Office of Generic Drugs

Fiscal Year (FY) 2021 New Research Awards

Each year, in alignment with the Generic Drug User Fee Amendments (GDUFA) Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter), FDA develops a list of GDUFA Research Priorities and acts on them. The Office of Generic Drugs (OGD) awarded the following new research grants and contracts in FY 2021 and they are reported according to the FY 2021 priorities. The FY 2021 GDUFA research priorities are found here.

A - Complex Active Ingredients, Formulations, or Dosage Forms

High quality, safe, and effective generic drugs are widely available for most drug products. However, 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 research program supports the development of new tools to characterize and evaluate complex products. OGD funded two grants and two contracts during FY 2021 to advance these priority initiatives.

1. **Characterization of Carboxymaltose Variability and Interactions in Ferric Carboxymaltose Complexes (75F40121C00189)**

   A contract awarded to Purdue University (Principal Investigator (PI): Eric J. Munson) focuses on characterizing the carbohydrate ligand of ferric carboxymaltose complexes (which is not evident based upon the labeling) and on the interaction between the carbohydrate and the iron core. Iron-carbohydrate drug products have played a critical role in treating iron deficiency, which is the most prevalent cause of anemia worldwide, and affects around 5 million Americans. Iron deficiency anemia disproportionately impacts underprivileged women and children, with a prevalence of nearly 20 percent in African American and Mexican American women.[1,2] Although OGD has developed product-specific guidances with bioequivalence (BE) recommendations for these products, generics have been notoriously difficult to develop, in large part, because the analytical methods to characterize these iron-carbohydrate complex drugs have been exceptionally challenging. The results from this research are expected to provide a practical solution to what has otherwise been an insurmountable problem and should make it feasible to finally develop a generic version of this drug product. This research addresses FY 2021 GDUFA science and research priority A1.

2. **Development of Advanced Analytical Methods for the Characterization of Iron Carbohydrate Complex - Ferric Derisomaltose (1U01FD007363)**

   A grant awarded to the University of Maryland, Baltimore (PI: Sarah L. Michel) focuses on ferric derisomaltose, a recently approved product that can allow complete iron repletion in a single dose, which appears to have fewer side effects relative to older products (including ferric carboxymaltose), and is now widely used in the treatment of iron deficiency.[3] The structure and composition of ferric derisomaltose is more complicated than that of ferric carboxymaltose, and the formula in the product labeling for ferric derisomaltose may be misleading, which creates a substantial hurdle for generic development. The results from this research are expected to clarify the composition of the drug substance and provide information on specific analytical characterization methods that generic developers can utilize to determine the structure of ferric derisomaltose, which should make it feasible to finally develop a generic version of this drug product. This project uses a somewhat different approach to characterize the iron-carbohydrate complexes than the one with ferric carboxymaltose and, collectively, the insights gained from both

[1] Miller, JL (2013) Iron Deficiency Anemia: A Common and Curable Disease. Cold Spring Harb Perspect Med. 2013 Jul; 3(7): doi: 10.1101/cshperspect.a011866

[2] Killip, S et al., (2007) Iron Deficiency Anemia. Am Fam Physician. 2007 Mar 1;75(5):671-678.

[3] Kassianides, X et al. (2020) An evaluation of ferric derisomaltose as a treatment for anemia. Expert Rev Hematol . 2021 Jan;14(1):7-29. doi: 10.1080/17474086.2021.1858406

research projects should greatly improve the understanding of this entire class of products, which should have a systemic impact in facilitating the development of generic versions of other iron-carbohydrate complex drugs. This research addresses FY 2021 GDUFA science and research priority A1.

3. **Enhancement and Validation of In Vitro - In Vivo Correlation Method for Long-Acting Injectable (LAI) Drug Products to Accelerate their Generic Development (75F40121C00133)**

   A contract awarded to the University of Connecticut (PI: Dianne Burgess) and Simulations Plus (PI: Viera Lukacova) will support research to incorporate in vitro release test (IVRT) data and critical quality attributes (CQAs) like drug particle size and morphology, formulation pH and viscosity, and sedimentation volume for four LAI suspension drug products. This research will also take into account the interaction of the drug products with the immune system, since inflammation may lead to the accumulation of fluid in the dosing compartment, which may change the rate and extent of drug dissolution in vivo. By their very nature, LAI drug products exert their effects over longer time scales than conventional drugs, which creates a hurdle for a prospective generic applicant to demonstrate that it has matched the rate and extent to which the drug becomes available at the site of action from the reference product. Consequently, many LAI suspension products have either no generics available, or very few. Physiologically based pharmacokinetic (PBPK) modeling provides a practical approach for supporting a demonstration of BE for LAI products. However, these models need further development to establish in vitro – in vivo correlations (IVIVCs). The results from this research are expected to help establish Level-A IVIVCs, which should provide clear and efficient pathways to develop and demonstrate BE for complex LAI generic products . This research addresses FY 2021 GDUFA science and research priority A4.

4. **In Vitro Tools to Simulate Chewing of Pharmaceutical Opioid Drug Products (75F40121C00178)**

   A contract supported by CDER funds for opioid research was awarded to the University of Auckland (PIs: Peter Xu; Feng Zhang) focusing on research and development to validate existing in vitro tools to simulate the chewing of opioid drug products and determine what study design parameters are critical when comparing the chewing of prospective generic opioid abuse-deterrent oral dosage forms to their reference products. The results of this research are expected to: produce orthogonal in vitro chewing methods that are better alternatives to existing methods (which have limitations); elucidate product characteristics; support the development of in vitro – in vivo relationships (IVIVRs) that can better predict whether a prospective generic product would provide suitable (non-inferior) abuse deterrence relative to its reference product; validate the ability of PBPK models to predict the PK of tablet products after being chewed; and support the development of in vitro BE options in PSGs for these products. This research addresses FY 2021 GDUFA science and research priority A5.

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 reference products 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) to the reference product. To encourage innovation and expand the eligibility 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. OGD funded five grants during FY 2021 to advance these priority initiatives.

1. **Dermal Drug Product Quality and Bioequivalence Assessment through Advanced Mechanistic Absorption Modeling and PBPK Simulation (1U01FD007320)**
2. **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 (1U01FD007323)**

The first of these grants was awarded to Simulations Plus (PI: Jessica Rose Spires) and the second to Certara UK (PI: Sebstian Polak). Both research projects focus on developing sophisticated, commercially available PBPK modeling platforms that mechanistically model topical dermatological drug absorption and, notably, allow product attributes (e.g., formulation pH, apparent viscosity, etc.) to be incorporated into the model to assess the influence of any differences between the prospective generic product and its reference product. In addition, both award recipients are developing PBPK modeling platforms that have the capability to perform virtual BE studies. This research will enable the commercial availability of PBPK modeling platforms, which provide an integrated workflow, for generic drug developers to assess the potential influence of physicochemical or structural differences between their prospective generic product and the reference product on the (virtual) BE of the products. In addition to making user-friendly modeling platforms readily available to generic drug developers, which can de-risk and accelerate the development of complex topical generics, model-integrated evidence from these modeling platforms will likely be crucial to supporting a demonstration of BE for non-Q1/Q2 topical drug products. This research (under both grants) addresses FY 2021 GDUFA science and research priorities B1 and B2.

3. **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 (1U01FD007348)**

   A grant was awarded to the University of Manchester (PI: Jill Barber) to enhance the understanding of excipients on topical drug absorption and evaluate in vitro BE methods for non-Q1/Q2 topical drug products applied to skin. This research focuses on supporting a demonstration of BE for non-Q1/Q2 topical drug products by accounting for the interaction between excipients in topical products and constituents of the skin, including diseased skin, and including different patient populations. This represents a tool to model the influence of Q1/Q2 differences between a prospective generic product and its reference product on BE. The results of this research will bridge a fundamental knowledge gap relating to the (unknown) risk of any difference in the Q1 or Q2 characteristics of a prospective generic topical product compared to its reference product and establish a reliable basis for mitigating the risk of potential failure modes for BE associated with non-Q1/Q2 topical generic drug products. This research addresses FY 2021 GDUFA science and research priorities B1 and B2.

4. **Computational Fluid Dynamics (CFD) Models to Aid the Development of Generic Metered Dose Inhalers (1U01FD007353)**

   A grant was awarded to Virginia Commonwealth University (PI: P. Worth Longest) to produce verified and validated predictions of regional lung deposition for a currently marketed solution-based metered dose inhaler (MDI) in human upper and lower airways. Locally acting inhalation dosage forms, including MDI products, have been exceptionally challenging to develop as a generic. While PBPK models have demonstrated their potential utility to support a demonstration of BE for such products, tools are needed to facilitate the prediction of both lung tissue concentrations and systemic concentrations for orally inhaled products. The results from this research are expected to provide generic drug developers of solution-based MDI drug products with a CFD method that can support more efficient BE approaches as an alternative to expensive and time-consuming comparative clinical endpoint studies. This research addresses FY 2021 GDUFA science and research priorities B1 and B3.

5. **A Physiologically Based Pharmacokinetic Model of Human Airway Epithelia (1U01FD007338)**

   A grant was awarded to the University of North Carolina, Chapel Hill (PI: Charles Richard Esther) to improve the utility of PBPK models for inhaled drugs by comprehensively assessing the levels of drug transporters and metabolizing enzymes in human airway epithelia. The results of this research will substantially improve the utility of PBPK modeling to support the development of generic inhaled drugs by overcoming current limitations of PBPK models for inhaled drugs by accounting for the actions of drug transporters and metabolizing enzymes that can influence the effective concentrations of inhaled drugs at the site of action. This research addresses FY 2021 GDUFA science and research priorities B1 and B3.

C - Complex Drug-Device Combination Products

Drug-device combination products have the unique distinction of having potential complexities not only associated with their formulations or routes of delivery, but also associated with the device constituents and 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 product 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 methods. Two grants were awarded during FY 2021 to advance these priority initiatives.

1. **Development of a Combination Product Taxonomy and Comparative Human Factors Testing Method for Drug-Device Combination Products Submitted in an ANDA (1U01FD007360)**

   A grant awarded to the University of Detroit, Mercy (PI: Megan O'Meara Conrad) focuses on establishing a framework for the visual taxonomic classification of drug-device combination products and for the utilization of relevant methods to assess and compare prospective generic drug device combination products with their reference products. This research will systematically analyze combination product user interface design attributes and facilitate the identification of minor and other design differences in a manner relevant to potential use errors that could cause harm or compromise medical treatment. This research is fundamental to resolving challenges with the current methodologies for assessing devices and user interfaces, which may be suitable for characterizing individual products, but are not ideal for comparative assessments between prospective generic and reference products. The results from this research are expected to establish a consistent framework for the comparative assessment of the substitutability of such products. This research addresses FY 2021 GDUFA science and research priority C1.

2. **Battelle User Interface Design for Generic vs. RLD Combination Products (1U01FD007359)**

   A grant awarded to Battelle Memorial Institute (PI: Patrick McCormack) focuses on characterizing and comparing the design of the user interface for a prospective generic drug-device combination product to its reference (RLD) product. This research is intended to support the categorization of differences in the design of the user interface (minor design differences or other design differences) and to explore in vitro or in vivo approaches to assess "other design differences" that could be alternatives to comparative use human factors (CUHF) studies. The results from this research are expected to improve the understanding of the factors related to design differences of the user interface that may impact substitutability between prospective generic and reference drug device combination products and, thereby, support the development of generic versions of these products. This research addresses FY 2021 GDUFA science and research priority C1.

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. Two grants and three contracts were awarded to advance research related to these priorities.

1. **In Vitro Assessment of Mixed Amphetamine Salt (MAS) Products (75F40121P00621)**

   A contract was awarded to Avomeen to characterize product quality attributes of three lots each of the reference product and each of the generic products. This research was initiated in response to FDA having received a high number of comments suggesting a potentially inadequate therapeutic effectiveness, particularly in adult patients with attention-deficit / hyperactivity disorder (ADHD), who are using a generic version of a medication containing amphetamine and dextroamphetamine mixed salts. Since L-amphetamine and D-amphetamine (dextroamphetamine) have a different efficacy in treating ADHD, this research will specifically assess whether there

may be differences in the recently manufactured lots of any of these products, which may have the potential to impact their therapeutic effectiveness. The results from this research are expected to support decisions relating to a prospective clinical study that may be performed with these reference and generic products. This research addresses FY 2021 GDUFA science and research priority D1.

2. Applying a Robotic Soft Esophagus (RoSE) to Assess the Swallowability of Opioid Drugs (75F40121C00178)

A contract awarded to the University of Auckland (PI: Peter Xu) focuses on how differences in size and shape between prospective generic tablets and their reference products may affect their swallowability. This research utilizes a robotic soft esophagus to assess swallowability and also focuses on opioid products because extended-release opioid tablets are relatively large, and patients on chronic opioid therapy commonly experience difficulties with swallowing. Notwithstanding the focus on opioid products, this project is aimed more generally at size differences of generic oral dosage forms. FDA issued a Guidance for Industry entitled *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (June 2015) recommending limits on how much bigger a generic tablet or capsule may be compared to its reference product, and allowed for applicants to produce generics with larger size differences if they provide adequate justification. The results of this research should provide information to assist with evaluating such justifications, and have the potential to revolutionize how generic developers and the FDA consider size differences when developing or assessing generic drug products. This research addresses FY 2021 GDUFA science and research priority D2.

3. 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 (1U01FD007352)

A grant was awarded to the University of Florida (PI: Rodrigo Cristofoletti) to expand the application of oral PBPK models in ways that address ANDA review issues that FDA is currently facing, including potential harmonization with and implementation of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline M13: *Bioequivalence for Immediate-Release Solid Oral Dosage Forms*. Currently, there are differences between FDA and the European Medicines Agency (EMA) relating to when both fed and fasted PK BE studies are recommended to support a demonstration of BE. The research will develop and apply oral PBPK models that can simulate the results of BE studies with modeling and simulations that would predict the impact of food on oral drug absorption for certain poorly soluble drugs, integrate biopharmaceutic data into the population PBPK framework under fasted conditions, and expand the developed PBPK modeling framework to hypochlorhydria populations. The results from this research are expected to provide a tool to support regulatory decision making related to fed BE studies and to help frame FDA's general recommendations relating to a reliance on evidence from fed BE studies. This research addresses FY 2021 GDUFA science and research priority D2.

4. Disintegration and Dissolution of Solid Dosage Forms and Influence of Food Induced Viscosity on its Kinetics; Tools and Methodologies for Bioequivalence and Substitutability Evaluation (75F40121C00020)

A contract was awarded to Johannes Gutenberg University (PI: Peter Langguth) to develop an evaluation algorithm that enables regulatory decision making about whether a fed state BE study should be recommended for generic products formulated as immediate release solid oral dosage forms. This research aligns closely with and complements that described for the previous grant. This research addresses FY 2021 GDUFA science and research priority D2.

5. Development of Machine Learning Approaches to Population Pharmacokinetic Model Selection and Evaluation of Application to Model-Based Bioequivalence Analysis (1U01FD007355)

A grant was awarded to Nuventra, Inc. (PI: Mark Sale) to improve the efficiency and robustness of population PK analysis, which utilizes mathematical/statistical models to study drug effects in a specific population by identifying sources of variability in the population. Population PK models can provide support for generalizing the conclusion of BE to groups that were not included in a BE study. For example, for some ophthalmic products, one subject only provides one time point of drug concentration in the aqueous humor for each eye in a PK BE study. In such cases, a routine PK BE analysis would be very inefficient, whereas a population PK analysis can facilitate a model-based BE analysis. A population PK analysis may also be beneficial to support a demonstration of BE in parallel study designs,

such as those for LAI products, and to simulate comparative clinical endpoint BE studies, and to construct virtual populations for mechanistic PBPK models. This research will develop and evaluate a deep learning/reinforcement learning (DL/RL) approach to population PK model selections. A common solution will link an existing genetic algorithm solution (ported to Python) and the DL/RL application to NONMEM®, which will be used for parameter estimation with the population PK models examined. The common solution should facilitate future work using other algorithms for model selection, e.g., particle swarm optimization or simulated annealing. The results from this research are expected to maximize the value of the models to support drug development decision-making, and to accelerate the timeline for developing population PK models for generic drug development. This research addresses FY 2021 GDUFA science and research priority D5.