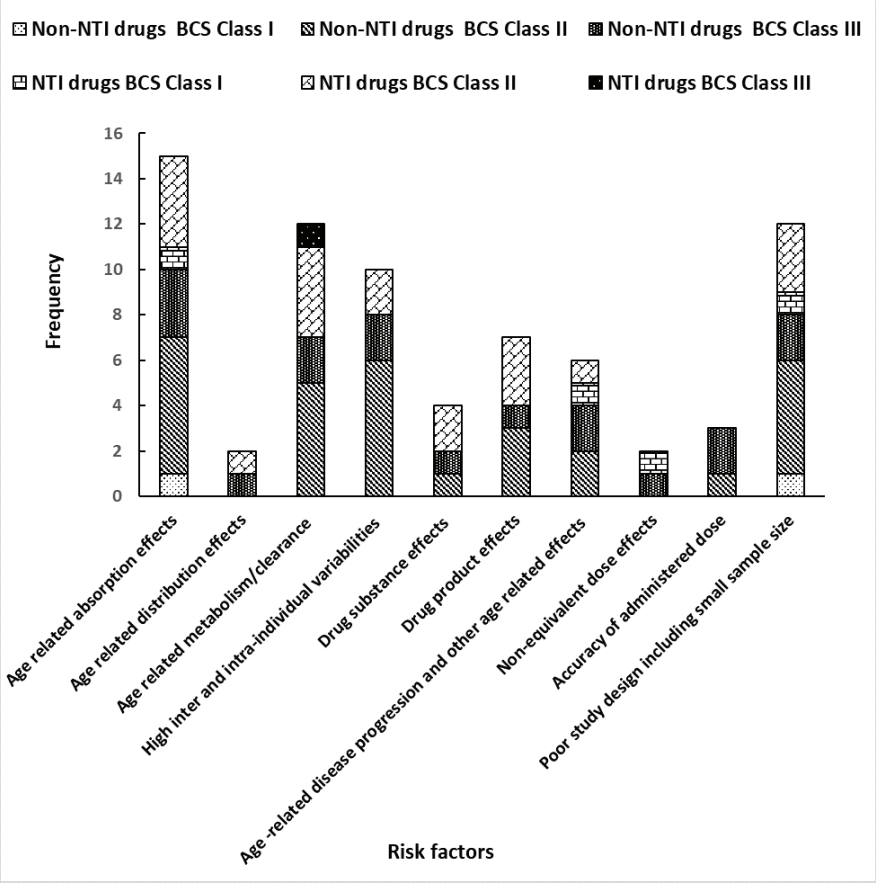

Figure 1: Bar chart showing the number of clinical trials involving non-NTI or NTI drugs under each risk factor analyzed

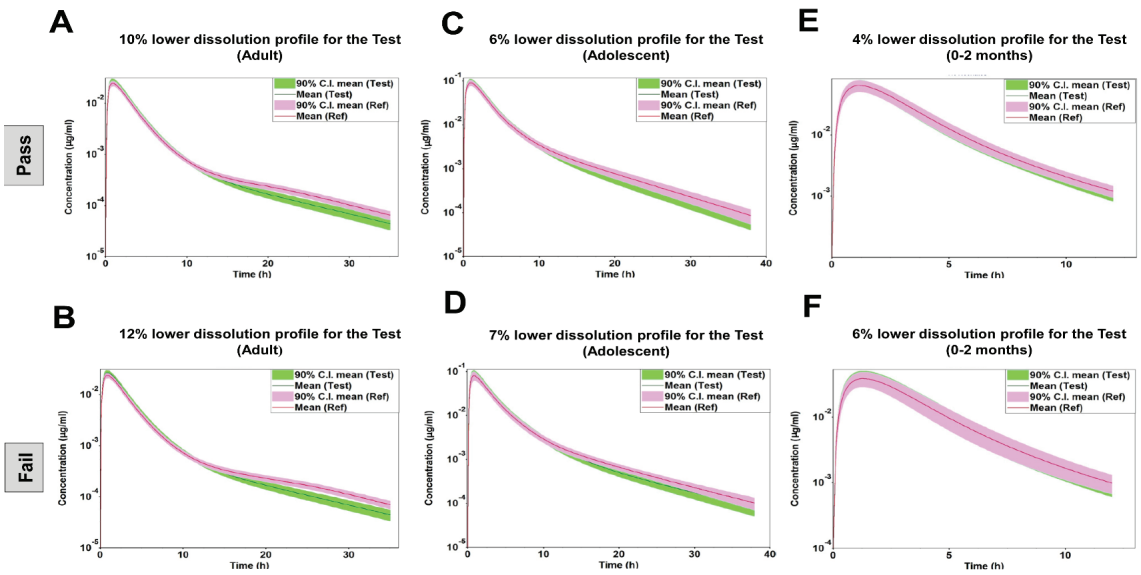

Figure 2: Population and virtual BE analysis between Test and Reference products in adults and pediatrics to determine BE dissolution "safe space" for OP. Virtual BE simulation and analysis for the reference and generic OP products with lower dissolution profiles. a, b: The virtual BE analysis in adults (n = 50 subjects) shows that lowering the dissolution profile by 10% is the BE safe space limit to maintain the BE with the reference OP product (a). However, lowering the dissolution profile by 12% fails to keep BE with the reference OP product (b). c, d: The virtual BE analysis in adolescent (9–18 years, n = 25 subjects) shows that lowering the dissolution profile by 6% is the BE safe space limit to maintain the BE with the reference OP product (c). However, lowering the dissolution profile by 7% fails to keep BE with the reference OP product (d). e, f: The virtual BE analysis in neonates (0–2 months, n = 25 subjects) shows that lowering the dissolution profile by 4% is the BE safe space limit to maintain the BE with the reference OP product (e). However, lowering the dissolution profile by 6% fails to keep BE with the reference OP product (f)

New Grant(s) and Contract(s)

- Grant (1U01FD007352-01) *Development and Validation of a Best Practices Framework for PBPK Analysis for Biopharmaceutic Applications in Support of Model-Informed Biowaivers of Fed State BE Studies for BCS Class II Drugs* with Rodrigo Cristofoletti at University of Florida.
- Contract (75F40121C00132) *Applying a Robotic Soft Esophagus (Rose) to Assess the Swallowability of Opioid Drugs* with Peter Xu at The University of Auckland.
- Contract (75F40121C00020) *Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on Its Kinetics, Tools and Methodologies for Bioequivalence and Substitutability Evaluation* with Peter Langguth at Johannes Gutenberg University.

Continuing Grant(s) and Contract(s)

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

Completed Grant(s) and Contract(s)

- Grant (1U01FD005978-P2) *Effect of Excipient Transporter Interactions on BCS Class III Drugs* with Kathleen M Giacomini at University of California, San Francisco.
- Contract (75F40119C10127) *Expanding BCS Class III Waivers for Generic Drugs to Non-Q1/Q2* with Chris Bode at Absorption Systems.
- Contract (223201810112C) *Better Understand Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products* with Marie-Christine Jones at University of Birmingham.

Active FDA Research

- *Analysis of the Predictability of Bioequivalence (BE) in the Fed State*
- *Baseline Correction in Bioequivalence (BE) 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 Machine Learning (ML) Model to Aid in Qualification of Formulation Differences across Strengths for Modified Release (MR) Drug Products*
- *Development of New Approaches to Bioequivalence (BE) Evaluations of Multi-Strength Modified Release (MR) Products*
- *Evaluating In Vitro Performance of Modified Release Drug Products When Sprinkled on Soft Food*
- *Evaluation of BCS Class III 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 Bioequivalence (BE) Studies*
- *Identification of the Critical Bioequivalence (BE) Issues for Gastro-Retentive Delivery Systems (GRDDS) Best Practice for Using Physiologically Based Pharmacokinetic (PBPK)*
- *Identification of Critical Factors for Oral Solution Bioequivalence (BE)*
- *Improvement of Drug Dissolution Method for Application to Nanocrystal Drugs*
- *Prioritization and Optimization of Modified Release Bioequivalence (BE) Guidances*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based Supports for Bioequivalence (BE) Assessment during the COVID-19 Public Health Emergency*

General Guidance(s)

- *Draft Guidance for Industry, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application*. (August 2021) Link to Posting.
- *Draft Guidance for Industry, Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications*. (November 2020) Link to Posting.
- *Draft Guidance for Industry, M9 Biopharmaceutics Classification System-Based Biowaivers*. (May 2021) Link to Posting.
- *Draft Guidance for Industry, The Use of Physiologically Based Pharmacokinetic Analyses - Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls*. (October 2020) Link to Posting.

Product-Specific Guidance(s) (PSG)

There were three new and four revised PSGs published in FY 2021 related to oral drug products. These PSGs were directly impacted by GDUFA-funded research in this area.

- *Revised Draft Guidance for Dasatinib Tablet*. (May 2021) Link to Posting.
- *New Draft Guidance for Ferric Maltol Capsule*. (March 2021) Link to Posting.
- *Revised Draft Guidance for Ferric Oxyhydroxide Tablet, Chewable*. (September 2021) Link to Posting.
- *Revised Draft Guidance for Lovastatin; Niacin Tablet, Extended Release*. (May 2021) Link to Posting.
- *Revised Draft Guidance for Pentosan Polysulfate Sodium Capsule*. (May 2021) Link to Posting.
- *New Draft Guidance on Quinidine Gluconate Extended-Release Capsule.* (May 2021) Link to Posting.
- *New Draft Guidance for Solriamfetol Hydrochloride Tablet*. (March 2021) Link to Posting.

Article(s)

- Bajaj R, Chong L, Zou L, Tsakalozou E, Ni Z, Giacomini K, and Kroetz D. *Interaction of Commonly Used Oral Molecular Excipients with P-Glycoprotein*. AAPS Journal. (2021) 23(5): Article 106. doi: https://doi.org/10.1208/s12248-021-00631-8. PMID: 34528148.
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Poster(s)

- Chan T, Ren P, Wang Y, Luke CM, Kim, and Zhang Y. *Assessment on the Formulation Similarity of Approved Generic Drug Products and their Respective Reference Products Which are Considered as Potential BCS Class III Drugs*. Poster Presentation at the 2020 American College of Clinical Pharmacy (ACCP) Annual Meeting. Virtual Meeting, October 24, 2020.
- Gong Y, Feng K, Lee J, Pan Y, Bai T, Li B, Kim C, Yoon M, Zhang P,

Fang L, and Zhao L. *Quantitative Modeling and Simulation to Evaluate Alternative Approaches to be Used in COVID-19 Interrupted Bioequivalence Studies*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, February 15, 2021.

- Jordan L, Hoover A, Zheng K, Feng X, Mahjabeen S, Sun W, Xia L, Lee S, Hwang S, Nwakama P, Xi X, Rodriguez J, 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 FDA Science Forum. Virtual Meeting, May 26, 2021.
- Owens K, Argon S, Yu J, Ragueneau-Majlessi I, Yang X, Wu F, Lee SC, Sun WJ, Ramamoorthy A, and Zhang L. *Exploring the Relationship of Drug BCS Classification, Food-Effect, and Gastric pH-Mediated Drug Interactions*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 15, 2021.
- Tian L, Tan M, Lin H, Jiang W, Ruzicka C, Rodriguez J, and Gao Z. *Biphasic Dissolution Study of Nifedipine Extended-Release (ER) Tablets*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 30, 2020.
- Wu F, Das S, Fang L and Polli JE. *Using Partial AUC to Characterize the Impact of Shape of Pharmacokinetic Profiles on Bioequivalence Evaluation*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 12, 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. *In Vitro Performance of Pantoprazole Sodium Delayed Release Granules when Sprinkled on Soft Foods*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 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. *In Vitro Performance of Pantoprazole Sodium Delayed Release Granules when Sprinkled on Soft Foods*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Zou L, Pottel J, Khuri N, Ngo H, Warren M, Huang Y, Schoichet B, and Giacomini K. *Interactions of Oral Molecular Excipients with Breast Cancer Resistance Protein, BCRP*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 15, 2021.

Presentation(s)

- Babiskin A. *Regulatory Perspective: Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use*. 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, September 30, 2021.
- Bajaj R. *Screening Oral Excipients against P-Glycoprotein*. Presentation at the 4th International Conference on Applied Biochemistry and Biotechnology (ABB) 2021. Virtual Meeting, August 11, 2021.
- Boyce H. *Establishing Bioequivalence for "Additional Strengths" of Oral Modified-Release Drug Products*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Pharmsci 360. Virtual Meeting, October 28, 2020.
- Gong Y. *Alternative BE Approaches for Data Analysis Due To COVID-19 Related Study Interruptions*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Sun W, and Wang R. *Generic Oral Modified Release Drug Products: Establishing Bioequivalence for Additional Strengths*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Webinar. Virtual Meeting, December 10, 2020.
- Wang Y. *Regulatory and Scientific Considerations on Characterizations of Complex Polymeric Excipients*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Pharmsci 360. Virtual Meeting, October 30, 2020.
- Wu F. *PBPK Absorption Modeling and Virtual Bioequivalence to Support Generic Drug Development and Regulatory Decision Making for Oral Products*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Zhao L. *Quantitative Methods and Modeling to Evaluate Alternative Approaches for COVID-19 Interrupted Bioequivalence Studies*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosums Conference. Virtual Meeting, November 9, 2020.

Patient Substitution of Generic Drugs

Summary of FY 2021 Activities

As part of Generic Drug User Fee Amendments (GDUFA)-funded research projects, FDA has ongoing research to evaluate generic substitution in various ways, including clinical studies of substitution in patients, analyzing medical informatics data to evaluate generic utilization and substitution, and patient and provider perceptions impacting generic substitution.

During FY 2021, ongoing research efforts were focused on evaluating the substitutability of approved generic products and their corresponding reference products. Research that was done in collaboration with the Yale University-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (CERSI) (Grant# 1U01FD005938-A2) was completed to characterize whether users of different generic levothyroxine products had equivalent clinical outcomes, in particular, thyroid stimulating hormone (TSH) levels. Preliminary results showed that there were no significant differences among the various generic levothyroxine products and there is no need to caution against switching between different generic products. A second award with the Yale-Mayo CERSI (Grant# 1U01FD005938-A10) was designed to control for unobserved confounding factors that are ubiquitous in observational studies. Previous efforts had successfully controlled for observed confounding factors such as age and other demographic factors. The preliminary results showed that the global treatment effect was not significantly different between generic and brand levothyroxine products following instrumental variable adjustment. A contract with BioPharma Services USA, Inc. (Contract# HHSF223201610004I-75F40120F19005) was awarded to investigate the bioequivalence (BE) of generic

tacrolimus in comparison with its reference product. The outcome of this study will help further the Agency's understanding about product pharmacokinetic (PK) performance in healthy subjects and improve review standards for equivalence. Internal research also investigated the feasibility of using Sentinel data to investigate the performance of generic products in terms of therapeutic equivalence with the reference product and to compare the outcomes of solid organ transplantation between these formulations.

Other ongoing internal research efforts include monitoring post-market performance of a first generic, Wixela Inhub® (fluticasone propionate and salmeterol xinafoate dry powder inhaler), which was approved as a generic for Advair Diskus® for the treatment of asthma/chronic obstructive pulmonary disease (COPD) (preliminary results shown in the **Research Highlight** section). Internal research has also been initiated to evaluate the application of pharmacogenomic (PGx) information for BE purposes. PGx information can be applied in BE study recommendations for generic drug development to further enhance subject safety and BE study design. The ongoing research will help determine when PGx information may be considered to help identify subjects vulnerable to serious adverse events, minimize carryover effects in a crossover study, and ensure balanced groups in a parallel study.

In the United States, drug costs associated with inhaled corticosteroid (ICS) and long acting β agonist (LABA) combination products have been increasing since 2001. In January 2019, the first generic ICS/LABA drug product, Wixela Inhub® (Reference Listed Drug, Advair Diskus®), was approved by the FDA. The impact of the first approved generic ICS/LABA drug product on wholesale cost-savings and prescription dispensing from 2019 to 2020 were investigated using the IQVIA data system.

The marketing of the first generic for fluticasone propionate and salmeterol xinafoate dry powder inhaler (FP-SX) was associated with up to $1 billion in drug cost-savings during the first year for this class of medications. Although the brand-name drug manufacturer concurrently introduced its authorized generic, these cost-savings were driven by the averaged unit-cost of the approved generic at $115, compared to $169 for the authorized generic and $334 for the branded product. However, overall dispensing of the first generic was lower than that of its branded product (**Figure 1**). As a comparison, in the case of budesonide and formoterol fumarate dry powder inhaler (Bud-FoF), marketing of authorized generics alone was not associated with any noticeable change in sales or prescription cost-saving.

It is estimated that more than 20% of prescription cost-saving was achieved for the ICS/LABA dry powder inhalers in the first year following the introduction of the first approved generic, even though the number of generic prescriptions dispensed remained lower than that of the branded counterpart.

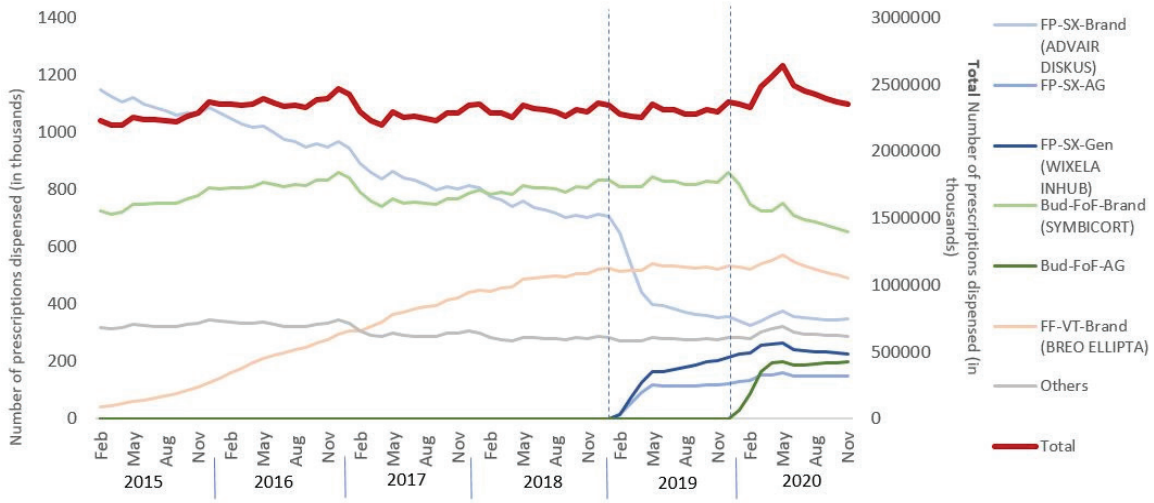

Figure 1: Prescriptions of selected orally inhaled drug products (OIDPs) with their generics in the United States. The first gridline indicates the launching of Wixela Inhub® and the authorized generic (AG) for Advair Diskus®; the second indicates that of AG for Symbicort®. The total is the sum of all OIDPS and displayed according to the secondary y-axis. Other products include Advair® HFA, Dulera®, Airduo® Respiclick® and its authorized generic, and Airduo® Digihaler®.

New Grant(s) and Contract(s)

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

Continuing Grant(s) and Contract(s)

- 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.
- 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.
- Contract (22320161004I-75F40120F19005) *A Randomized, Open Label, Two-Treatment, Four-Period, Single Dose, Fully Replicate, Crossover Bioequivalence (BE) Study of Tacrolimus Capsules 5 Mg* with Kathleen Doisy at BioPharma Services USA, Inc.

Completed Grant(s) and Contract(s)

- Grant (1U01FD005240) *Pharmacokinetic Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder* with Thomas J. Spencer at Massachusetts General Hospital.
- Grant (1U01FD005271) *Prospective Study Comparing Brand and Generic Immunosuppression on Transplant Outcomes adherence And Immune Responses* with Suphamai Bunnapradist at University of California Los Angeles.

Active FDA Research

- *Bioequivalence (BE) of an Approved Tacrolimus Product*
- *COVID-19 Generic Drug Utilization*
- *Postmarketing Surveillance of Generic Drug Using Sentinel*
- *Utilization of Pharmacogenomics in Bioequivalence (BE) Studies for Generic Drug Development*

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Poster(s)

- Oguntimein O, Le C, Ngooi S, Chee M, Moriates C, Wallingford S, Cardin T, Weissman A, Farnan J, Samarth A, Shah N, Cook M, and Arora V. *Identifying Message to Promote Value Education (IMPROVE) of Generic Oral Contraceptive Prescribing*. Poster Presentation at the Association of Military Surgeons United States (AMSUS) 2020 Annual Meeting. Virtual Meeting, December 6, 2020.

Presentation(s)

- Jiang W. *FDA Bioequivalence Standards*. Presentation at the 2021 Pharmaceutical Outcomes Policy Seminar. Virtual Meeting, March 6, 2021.
- Wang Y. *Regulatory and Scientific Considerations on Characterizations of Complex Polymeric Excipients*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Pharmsci 360. Virtual Meeting, October 30, 2020.
- Zhao L. *Quantitative Methods and Modeling to Evaluate Alternative Approaches for COVID-19 Interrupted Bioequivalence Studies*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 9, 2020.

Quantitative Clinical Pharmacology

Summary of FY 2021 Activities

Quantitative Clinical Pharmacology (QCP) is a discipline that quantitatively describes drug disposition, drug action, and associated variability in humans. In generic drug product development and regulatory assessment, QCP approaches are used to develop clinically relevant bioequivalence (BE) criteria, design efficient BE studies, and explore alternate BE approaches to support decision making in various regulatory activities such as product-specific guidance (PSG) development, controlled correspondences, abbreviated new drug application (ANDA) consultations, pre-ANDA meetings, and citizen petition assessments.

In FY 2021, FDA continued to invest in the development of innovative QCP approaches to address BE issues for generic products that are challenging to develop and assess, such as long-acting injectable (LAI) and implantable products. Together with Uppsala University (Contract# 75F40119C10018), FDA is developing and evaluating population pharmacokinetic (PK) model-integrated BE approaches for LAI products, which will allow innovative BE study designs that can address challenges associated with long study durations. An R-package has been developed to help implement a model-integrated BE analysis for LAI products. Leveraging the FDA research in this area, a public workshop was held in collaboration with the Center for Research on Complex Generics (CRCG) to build consensus on the model-integrated evidence to demonstrate BE for complex generics, using LAI products as an example.

FDA has also continued work on the development of methodologies to address complex BE issues such as

statistical and model-based BE analysis in patient PK BE studies. Ongoing model-based BE research (Contract# 75F40119C10111) demonstrates that a model-based statistical approach may serve as an alternative to a non-compartmental approach (NCA) for patient PK studies with sparse sampling. As part of another contract (HHSF223201710015C), a user-friendly R-package has been developed, and incorporated both NCA-based and model-based BE analysis methods for situations where NCA is practically challenging, such as patient PK BE studies with sparse data. FDA is also investing the development of BE methodologies to address emerging BE issues with complex inhalation products (Contract# 75F40119C10068), where innovative QCP approaches are being applied to address the uncertainty associated with high batch-to-batch variability of certain inhalation products such as oral powder inhalation products.

FDA is dedicated to advancing BE approaches and methodologies that enhance patient access to quality generics. Research (Grant#1U01FD006549) is ongoing to develop a virtual BE trial simulation platform that integrates population PK and physiologically-based PK modeling approaches. Currently, mechanistic models describing skin absorption and inhalation of compounds have been developed and made available as an open-source platform. A clinical trial simulation tool is being developed for the platform. The ultimate goal is to leverage the integrated QCP modeling and simulation tools to generate BE evidence in silico for complex locally acting drug products and reduce/replace in vivo BE studies, improving efficiency in generic drug development and approval.

QCP approaches also allowed FDA to provide timely guidance to industry on the challenges posed by the COVID-19 pandemic such as affected clinical studies with disrupted study designs, missing samples, and expired products as well as other protocol modifications. In addition to publishing guidances, FDA interacted with industry providing specific recommendations on variations in protocols or alternative BE study designs in response to challenges posed by the public health emergency.

Development of model-integrated strategies for generic LAI products

The aim of the model-integrated BE strategies is to reduce the duration and/or sample size of BE studies, to help design more feasible BE studies for LAI products. The model-integrated approaches (**Figure 1**) proposed for BE analysis of LAI products directly apply modeling and simulation in the BE analysis procedure. First, BE data from a multiple-dose crossover switch study or a single dose parallel study are analyzed using a previously developed PK model with treatment effects on all absorption parameters. From the resulting estimates, along with their uncertainty, researchers can perform population simulations of a single-dose crossover BE study, the standard design for BE trials, without any covariate effects. Across all population simulations, 90% confidence intervals of the geometric mean of metrics of interest can be calculated and used for a final BE conclusion. The described model-integrated BE analysis method has been shown to have acceptable Type 1 error and higher power than an NCA-based method in sparse sampling scenarios (**Figure 2**). The advantages of using the model-integrated approach includes that it allows higher power while handling differences in the rate and extent of absorption with controlled Type 1 error. In addition, this approach can account for uncertainties related to model structure and parameters. Predefining models may be challenging but can be done, and the analysis may be not as simple as a traditional NCA approach. Overall, the outcome of this research can support innovative BE study designs to facilitate the development of LAI products (Contract 75F40119C10018).

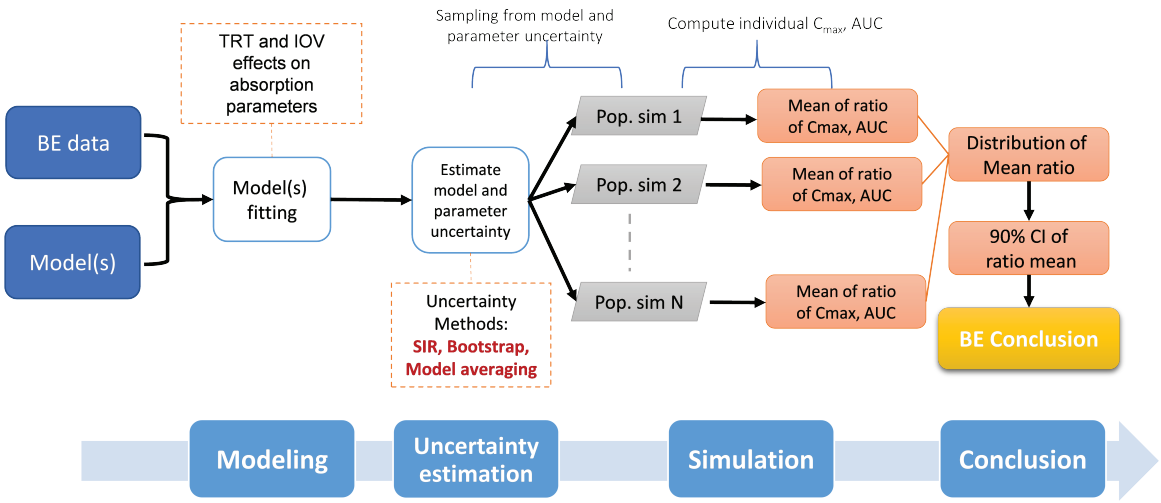

Figure 1: Schematic of a model-integrated approach to demonstrating BE
This scheme illustrates the work flow of model-integrated BE methods. The process involves model fitting of candidate models to data, parameter and model uncertainty estimation, simulations of populations, computations of BE metrics (AUC and Cmax) in those simulated populations, and a conclusion about BE based on the distribution of those BE metrics. Abbreviations: TRT (treatment), IOV (inter-occasion variability), SIR (sampling importance resampling), Pop. sim (population simulation), Cmax (maximum concentration), AUC (area under the curve), CI (confidence interval), BE (bioequivalence).

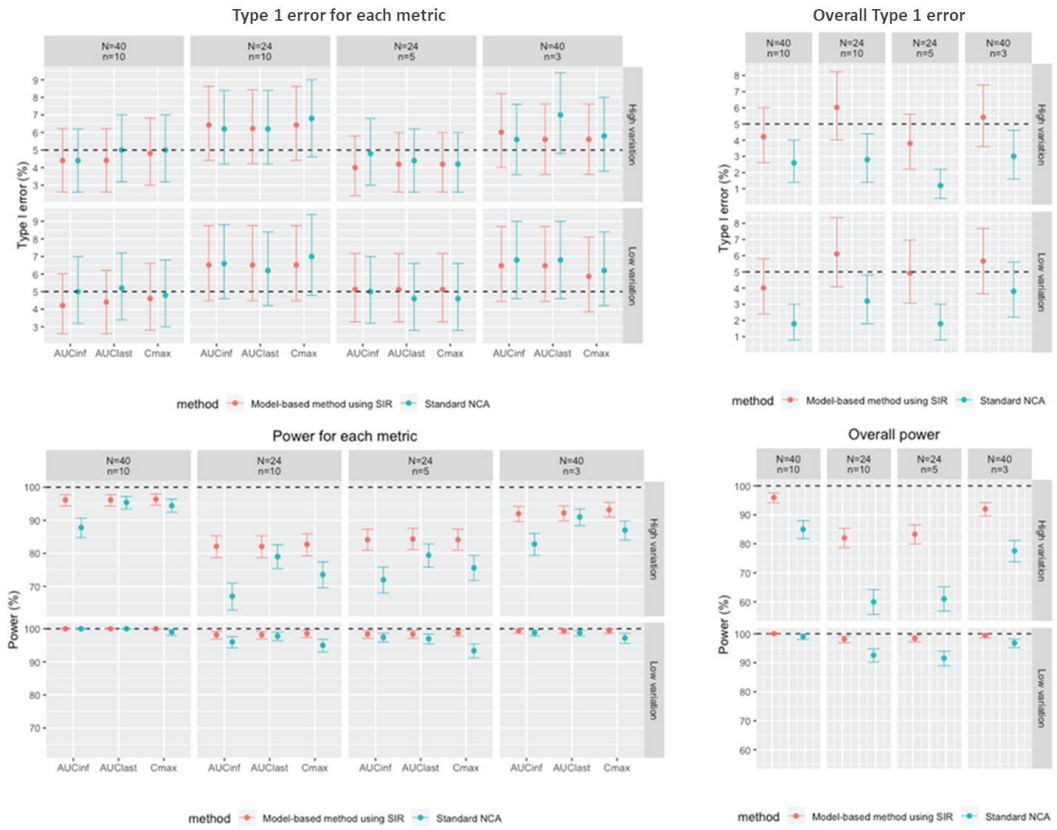

Figure 2: Control of Type 1 error (upper two panels) and achievement of higher power compared to NCA-based method exemplified with one type of model-integrated bioequivalence approach (bottom two panels). In this example, the model for the reference product is assumed to be known. Model components are added that estimate treatment differences and inter-occasion variability on all absorption parameters (including relative bioavailability between the reference and test product). Model parameter uncertainty is estimated using sampling importance resampling (SIR). Data was simulated with lower and higher variation (relatively low and high inter-individual and residual variation), with study designs that ranged from rich (many individuals, N, and many samples per individual, n) to sparse (few individuals and samples), and with bioequivalent products or not. The power to identify bioequivalent products is seen to be larger for the model-integrated approach especially in cases with high variation. The Type 1 error is controlled for both the NCA-based and model-integrated approaches for each metric separately (AUC_{inf}, AUC_{last} and C_{max}). The overall Type 1 error (rejecting all three tests) is lower than expected for the NCA-based methods due to multiple testing, while the model-integrated method maintains the expected 5% error rate.

New Grant(s) and Contract(s)

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

Continuing Grant(s) and Contract(s)

- 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 (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).

Completed Grant(s) and Contract(s)

- Contract (75F40119C10068) *Batch-to-Batch Variability: Exploring Solutions for Generic BE Pathway* with Joga Gobburu at University of Maryland.
- Contract (75F40119C10018) *Development of Model-Informed Bioequivalence Evaluation Strategies for Long-Acting Injectable Products* with Mats O. Karlsson at Uppsala University
- Contract (223201710015C) *Evaluation and Development of Model-Based Bioequivalence Analysis Strategies* with Andrew Hooker at Uppsala University.
- Contract (223201810112C) *Research Proposal to Better Understand Risk Mitigation in the Evaluation of Relative Bioavailability of Pediatric Generic Products* with Hannah Batchelor at University of Birmingham, UK.

Active FDA Research

- *Assessment of Variability and Dose Sensitivity of Forced Expiratory Volume (FEV1) in Comparative Clinical Endpoint Bioequivalence (BE) Studies of Orally Inhaled Drug Products (OIDPS)*
- *Clinical Trial Simulation for Clinical Endpoint Bioequivalence (BE) Studies*
- *Improve Bioequivalence (BE) Analysis for Narrow Therapeutic Index (NTI) Drugs*
- *Model-Based Adaptive Learning Design in Bioequivalence (BE) Assessments*
- *Model-Based Assessment on Bioequivalence (BE) Limits for Anticoagulants*
- *New Approaches to Identify Clinically Relevant Partial AUC (pAUC) Measures for Bioequivalence (BE)*
- *Quantitative Clinical Pharmacology Modeling and Simulation-Based*

Supports for Bioequivalence (BE) Assessment During the COVID-19 Public Health Emergency

- *Topical Dermatological Corticosteroid Dose Selection Using Model-Based Approach*

Product-Specific Guidance(s) (PSG)

There were eight new and three revised PSGs published in FY 2021 related to quantitative clinical pharmacology. These PSGs were directly impacted by GDUFA-funded research in this area.

- *New Draft Guidance for Calcifediol Oral Capsule, Extended Release*. (March 2021) Link to Posting.
- *New Draft Guidance for Estradiol Transdermal Gel, Metered*. (August 2021) Link to Posting.
- *Revised Draft Guidance for Leuprolide Acetate for Intramuscular Injection*. (August 2021) Link to Posting.
- *New Draft Guidance for Leuprolide Acetate for Subcutaneous Injection*. (August 2021) Link to Posting.
- *Revised Draft Guidance for Liothyronine Sodium Tablet*. (August 2021) Link to Posting.
- *New Draft Guidance for Midazolam Spray, Nasal*. (May 2021) Link to Posting.
- *New Draft Guidance for Naloxone Hydrochloride; Oxycodone Hydrochloride Oral Tablet, Extended Release*. (November 2020) Link to Posting.
- *Revised Draft Guidance for Orlistat Capsule*. (August 2021) Link to Posting.
- *New Draft Guidance for Paliperidone Palmitate Suspension, Extended Release*. (August 2021) Link to Posting.
- *New Draft Guidance for Quinidine Gluconate Oral Tablet, Extended Release*. (May 2021) Link to Posting.
- *New Draft Guidance for Sufentanil Citrate Tablet, Sublingual*. (August 2021) Link to Posting.

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- Lee J, Gong Y, Bhoopathy S, Diliberti C, Hooker A, Rostami-Hodjegan A, Schmidt S, Suarez-Sharp S, Lukacova V, Fang L, and Zhao L. *Public Workshop Summary Report on FY 2021 Generic Drug Regulatory Science Initiatives: Data Analysis and Model-Based Bioequivalence*. Clinical Pharmacology & Therapeutics. (2021) 110(5): 1190-1195. doi: https://doi.org/10.1002/cpt.2120. PMID: 33236362.
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Poster(s)

- Alam K, Sharan S, Fang L, Jiang W, Kim M, Zhao L, Zhang L, and Lionberger R. *Assessing Whether Partial AUCs are Needed to Demonstrate Bioequivalence for Liposomal Doxorubicin*. Poster Presentation at the 2020 American College of Clinical Pharmacy (ACCP) Annual Meeting. Virtual Meeting, October 24, 2020.
- Gong Y, Feng K, Lee J, Pan Y, Bai T, Li B, Kim C, Yoon M, Zhang P, Fang L, and Zhao L. *Quantitative Modeling and Simulation to Evaluate Alternative Approaches to be Used in COVID-19 Interrupted Bioequivalence Studies*. Poster Presentation at the American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2021. Virtual Meeting, March 9, 2021.
- Guhl M, Mercier F, Sharan S, Feng K, Sun G, Sun W, Grosser S, Zhao L, Fang L, Mentré F, Comets E, and Bertrand J. *Model-Based Tests of Bioequivalence: Impact of a Model Misspecification*. Poster Presentation at the 42nd Annual Conference of the International Society for Clinical Biostatistics (ISCB) 2021. Virtual Meeting, July 19, 2021.
- Guhl M, Mercier F, Sharan S, Donnelly M, Feng K, Sun G, Sun W, Grosser S, Zhao L, Fang L, Mentré F, Comets E, and Bertrand J. *Model-Based Tests of Bioequivalence: Impact of a Model Misspecification*. Poster Presentation at the Population Approach Group Europe (PAGE) 2021 Annual Meeting. Virtual Meeting, September 7, 2021.
- Lee J, Feng K, Xu M, Gong X, Sun W, Kim J, Zhang Z, Wang M, Fang L, and Zhao L. *Applications of Adaptive Designs in Generic Drug Development*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 9, 2021 .
- Tardivon C, Loingeville F, Sharan S, Donnelly M, Feng K, Sun W, Sun G, Grosser S, Zhao L, Fang L, Mentre F, and Bertrand J. *Evaluation of Model-Based Bioequivalence Approach for One Single Sample Pharmacokinetic Studies*. Poster Presentation at the Population Approach Group Europe (PAGE) 2021 Annual Meeting. Virtual Meeting, September 2, 2021.
- Wu F, Das S, Fang L, and Polli J. *Using Partial AUC to Characterize the Impact of Shape of Pharmacokinetic Profiles on Bioequivalence Evaluation*. Poster Presentation at the American Society for Clinical Pharmacology Therapeutics (ASCPT) 2021. Virtual Meeting, March 12, 2021.

Presentation(s)

- Feng K. *Applications and Lessons Learned for Conducting Adaptive Designs in Generic Drug Development*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Gong Y. *Alternative Bioequivalence Approaches for Data Analysis Due to COVID-19 Related Study Interruptions*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 21, 2021.
- Ince I, and Dallmann A. *Predictive Performance of PBPK Dose Estimates for Pediatric Trials*. Presentation at the Center of Excellence in Regulatory Science and Innovation (M-CERSI) "Pediatric Dose Selection" Virtual Conference. Virtual Meeting, October 22, 2020.
- Lee J. *Quantitative Methods and Modeling to Support Bioequivalence Evaluation of Orally Inhaled and Nasal Drug Products (OINDPs)*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Sharan S. *Long-Acting Complex Generic Drug Products with Nanotechnology*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.
- Yoon M. *Model-Integrated Evidence for BE Assessment of Complex Generic Drugs*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Zhao L. *Quantitative Methods and Modeling to Evaluate Alternative Approaches for COVID-19 Interrupted Bioequivalence Studies*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 9, 2020.
- Zhao L. *Application of Quantitative Clinical Pharmacology in the Development of Long-Acting Injectable (LAI) Drug Products*. Presentation at the Product Quality Research Institute (PQRI) 2021 Webinar. Virtual Meeting, April 8, 2021.

Topical Dermatological Products

Summary of FY 2021 Activities

During FY 2021, FDA's Generic Drug User Fee Amendments (GDUFA)-funded research continued to support the development of efficient bioequivalence (BE) approaches for topical dermatological drug products, as part of an effort to facilitate generic drug development and enhance patient access to these topical products.

One goal of this program is to aid in the development of generic products that are essentially identical to the reference products. During FY 2021, studies at the University of Mississippi (Grant# 1U01FD005233), the University of South Australia (Grant# 1U01FD005226), the University of Maryland (Baltimore) (Grant# 1U01FD004947), and FDA laboratories (see **Research Highlight**) supported the expansion of characterization-based BE approaches to a majority of topical dermatological products. Related research at the University of Rhode Island (Grant# 1U01FD006721) made advances toward the development of similar characterization-based BE approaches for vaginal and rectal products.

Additionally, FDA sought to understand the mechanisms that allow T and R topical products to be clinically bioequivalent when they are not the same, but are similar in components, composition, and/or Q3 attributes (analogous to the similarity of pre-change and post-change R products that undergo post-approval changes, for example). To elucidate these mechanisms, in vitro experiments and in silico modeling and simulation were performed through FDA internal research and the

Agency's collaborations with the University of South Australia (Grant# 1U01FD006496) and the University of Mississippi (Grant# 1U01FD006507). These independent research collaborations sought to understand how compositional changes of inactive ingredients in a topical formulation can change the thermodynamic activity of the drug; how the changing the formulation of the dosage form can modulate that thermodynamic activity; and the resulting influence on the rate and extent to which the drug is delivered and becomes available in the skin. Additionally, a research collaboration with the University of Queensland (Grant# 1U01FD006700) studied how specific Q3 attributes of topical dermatological products may be perceived by human subjects.

Another goal was to develop efficient BE approaches for topical dermatological products to explore the development of efficient PK-based methods to directly monitor the rate and extent of a drug's bioavailability at or near its site(s) of action in the skin. During FY 2021, in vivo BE studies in human subjects were successfully performed at Joanneum Research (Grant# 1U01FD005861) using dermal open flow microperfusion (dOFM) for diclofenac gel and solution products. A new research project was initiated at Long Island University (Grant# 1U01FD006930) to elucidate how PK principles should be applied or adapted when evaluating the rate and extent to which a topically applied compound becomes available in the dermis. Independently, University of Bath (Grant# 1U01FD006533) and Massachusetts General Hospital/Harvard Medical School (Grant# 1U01FD006698) have been developing non-invasive cutaneous PK-based methods using advanced confocal Raman imaging techniques.

Two new grants were also awarded during FY 2021 to Certara UK, LTD (1U01FD007323) and Simulations Plus, Inc. (1U01FD007320) to enhance mechanistic physiologically based pharmacokinetic (PBPK) models for dermatological drug products to predict the absorption of active ingredients through the skin. For more information on the newly awarded grants, refer to the FY 2021 GDUFA Science and Research Report: Locally Acting Physiologically-Based Pharmacokinetic Modeling.

Incorporating porous microparticles in topical drug products may offer many advantages such as controlled release of the active ingredient, improved efficacy, decreased irritation, and prolonged stability, among others. Porous microparticles are spherical, solid, water-insoluble, particles with a network of interconnected pores that open on the particle surface and allow for free diffusion of the active ingredient within the microparticle and into the dosage form (**Figure 1**). However, incorporation of microparticles within topical drug products results in unique complexities in the microstructure. Physicochemical and structural properties of a topical drug product may depend on the methodologies used for manufacturing the microparticles, drug loading, and processing parameters of incorporating microparticles into the drug product. FDA laboratories developed tools that may be utilized for characterization of these complex dosage forms to support demonstration of BE.

Tretinoin topical gels containing microparticles were manufactured using various materials and different process parameters. The drug loaded microparticles were characterized using advanced imaging techniques (Raman-in-SEM SCA: Raman spectroscopy-in-scanning electron microscopy structural and chemical analyzers) to assess the impact of manufacturing processes on the distribution of drug within the microparticles and to understand the surface morphology. The molecular interactions between tretinoin and the microparticles were also characterized using X-Ray diffractometry (XRD), differential scanning calorimetry (DSC), and Fourier transform infrared (FTIR) spectroscopy. The gels were further characterized to evaluate the particle size distribution, rheology, and drug release of tretinoin from the microparticle containing tretinoin topical gels. The imaging data demonstrated that tretinoin was predominantly located at the outer periphery of the in-house tretinoin loaded microparticles compared to the inside core (**Figure 2A**). The interaction study indicated that tretinoin is molecularly dispersed within the pore structure of the microspheres and interacted with the acrylate matrix of microspheres via hydrogen bonding. The release profiles of tretinoin indicated that drug release from the gel was controlled predominantly by the physicochemical and structural properties of the microparticles with minimal contribution of the gel matrix. An increase in the tretinoin release rate was observed with an increase in the nominal drug loading ($p < 0.05$) of the microparticles. The drug release data were utilized to understand the impact of differences in manufacturing processes, and corresponding differences in the physicochemical and structural properties of topical gels, on drug release and thereby bioavailability of tretinoin from these complex dosage forms.

The study also assessed the proportionality of tretinoin release rates across various strengths of tretinoin topical gels manufactured using different methods. Retin-A Micro® topical gel is prepared with porous microparticles and is marketed in four strengths, 0.1%, 0.08%, 0.06% and 0.04%. To develop generic products of these four strengths, the gels may be manufactured by: i) incorporation of different amounts of microparticles loaded with a given concentration of tretinoin, or ii) incorporation of a fixed amount of microparticles loaded with different concentrations of tretinoin. The results from the study indicated that the release of tretinoin from porous microparticle containing tretinoin topical gels were proportional to the nominal strength across various strengths, when

manufactured using the two different methods (**Figure 2B**). However, the physicochemical and structural properties of these gels were different depending on the manufacturing process. These results indicated that an adequate understanding of the impact of the manufacturing processes on the quality and performance of the drug product is important for development of microparticle containing tretinoin topical gels.

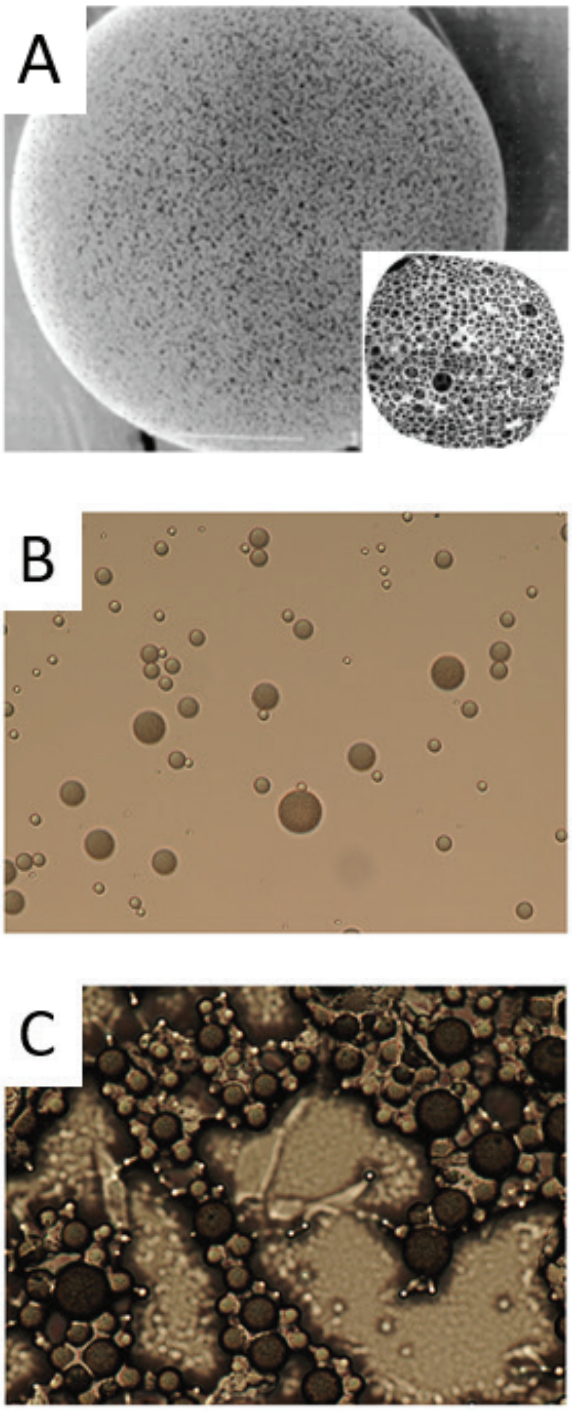

Figure 1: (A) Cartoon and scanning electron microscopy (SEM) images, (B) polarized light optical images of the porous microparticles, and (C) polarized light optical images of tretinoin gel containing microparticles.

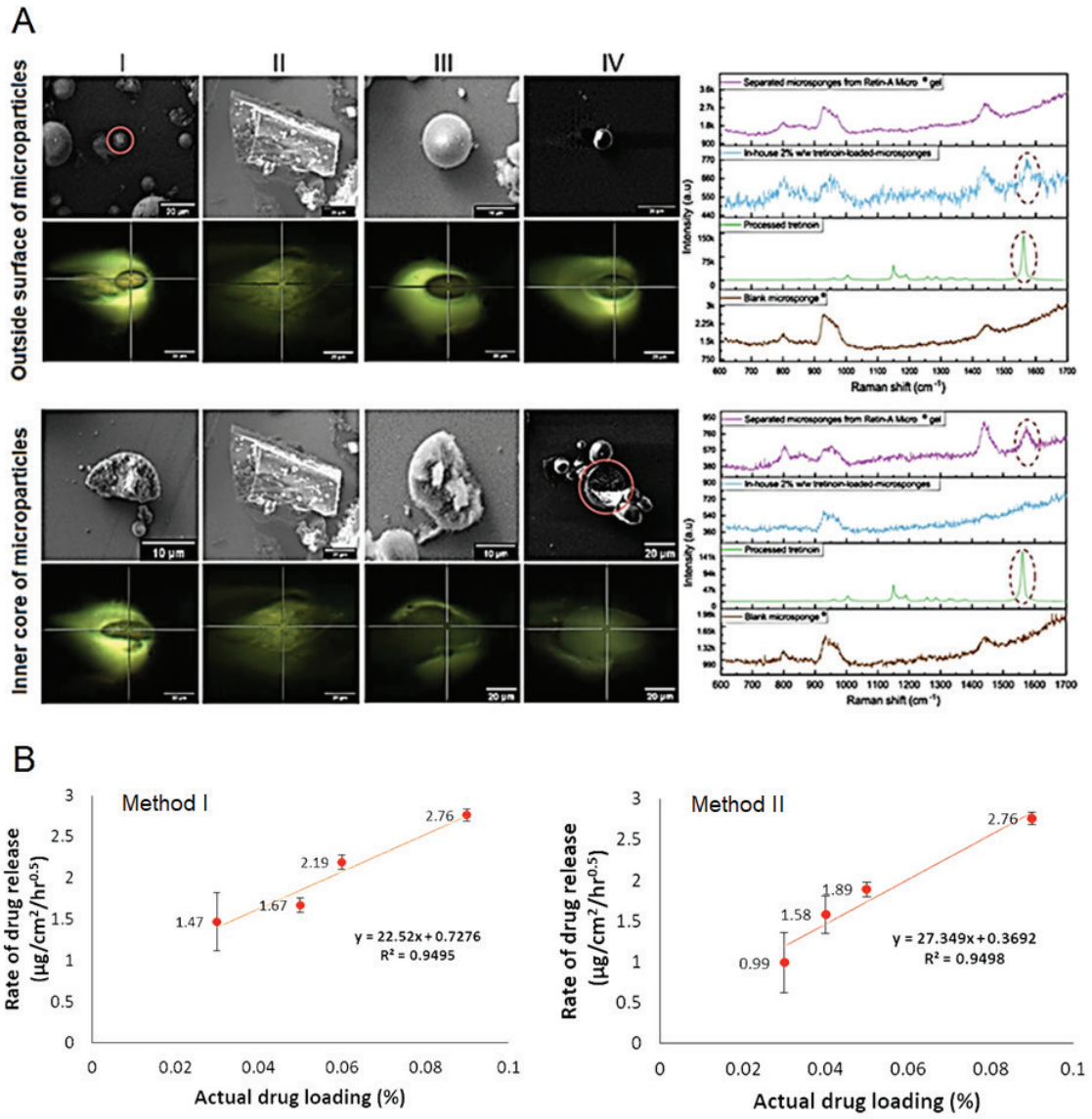

Figure 2: (A) Raman-in-SEM SCA data of microparticles at the surface and inside of sliced microparticles. Columns I, II, III and IV show SEM and corresponding SCA images of blank microparticles, tretinoin powder, 2% drug loaded microparticles and separated microparticles from gel, respectively, in intact and sliced forms. The top and bottom spectra show the Raman analysis of intact and sliced microparticles, respectively. The peak of tretinoin at ~1561-1590 cm^{-1} is shown in red dotted ellipse. (B) Proportional release of tretinoin from tretinoin (porous microparticle-based) topical gels, 0.1%, 0.08%, 0.06% and 0.04% manufactured using Method I (left) and Method II (right). Data are shown as mean ± SD (n=6).

New Grant(s) and Contract(s)

- Grant (1U01FD007320) *Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and Physiologically-Based Pharmacokinetic Simulation* with Jessica Rose Spires at University of Simulations Plus, Inc.
- Grant (1U01FD007323) *Progressing Integration of In Vitro Topical Formulation Characterization, Release and Permeation Data to the Next Level-PBPK Based Extrapolation to Bioequivalence Assessment in Virtual Populations* with Sebastian Polak at Certara UK, LTD.

Continuing Grant(s) and Contract(s)

- Grant (1U01FD006533) *Assessing the Skin Pharmacokinetics of Topical Drugs, and the Bio(in) equivalence of Topical Drug Products, Using Non-Invasive* with Richard H. Guy at University of Bath.
- Grant (1U01FD006721) *Bioequivalence Considerations of Topical Rectal and Vaginal Suppositories* with Jie Shen at University of Rhode Island.
- Grant (1U01FD006496) *Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations* with Michael Roberts at University of South Australia.
- Grant (1U01FD006521) *Characterization of Key System Parameters of Mechanistic Dermal PBPK Models in Various Skin Diseases and Performance Verification of the Model Using Observed Local and Systemic Concentrations* with Sebastian Polak at Simcyp, LTD.
- Grant (1U01FD006930) *Elucidating Fundamental Principles of Dermal Pharmacokinetics via Microdialysis* with Grazia Stagni at Long Island University, Brooklyn Campus.
- Grant (1U01FD006700) *Elucidating the Sensorial and Functional Characteristics of Compositionally Different Topical Formulations* with Yousuf Hussain Mohammed at University of Queensland.
- Grant (1U01FD006507) *Impact of Formulation Composition on the Structure and Performance Attributes of Topical Products* with Sathyanarayana N Murthy at University of Mississippi.
- Grant (1U01FD006698) *Pharmacokinetic Tomography for the Measurement of Topical Drug Product Bioequivalence* with Conor Lee Evans at Massachusetts General Hospital/ Harvard Medical School.

Completed Grant(s) and Contract(s)

- Grant (1U01FD005861) D*evelopment of a Universal Bioequivalence Test Method for Topical Drugs Using dOFM* with Frank Sinner at Joanneum Research.
- Grant (1U01FD004947) *Bioequivalence of Topical Drug Products: In Vitro-In Vivo Correlations* with Audra L Stinchcomb at University of Maryland.
- Grant (1U01FD005226) *Characterization of Critical Quality Attributes for Semisolid Topical Drug Products* with Michael Roberts at University of South Australia.
- Grant (1U01FD006522) *Formulation Drug Product Quality Attributes in Dermal Physiologically-Based Pharmacokinetic Models for Topical Dermatological Drug Products and Transdermal Delivery Systems* with Michael Roberts at University of Queensland.
- Grant (1U01FD006526) *Assessment of Transdermal Drug Product Quality and Performance Attributes via Enhanced Virtual Bioequivalence Simulations* with Jessica Spires at Simulations Plus, Inc.

Active FDA Research

- *Computational Fluid Dynamics (CFD) Analysis of Spreadability of Topical Formulations*
- *Development of a Novel Bio-Relevant In Vitro Skin Permeation Test (IVPT) for Hydrophobic Drugs using In-Line Flow Through Diffusion Cells (FTC)*
- *Topical Dermatological Corticosteroids Dose Selection Using Model-Based Approach*

Product-Specific Guidance(s) (PSG)

There were four new and four revised PSGs published in FY 2021 related to topical dermatological products. These PSGs were directly impacted by GDUFA-funded research in this area.

- *Revised Draft Guidance for Budesonide Rectal Aerosol Foam*. (November 2020) Link to Posting.
- *New Draft Guidance for Estradiol Transdermal Gel, Metered*. (August 2021) Link to Posting.
- *New Draft Guidance for Ethinyl Estradiol; Levonorgestrel Transdermal System*. (August 2021) Link to Posting.
- *Revised Draft Guidance for Hydrocortisone Acetate Rectal Aerosol Foam, Metered*. (November 2020) Link to Posting.
- *New Draft Guidance for Indomethacin Rectal Suppository*. (August 2021) Link to Posting.
- *Revised Draft Guidance for Nystatin Powder*. (August 2021) Link to Posting.
- *Revised Draft Guidance for Tazarotene Topical Cream*. (August 2021) Link to Posting.
- *New Draft Guidance for Trifarotene Topical Cream*. (May 2021) Link to Posting.

Article(s)

- Evans C, Hermsmeier M, Yamamoto A, and Chan K. *Visualizing Topical Drug Uptake with Conventional Fluorescence Microscopy and Deep Learning*. Biomedical Optics Express. (2020) 11(12): 6864-6880. doi: https://doi.org/10.1364/BOE.405502. PMID: 33408967.
- Kuzma B, Senemar S, Ramezanli T, Ghosh P, Raney S, and Stagni G. *Evaluation of Local Bioavailability of Metronidazole from Topical Formulations Using Dermal Microdialysis: Preliminary Study in a Yucatan Mini-Pig Model*. European Journal of Pharmaceutical Sciences. (2021) 159: Article 105741. doi: https://doi.org/10.1016/j.ejps.2021.105741. PMID: 33540039.
- Liu X, Anissimov YG, Grice JE, Cheruvu HS, Ghosh P, Raney SG, Maibach HI, and Roberts MS. *Relating Transdermal Delivery Plasma Pharmacokinetics with In Vitro Permeation Test (IVPT) Findings Using Diffusion and Compartment-in-Series Models*. J Control Release. 2021 (334): 37-51. doi: https://doi.org/10.1016/j.jconrel.2021.04.010. PMID: 33857564.
- Shin S, Rantou E, Raney S, Ghosh P, Hassan H, and Stinchcomb A. *Cutaneous Pharmacokinetics of Acyclovir Cream 5% Products: Evaluating Bioequivalence with an In Vitro Permeation Test and an Adaptation of Scaled Average Bioequivalence*. Pharmaceutical Research. (2020) 37(10): Article 210. doi: https://doi.org/10.1007/s11095-020-02821-z. PMID: 33001286.
- Tsakalozou E, Babiskin A, and Zhao L. *Physiologically-Based Pharmacokinetic Modeling to*

Support Bioequivalence and Approval of Generic Products: A Case for Diclofenac Sodium Topical Gel, 1%. CPT: Pharmacometrics & Systems Pharmacology. (2021) 10(5): 399-411. doi: https://doi.org/10.1002/psp4.12600. PMID: 33547863.

- Tsakalozou E, Alam K, Babiskin A, and Zhao L. *Physiologically-Based Pharmacokinetic Modeling to Support Determination of Bioequivalence for Dermatological Drug Products: Scientific and Regulatory Considerations*. Clinical Pharmacology & Therapeutics. (2021) July 29. Online ahead of Print. doi: https://doi.org/10.1002/cpt.2356. PMID: 34231211.

Poster(s)

- Ajjarapu S, Rangappa S, Ghosh P, Kelchen M, Raney S, Urena-Benavides E, Maibach H, and Narasimha-Murthy S. *A Mechanistic Evaluation of How Metamorphosis of a Topical Dosage Form Impacts Permeation*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Ajjarapu S, Rangappa S, Ghosh P, Kelchen M, Raney S, Urena-Benavides E, Maibach H, and Narasimha Murthy S. *A Mechanistic Evaluation of the Impact of Formulation Viscosity and Fractional Solubility on Drug Release and Permeation*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Arora S, Polak S, Jamei M, Tsakalozou E, Ghosh P, Alam K, Liu X, Namjoshi S, Grice J, Mohammed Y, and Roberts M. *Integrating Drug Product Quality Attributes in a Bottom-up Physiologically Based Pharmacokinetic (PBPK) Model to Simulate In Vitro Skin Permeation of Acyclovir Commercial Formulations*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Bolla P, Hamad G, Jiang Y, Ramezanli T, Ghosh P, and Raney S. *Feasibility of In Vitro Permeation Testing for Cleocin T® (Clindamycin Phosphate) Topical Lotion to Support the Demonstration of Bioequivalence*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Bolla P, Hamad G, Jiang Y, Ramezanli T, Ghosh P, and Raney S. *Feasibility of In Vitro Permeation Testing for Cleocin T® (Clindamycin Phosphate) Topical Lotion to Support a Demonstration of Bioequivalence*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Hamad G, Niu M, Ghosh P, Ramezanli T, Raney S, Ashraf M, and Zidan A. *Interaction Studies of Tretinoin with Microspheres in Tretinoin Topical Gel*. Poster Presentation at the American

Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.

- Hamad G, Niu M, Ghosh P, Ramezanli T, Raney S, Ashraf M, and Zidan A. *Preparation, Characterization and In Vitro Release Test (IVRT) Study of Tretinoin-Loaded Microspheres in a Topical Gel Product*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Hamad G, Niu M, Ghosh P, Ramezanli T, Raney S, Ashraf M, and Zidan A. *Interaction Studies of Tretinoin with Microspheres in Tretinoin Topical Gel*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Hamad G, Bolla P, Kelchen M, Ghosh P, Ramezanli T, Raney S, Ashraf M, and Zidan A. *A Mechanistic Evaluation of Drug Availability from Imvexxy® (Estradiol) Vaginal Inserts*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Hamad G, Willett D, Yilmaz H, Ahmed S, Niu MM, Bolla P, Ghosh P, Ramezanli T, Raney S, Ashraf M, Zidan A. *Investigating the Relationship Between Tretinoin Distribution in Microsponges and Release Mechanism Using In-SEM Raman Spectroscopy*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Haq A, Chandler M, and Michniak-Kohn B. *Solubility-Physicochemical-Thermodynamic Theory of Penetration Enhancer Mechanism of Action*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Jiang Y, Simamora M, Ramezanli T, and Raney S. *Factors Influencing Transepidermal Water Loss Measurements Used to Test Skin Barrier Integrity In Vitro: A Literature Review*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Mohammed Y, Namjoshi S, Dabbaghi M, Ramezanli T, Raney S, Grice J, and Roberts M. *Scanning Electron Micrographic Structural Characterization of Microsponge Gel Products*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Mohammed Y, Namjoshi S, Silva L, Dabbaghi M, Ramezanli T, Raney S, Grice J, Chen T, Lian G, and Roberts M. *Experimental Measurements and Mathematical Modelling of Volatile Loss from Binary Solvent Systems*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Mohammed Y, Namjoshi S, Dabbaghi M, Ramezanli T, Raney S, Jiang Y, Grice J, and Roberts M. *Microstructural Characterization of Microsponge-Based Gel Products Using CryoSEM*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.

- Ramezanli T, Jiang Y, Ghosh P, Dabbaghi M, Tiffner K, Mohammed Y, Namjoshi S, Birngruber T, Bodenlenz M, Roberts M, Sinner F, and Raney S. *Correlation of Physico-Structural (Q3) Properties of Lidocaine/Prilocaine Topical Products with Product Performance In Vitro and In Vivo*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Ramezanli T, Jiang Y, Dabbaghi M, Tiffner K, Mohammed Y, Namjoshi S, Birngruber T, Bodenlenz M, Raney S G, Roberts M, and Sinner F. *Correlation of Physical and Structural (Q3) Properties of Lidocaine/Prilocaine Topical Products with Product Performance In Vitro and In Vivo*. Poster Presentation at the FDA Science Forum. Virtual Meeting, May 26, 2021.
- Rangappa S, Ajjarapu S, Ghosh P, Kelchen M, Raney S, Repka M, Maibach H, and Narasimha Murthy S. *Comparative Evaluation of the Permeation of Metronidazole Using Static Diffusion Cells and Flow-through Diffusion Cells*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Rangappa S, Ajjarapu S, Ghosh P, Kelchen M, Raney S, Repka M, Maibach H, and Narasimha Murthy S. *Critical Quality Attributes of Topical Clobetasol Propionate Foams*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Tiffner K, Ramezanli T, Birngruber T, Bodenlenz M, Lackner B, Raml R, Schwagerle G, Kainz S, Gander E, Raney S, and Sinner F. *A Clinical Study to Assess the Bioequivalence of Lidocaine and Prilocaine Topical Drug Products Using Dermal Open Flow Microperfusion*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Tsakalozou E, Alam K, Babiskin A, Fang L, and Zhao L. *Development of a Dermal PBPK Modeling for an Ethinyl Estradiol-Containing Transdermal Delivery System*. Poster Presentation at the American Society for Clinical Pharmacology & Therapeutics (ASCPT) 2021. Virtual Meeting, March 12, 2021.
- Tsakalozou E, Alam K, Babiskin A, and Zhao L. *PBPK modeling of Percutaneous Pharmacokinetics for Tazarotene and Tretinoin Creams: Applicability and Challenges*. Poster Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, September 29, 2021.
- Varadarajan A, Ajjarapu S, Rangappa S, Ghosh P, Raney S, Repka M, Narasimha Murthy S, and Kundu S. *Rheological Characterization of Topical Clobetasol Propionate Foams*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Vitry P, Tabosa A, Belsey N, Tsikritsis D, Woodman T, Bunge A, Delgado-Charro M, and Guy R. *Assessing Topical Drug Clearance from the Skin Using Raman*

Spectroscopy. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.

- Vitry P, Tabosa A, Belsey N, Tsikritsis D, Woodman T, Bunge A, Delgado-Charro M, and Guy R. *Assessing Topical Drug Penetration into the Skin Using Raman Spectroscopy*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Xie L, Kelchen M, Ghosh P, Raney S, and Shen J. *Development of an In Vitro Release Testing Method for Rectal Suppositories*. Poster Presentation at the American Association of Pharmaceutical Scientists (AAPS) 2020. Virtual Meeting, October 26, 2020.
- Xie LX, Yue WZ, Kelchen M, Ghosh P, Niu MM, Raney S, and Shen J. *Impact of Material Attributes on In Vitro Release Characteristics of Rectal Suppositories*. Poster Presentation at the Controlled Release Society (CRS) 2021 Annual Meeting. Virtual Meeting, July 25, 2021.
- Zarmpi P, Maciel-Tabosa M, Vitry P, Belsey N, Vorng J, Tsikritsis D, Woodman T, White K, Bunge A, Delgado-Charro M, and Guy R. *Correlative Raman and Mass Spectroscopic Imaging to Quantify Drug Delivery into the Skin*. Poster Presentation at the 2021 Academy of Pharmaceutical Science UK meeting. Virtual Meeting, September 7, 2021.

Presentation(s)

- Ajjarapu S. *Impact of Fractional Solubility on Drug Permeation from Topical Formulations*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) PharmSci 360. Virtual Meeting, November 4, 2020.
- Ajjarapu S. *Influence of Metamorphosis on the Performance of Topical Formulations*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Community. Virtual Meeting, March 26, 2021.
- Alam K. *Research Overview and Regulatory Experience on Mechanistic Modeling for Generic Dermatological Drug 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, September 30, 2021.
- Alam K, and Tsakalozou E. *Challenges and Considerations with Model-Based Virtual Bioequivalence Assessments for Generic Dermatological Products, Part 2*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.

- Arora S. *Integrating Topical Drug Product Quality Attributes Within Physiologically-Based Pharmacokinetic Models*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) PharmSci 360 Webinar. Virtual Meeting, October 24, 2020.
- Arora S. *Modeling Dermal Drug Absorption from Complex Semisolid Formulations: Insights from Multi-Phase, Multi-Layer MechDermA Model*. Presentation at the the American Association of Pharmaceutical Scientists (AAPS) Topical and Transdermal Community. Virtual Meeting, February 26, 2021.
- Belsey N. *Imaging Formulated Product Performance Using Optical Spectroscopy*. Presentation at the UK Surface Analysis Forum (UKSAF) Meeting. Virtual Meeting, January 5, 2021.
- Evans C. *Imaging and Quantifying Topical Drug Uptake in Human Tissue*. Presentation at the Society of Photo-Optical Instrumentation Engineers (SPIE) Photonics West 2021. Virtual Meeting, March 6, 2021.
- Evans C. *Multiphoton Chemical Imaging to Assess Dermal Pharmacokinetics and Pharmacodynamics*. Presentation at the Society of Photo-Optical Instrumentation Engineers (SPIE) Photonics West 2021. Virtual Meeting, March 6, 2021.
- Evans C. *SRS Pharmacokinetic Tomography*. Presentation at the Great Scientific Exchange (SCIX) 2021. Virtual Meeting, September 26, 2021.
- Ghosh P. *Evaluation of Cutaneous Pharmacokinetics the Past, the Present, and the Future*. Presentation at the Society of Photo-Optical Instrumentation Engineers (SPIE) Photonics West 2021. Virtual Meeting, March 6, 2021.
- Ghosh P. *Panel Discussion: IVPT Data Challenges and Statistical Analysis*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Ghosh P. *Theoretical Principles and Best Practices In Vitro Permeation Testing (IVPT)*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Ghosh P. *Advanced Technologies and Evolving Paradigms: Characterization of Topical Semisolid Dosage Forms*. Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, September 29, 2021.
- Ghosh P. *Towards Building a Dermal Model for BE Assessment: The Role of Drug Product Characterization Performance Data*. 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, September 30, 2021.

- Guy R. *Prediction, Assessment and Optimisation of Drug Delivery into and through the Skin*. Presentation at the Leo Foundation Center for Cutaneous Drug Delivery. Virtual Meeting, March 1, 2021.
- Kelchen M. *An FDA Perspective on the Comparative Analyses of Critical Material, Quality, and Design Attributes for Topical, Transdermal, Rectal, and Vaginal Drug-Device Combination Products*. Presentation at the Drug Information Association (DIA)/FDA Complex Generic Drug-Device Combination Products Conference 2020. Virtual Meeting, October 19, 2020.
- Kelchen M. *"No Difference" Standard vs. Q1/Q2 Sameness for Topical Drug Products*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Kozak D. *Advanced Analytical Methods in Generic Drug Development and Approval*. Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Kuzma B. *Recent Advancements in Dermal Microdialysis to Assess Topical Bioavailability And Bioequivalence*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) Topical Transdermal Community Webinar. Virtual Meeting, April 30, 2021.
- Murthy S. *Role of Excipients in Dermal and Transdermal Delivery of Drugs*. Presentation at the Controlled Release Society (CRS) Annual Meeting. Virtual Meeting, July 25, 2021.
- Ramezanli T. *IVRT Method Development, Validation, and Transfer Theoretical Principles and Practical Challenges*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Ramezanli T. *Theoretical Principles and Best Practices In Vitro Release Testing (IVRT)*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Ramezanli T. *Development of Efficient Alternative Bioequivalence Approaches for Topical Dermatological Drug Products*. Presentation at the Innovations in Dermatological Sciences Conference. Virtual Meeting, September 29, 2021.
- Raney S. *Overview of Breakout Session on Topical Drug Products: Workshop on Complex Generic Drug Products (CGDPs)*. Presentation at the 2020 Association for Accessible Medicines (AAM): GRx+Biosims Conference. Virtual Meeting, November 10, 2020.

- Raney S. *In Vitro Permeation Test (IVPT) Fundamentals: Scientific and Practical Considerations*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Raney S. *In Vitro Release Test (IVRT) Fundamentals: Scientific and Practical Considerations*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Raney S. *Use of Q3 Characterization Tests for Topical Semisolid Drug Products*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Raney S. *Physicochemical, Structural, and Performance Characterization of Topical Semisolid Products*. Presentation at the Florida Chapter Society of Cosmetic Chemists Sunscreen Symposium 2021. Virtual Meeting, September 25, 2021.
- Rantou E. *Statistical Considerations in Assessing BE of IVPT Data*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Stinchcomb A. *IVPT Studies with Topical and Transdermal Products*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Tabosa A. *Assessing Topical Drug Bioavailability in the Skin Using Raman Spectroscopy*. Presentation at the American Association of Pharmaceutical Scientists (AAPS) PharmSci 360. Virtual Meeting, November 4, 2020.
- Tsakalozou E, and Alam K. *Challenges and Considerations with Model-Based Virtual Bioequivalence Assessments for Generic Dermatological Products, Part 1*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.
- Tsakalozou E. *Scientific and Regulatory Considerations on Dermal PBPK Modeling for Virtual Bioequivalence Assessments and Decision-Making*. 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, September 30, 2021.

- Zidan A. *Diffusion Cell Apparatus: Scientific Principles and Practical Challenges I*. Presentation at the FDA and the Center for Research on Complex Generics (CRCG) Workshop, In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions. Virtual Meeting, August 18, 2021.
- Zidan A. *Recent Research Related to Q3 Characterization of Topical Products Containing Porous Microparticles*. Presentation at the 2021 Small Business & Industry Assistance (SBIA) Workshop, Advancing Generic Drug Development: Translating Science to Approval. Virtual Meeting, September 22, 2021.

The FY 2021 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:

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