# Office of Generic Drugs

## Fiscal Year (FY) 2022 Awarded GDUFA Science and Research Contracts and Grants

Each year, in alignment with the Generic Drug User Fee Amendments (GDUFA) Reauthorization Performance Goals and Program Enhancements Fiscal Years (FYs) 2018-2022 (GDUFA II Commitment Letter), FDA develops a list of GDUFA Research Priorities and acts on them. The following new research grants and contracts were awarded by the Office of Generic Drugs (OGD) in FY 2022 and are organized based on the FY 2022 priority areas they address, and sorted alphanumerically by the FY 2022 GDUFA research priorities they address (e.g., B1, B2, B3).

The FY 2022 GDUFA research priorities are found here, and information about research grants and contracts that receive continued funding are found in annual GDUFA Science and Research Reports which summarize the research activities in each FY, describe research highlights, and provide comprehensive lists of ongoing and completed grants and contracts, as well as citing outcomes generated from the GDUFA-funded Science and Research program in each FY. Additional information on outcomes from the GDUFA Science and Research program are shared annually in separate GDUFA Science and Research Outcomes Reports.

## A - Complex Active Ingredients, Formulations, or Dosage Forms

There are several drug products with complex scientific issues that arise from the nature of their active ingredients, formulations, or dosage forms whose complexity makes it challenging to develop as generic products. To address these challenges, the GDUFA science and research program supports the development of new tools to characterize and evaluate complex products.

During FY 2022, OGD awarded continued funding to multiple ongoing research projects in this area, and additionally funded one new grant and two new contracts to advance these priority initiatives.

1. **Multidimensional Analytical and Computational Approach to Determine Diastereomer Compositions in Oligonucleotide Drug Products (U01FD007651)**

   A grant awarded to the University of Maryland, Baltimore focuses on developing and validating a sensitive and reproducible method/approach to analyze the diastereomeric composition of an FDA-approved phosphorothioate oligonucleotide drug, TEGSEDI (inotersen) or SPINRAZA (nusinersen), to assess the potential batch-to-batch variability in diastereomeric composition for the reference listed drug (RLD) product. A key aim of the research is to investigate the effect of activators and coupling conditions on the stereochemical outcome in phosphorothioate linkage formation during the synthesis of inotersen or nusinersen, and to compare the corresponding diastereomeric composition results between the RLD product and the lab-prepared oligonucleotide samples. This grant will explore an approach using various sensitive analytical tools, collectively, to develop a comprehensive method to analyze the diastereomeric composition of a phosphorothioate oligonucleotide. This research will also provide critical data on the effect of activators and coupling conditions on the stereochemical outcome of the phosphorothioate linkage, which inform the development of generic oligonucleotide products. This research addresses FY 2022 GDUFA science and research priority A1.

2. **Correlation Between Material Properties, Manufacturing Process, Structural Properties, and Quality Attributes of Long-Acting, Biodurable Implants (75F40122C00019)**

A contract awarded to the University of Texas, Austin focuses on elucidating specific considerations that may be uniquely relevant to evaluating the bioequivalence (BE) of non-biodegradable implants that are made of ethylene vinyl acetate (EVA) polymers. EVA is a non-biodegradable polymer commonly used in subcutaneous implants and intravaginal systems, formulated into products designed for prolonged in vivo drug delivery. This research will characterize EVA polymers from difference sources, identify suitable methods for measuring quality attributes of the EVA polymers and the corresponding finished formulations, and systematically explore the potential impact of formulation and manufacturing parameters on product performance. The outcomes of this research are expected to help FDA further improve the efficiency of current BE approaches for EVA-based implant products that involve a combination of in vivo and in vitro studies. This research addresses FY 2022 GDUFA science and research priority A4.

3. **Correlative 3D Imaging and AI Analysis to Establish Critical Performance Attributes of Polymeric Microsphere Products in Support of Performance Evaluation (75F40122C00163)**

   A contract awarded to DigiM Solution LLC and the University of Connecticut focuses on using correlative X-ray microscopy and 3D-focused ion beam scanning electron microscopy (FIB-SEM) imaging technologies along with artificial intelligence (AI)-based image analysis tools to characterize critical performance attributes of complex, long-acting polymeric microsphere drug products. The research involves a combination of formulation manufacturing, quality and performance characterizations, and image analysis, as well as the development of AI-based models for evaluating complex polymeric drug delivery systems. The outcomes of this research are expected to help FDA further improve the efficiency of current BE approaches for complex polymeric injectable products. This research addresses FY 2022 GDUFA science and research priority A4.

## B - Complex Routes of Delivery

Locally-acting drug products have been one of the most challenging types of complex products for generic drug development. Most of the RLDs in this class have very few approved generics, and many still have none. The outcomes of GDUFA-funded research have greatly improved the feasibility of developing generic products utilizing in vitro BE approaches, but many of these options are limited to situations when the formulation of the generic product is precisely matched (e.g., qualitatively (Q1) and quantitatively (Q2) ) the same as that of the reference standard. To encourage innovation and expand the ability of other prospective generic products to utilize more efficient BE pathways, the GDUFA research program helps develop and quantify the relationship between product attributes and the delivery of drug to the site(s) of action. This knowledge helps FDA develop, and helps industry implement, in vitro BE approaches for locally acting products.

During FY 2022, OGD awarded continued funding to multiple ongoing research projects in this area, and additionally funded three new grants and three new contracts to advance these priority initiatives.

1. **Advancing In Vitro and (Patho)physiology-Based Pharmacokinetics Models to Understand and Predict Pulmonary Absorption and Tissue Retention of Inhaled Drugs (75F40122C00182)**

   A contract awarded to the University of Florida focuses on enhancing a commercially available physiologically based pharmacokinetic (PBPK) model for orally inhaled drug product (OIDP) delivery to the lungs. In vitro measurements of paracellular and transcellular permeability will be collected with a dedicated biopredictive cell layer system to better understand mechanisms contributing to active pharmaceutical ingredient permeation and retention. The model will be modified to include disease models for asthma and chronic obstructive pulmonary disease (COPD) as well to sub-divide the lung tissue into epithelial and lamina propria compartments, where the updated model will be validated using data available in-house and the literature. The research involves in vitro data collection and in silico model development pertaining to OIDP delivery. The outcomes of this research are expected to help FDA further improve the efficiency of current BE approaches for OIDPs, incorporating in vitro and in silico methods, and providing an enhanced PBPK tool that may be used to facilitate generic OIDP development. This research addresses FY 2022 GDUFA science and research priority B1.

2. **Integration of Drug Release and Permeability with Systems Data Relevant to PBPK Model of Nose-to-Brain Axis and Verification Using Clinical Data (U01FD007657)**

   A grant awarded to the University of Manchester focuses on developing a physiologically based pharmacokinetic (PBPK) model for drug products that target nose-to-brain delivery. This newly developed model will consider dissolution, mucociliary clearance, lysosomal sequestration, and ionized drugs; the model will be combined with a pre-existing five-compartment brain PBPK model. To support model parameterization and validation, plasma pharmacokinetics (PK) data will be obtained in a six-way crossover study with three drugs administered intravenously and intranasally, where the model will be validated using these data as well as brain PK data available from literature. The research involves in vitro and in vivo data collection and in silico model development pertaining to nose-to-brain drug delivery. The outcomes of this research are expected to help elucidate the complex behavior of nose-to-brain drug products and to assist FDA's development of efficient BE recommendations. This research addresses FY 2022 GDUFA science and research priority B1.

3. **Development of a Physiologically-Based Biopharmaceutics Modeling (PBBM) Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients (U01FD007660)**

4. **Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the Gastro-Intestinal (GI) Tract (U01FD007662)**

   Two complementary grants awarded to the University of Bath (U01FD007660) and the University of Florida (U01FD007662) focus on identifying product formulation quality attributes and physiological or pathological variables that can influence the local and systemic bioavailability of locally-acting drug products in the gastrointestinal (GI) tract. Also, both grants aim to use these insights to enhance existing PBPK models, integrate in vitro (biopredictive dissolution) information into the enhanced PBPK models, evaluate the relationship between systemic and local drug exposures, and assess whether the enhanced model can support a demonstration of BE for complex generic locally-acting drugs in the GI tract. The grant awarded to the University of Bath (U01FD007660) is particularly focused on enhancing the sophistication of (patho)physiological parameters (working with the GastroPlus™ software platform), while the grant awarded to the University of Florida (U01FD007662) is particularly focused on enhancing the sophistication of product formulation quality parameters (working with the Simcyp™ software platform). The outcomes of this research are expected to help FDA assess whether model-integrated approaches using predictive in vitro data can be extended to locally acting drug products in the GI tract that involve low solubility drugs or modified release formulations, or whether these models can optimize the interpretation of PK data from locally acting drugs to maximize the efficiency of BE evaluations. This research addresses FY 2022 GDUFA science and research priorities B1 and D2.

5. **In Vitro Based Approaches to Evaluate the Bioequivalence of Locally-Acting Rectal and Vaginal Semi-Solid Drug Products (U01FD007656)**

   A grant awarded to the University of Rhode Island focuses on research and development that will characterize the specific and unique considerations relevant to evaluating the BE of rectal and vaginal (topical) drug products. This research involves the development of biorelevant performance tests that may be useful as a component of product characterization-based BE approaches for rectal and vaginal drug products, such as in vitro release test (IVRT) studies and biorelevant in vitro permeation test (IVPT) studies. Key aims of this research are to correlate the physicochemical and structural attributes of rectal and vaginal semi-solid dosage forms with product performance, to develop (or modify existing) IVRT methods to incorporate bio-relevant considerations, and to develop (or modify existing) IVPT methods using rectal and vaginal mucosal membranes to support comparative product characterization-based BE approaches for semi-solid rectal and vaginal drug products. The outcomes of this research are also expected to inform relevant method validation considerations that would support the utility of the aforementioned methods in a regulatory context. This research involves a combination of formulation manufacturing, quality and performance characterizations, and an evaluation of in vitro and ex vivo approaches for evaluating the BE of rectal and vaginal products. The outcomes of this research are expected to help FDA expand in

vitro BE approaches to topical products that are applied using the rectal and vaginal routes of delivery. This research addresses FY 2022 GDUFA science and research priority B2.

6. **Optimized Clinical Dermal Open Flow Microperfusion Study Design to Demonstrate Bioequivalence Based on Cutaneous Pharmacokinetics (U01FD007669)**

   A grant awarded to Joanneum Research focuses on optimizing clinical study designs and data analysis techniques that can support a comparative assessment of the relative bioavailability of topically administered drugs, and which can support a demonstration of BE for prospective generic topical products. The specific aims of this research would include comparing in vivo cutaneous PK measurements by independent techniques such as dOFM, dMD, or spectroscopic tomography; exploring the removal of the topical formulations at different time points and characterizing the resulting PK profiles of the test product and the reference standard; developing data analysis techniques; and identifying appropriate PK endpoints for the evaluation of topical BE. The outcomes of this research are expected to help FDA improve the efficiency of current BE approaches for topical generic products with compositional differences relative to the reference standard. This research addresses FY 2022 GDUFA science and research priority B2.

7. **DissolvIt® – An in Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution and Absorption of Drugs Administered via the Inhalation Route (75F40122C00197)**

   A contract awarded to Inhalation Sciences Sweden AB focuses on evaluating the DissolvIt® in vitro dissolution system and its sensitivity in detecting performance differences between inhalation products, including those manufactured using different processes as well as commercially available brand and generic products. Results from these drug release studies will then be correlated with available in vivo PK data to determine whether an in vitro - in vivo relationship can be established. The outcomes of this research will help to determine the potential impact that a more physiologically relevant dissolution system may have to detect performance differences between inhalation products, and to correlate dissolution results in such a system with in vivo performance metrics. This research addresses FY 2022 GDUFA science and research priority B3.

8. **Identification of Drug Distribution in Aerosols: A Nanospectroscopy and NanoThermal Analysis (75F40122C00202)**

   A contract awarded to the University of Sydney focuses on evaluating the ability of optical photothermal infrared (O-PTIR) microscopy, nano thermal analysis (NanoTA), and atomic force microscopy infrared microscopy (AFM-IR) to characterize the inter- and intra-particle distribution of active and inactive ingredients in an inhalation product such as a dry powder inhaler (DPI). Several DPI products will be tested using these in vitro methods to determine the sensitivity of the methods to detect differences between formulations. Next, conventional in vitro studies will characterize the particle size distribution and dissolution of the formulations to examine how detected differences in particle surface properties may relate to product performance. The outcomes of this research are expected to elucidate the clinical relevance of differences in inter- and intra-particle characteristics between inhalation products, which could impact local drug delivery. This research addresses FY 2022 GDUFA science and research priority B3.

## C - Complex Drug-Device Combination Products

Drug-device combination products have the unique distinction of having complexities not only associated with their formulations or routes of delivery, but also complexities associated with the device constituents and with the manner in which patients utilize the product (i.e., user interface issues). These myriad complexities have made it exceptionally challenging to successfully develop generics for drug-device combination products as well as challenging for FDA to assess ANDAs submitted for such prospective generics. Thus, OGD's research priorities related to this class of products were to evaluate the impact of identified differences in the user interface from the reference listed drug on the therapeutic equivalence of complex generic drug-device combination products and to develop criteria for device performance comparisons that would support a BE demonstration by in vitro methods and eliminate the need for in vivo BE.

During FY 2022, OGD awarded continued funding to multiple ongoing research projects in this area, and initiated new research to advance these priority initiatives as part of two contracts described above under Section B. These contracts are intended to support the development of criteria for device performance comparisons that could support a demonstration of BE by in vitro methods.

1. **DissolvIt® – An in Vitro Test Model Built to Resemble Relevant Lung Physiology for Evaluating the Dissolution and Absorption of Drugs Administered via the Inhalation Route (75F40122C00197)**

   Please refer to Section B, above, for a description of this research contract, which addresses FY 2022 GDUFA science and research priorities B3 and C2.

2. **Identification of Drug Distribution in Aerosols: A Nanospectroscopy and NanoThermal Analysis (75F40122C00202)**

   Please refer to Section B, above, for a description of this research contract, which addresses FY 2022 GDUFA science and research priorities B3 and C2.

## D - Tools and Methodologies for BE and Therapeutic Equivalence Evaluation

Although much of the GDUFA research program focuses on complex products, generic versions of non-complex products are essential to the health care system. For solid oral products, the GDUFA research program helps support global harmonization of the most efficient BE recommendations and advance predictive in vitro dissolution methods. This includes research on strategies to reduce risks associated with harmful impurities such as nitrosamine adducts, including nitrosamine drug substance related impurities (NDSRIs); this research includes the exploration of methods to mitigate the formation of such impurities, the development of computational toxicology tools, and the assessment of human exposure risks.

During FY 2022, OGD awarded continued funding to multiple ongoing research projects in this area, and additionally funded three new grants and three new contracts to advance these priority initiatives.

1. **Model-Integrated Statistical BE Methodology for Parallel Studies of Drugs with High Variability (75F40122C00139)**

   A contract awarded to Uppsala University focuses on exploring and testing statistical criteria in combination with population PK modeling and simulation to provide options and solutions for the design and analysis of clinical study scenarios with high variability and for drugs with long half-lives. The research explores alternatives to standard reference-scaled average bioequivalence (RSABE) designs and analysis methods, which will be investigated through stochastic simulation-estimation experiments. Alternative design strategies will include crossover studies where the washout is incomplete between periods. Population PK model-based estimates of the within-subject variability will be used to adjust standard analysis criteria limits (model-informed analysis) or to perform fully model-based BE assessment. The outcomes of this research are expected to help FDA develop more efficient alternative RSABE study designs and analyses for situations when conducting an RSABE study, either a partially or fully replicated crossover study, may be too cumbersome. This research addresses FY 2022 GDUFA science and research priority D1.

2. **Development of a Physiologically-Based Biopharmaceutics Modeling (PBBM) Framework to Support an Assessment of Bioequivalence for Locally-Acting Drugs in the Gastrointestinal Tract in Healthy Subjects and Patients (U01FD007660)**

   Please refer to Section B, above, for a description of this research grant, which addresses FY 2022 GDUFA science and research priorities B1 and D2.

3. **Development and Verification of In Vitro Integrated Mechanistic Population-Based PBPK Model Framework Towards Virtual Bioequivalence Assessment of Locally Acting Drug Products in the Gastro-Intestinal (GI) Tract (U01FD007662)**

Please refer to Section B, above, for a description of this research grant, which addresses FY 2022 GDUFA science and research priorities B1 and D2.

**4. Permeability Assessments of BCS Class 3 Drug Substances in the Presence of Antioxidants (75F40119D10024-75F40122F19003)**

A contract awarded to Absorption Systems, Inc. focuses on characterizing how specific antioxidants, which may be incorporated into drug product formulations to mitigate the formation of harmful impurities such as NDSRIs, may impact the in vitro permeability of selected drugs. The research includes testing with multiple antioxidants evaluated at multiple concentrations with multiple drugs. One of the aims of this research is to elucidate whether incorporating antioxidants into drug product formulations at concentrations that may be sufficient to mitigate the formation of harmful impurities such as NDSRIs would be likely to alter the bioavailability or BE of generic drug products. The outcomes of this research are expected to inform the development of efficient strategies to mitigate potential risks associated with harmful impurities such as NDSRIs in generic drug products, and to assess whether efficient in vitro tests may support a demonstration of BE for generic products that reformulate to incorporate antioxidants. This research addresses FY 2022 GDUFA science and research priorities D2 and D3.

**5. Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters (U01FD005978)**

A grant awarded to the University of California, San Francisco and Stanford University joint Center of Excellence in Regulatory Science and Innovation focuses on using medium throughput screening to characterize the interaction of multiple antioxidants with multiple efflux and influx intestinal transporters. The aims of the research are to characterize the interaction of antioxidants with key intestinal transporters, determine the potency of interaction, and identify which antioxidants may inhibit, or not inhibit, these transporters. The outcomes of this research are expected to inform generic drug developers about the selection of specific antioxidants that may mitigate the formation of harmful impurities such as NDSRIs with a low likelihood of impacting the bioavailability or BE of the generic drug product, and to assess whether efficient in vitro tests may support a demonstration of BE for generic products that reformulate to incorporate antioxidants. This research addresses FY 2022 GDUFA science and research priorities D2 and D3.

**6. Machine-Learning Based Heterogeneous Treatment Effect Models for Prioritizing Product-Specific Guidance Development (75F40122C00121)**

A contract awarded to the Drexel University focuses on developing and implementing a novel machine learning (ML) algorithm for estimating heterogeneous treatment effects. A data-driven ML method will be built on top of recent advances in deep learning for handling real-world data (e.g., mitigating confounding effects) and for estimating the treatment effect, which allows for the identification of individual-level causal effects based on observational data for the accurate prediction of predefined outcomes (e.g., abbreviated new drug application (ANDA) submissions) based upon the availability of product-specific guidances (PSGs). The model evaluation and explanation will be conducted with synthetic datasets and real-world PSG data. The proposed algorithm will be capable of providing more efficient and accurate treatment effect estimations that can optimize the process of PSG development and, thereby, facilitate generic drug development. The proposed ML algorithm will be compared with mainstream/conventional methods and existing ML models using extensive synthetic datasets and previous benchmarks focused on treatment effect estimation, and validated with the real-world PSG data. It is anticipated that a study using comprehensive and enriched data will provide a better understanding of the impact of PSG availability, support the prioritization of PSG development, and facilitate generic drug development and approval. This research addresses FY 2022 GDUFA science and research priority D5.