Fiscal Year (FY) 2023 Awarded GDUFA Science and Research Contracts and Grants

In alignment with the Generic Drug User Fee Amendments (GDUFA) Reauthorization Performance Goals and Program Enhancements Fiscal Years (FYs) 2023-2027 (GDUFA III Commitment Letter), FDA developed a list of GDUFA Science and Research Priority Initiatives for FY 2023. Some of these GDUFA priority initiatives are addressed by ongoing research grants and contracts that were originally awarded in previous years, and that received continuation funding during FY 2023. Information about those research grants and contracts can be found in annual GDUFA Science and Research Reports.

Those annual reports 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 in each FY from the GDUFA-funded Science and Research program. Additional metrics related to outcomes from the GDUFA Science and Research program are shared annually in separate GDUFA Science and Research Outcomes Reports.

The information below focuses on new research grants and contracts that were awarded in FY 2023. They are organized based on the GDUFA III priority initiative(s) they address, and thereafter, sorted alphanumerically by the specific FY 2023 GDUFA research priorities they address (e.g., 5A, 5B, 5C).

1. Develop Methods for Generics to Address Impurities such as Nitrosamines:

This research initiative focuses on understanding how ingredients in drug products may either contribute to or mitigate the formation of potentially harmful impurities such as nitrosamine adducts (e.g., nitrosamine drug substance related impurities (NDSRIs)), evaluating the risk of human exposure to these impurities and developing methods for abbreviated new drug application (ANDA) applicants to efficiently address the potential risks.

Based upon the imperative to bring ongoing research efforts to fruition related to establishing the utility of reformulating generic products with antioxidants that mitigate the formation of NDSRIs and establishing an approach for ANDA applicants to efficiently address the potential risks associated with such impurities, no new external research awards were funded for this initiative during FY 2023, but FDA internal research activities continue.

2. Enhance the Efficiency of BE Approaches for Complex Active Ingredients:

This research initiative focuses on improving advanced orthogonal methods for the characterization of chemical compositions, molecular structures, and distributions of complex active ingredients that can elucidate attributes of complex active ingredients that may be critical to their performance and, thereby, support the development of efficient characterization-based bioequivalence (BE) approaches.

- **Investigating the Impact of API Purity, Lipid Source and Manufacturing Process on Performance and Quality of Complex siRNA Lipid Nanoparticles (75F40123C00118)**

  A contract awarded to the University of Connecticut focuses on a lipid-based nanoparticle (LNP) product that contains a complex active pharmaceutical ingredient (API), patisiran, to characterize the small interfering ribonucleic acid (siRNA) API, identify the potential impact of API impurities on generic products with siRNAs, and elucidate how the source of LNP excipients or the process used to manufacture them may impact critical quality attributes (CQAs) for these complex dosage forms. This research will develop methods to characterize and compare siRNA APIs such as patisiran, as well as LNP formulations, and will provide an understanding of which product attributes may be critical to product performance. The outcomes of this research are expected to establish methods for characterizing the sameness of oligonucleotide APIs and evaluating associated impurities to support the development of efficient BE approaches for these generic products. This research addresses FY 2023 GDUFA Science and Research Priority 2A.

3. Enhance the Efficiency of BE Approaches for Complex Dosage Forms and Formulations:

This research initiative focuses on improving efficient characterization-based (in vitro) BE approaches for complex dosage forms by identifying relevant CQAs to characterize and suitable test methods for doing so.

- **Impact of API CQAs on In Situ Forming Implants and Understanding In Vitro and In Vivo Performance Differences (75F40123C00142)**

  A contract awarded to the University of Connecticut focuses on investigating the impact of API attributes on the quality and performance of poly [lactic-co-glycolic acid] (PLGA)-based in situ forming implant products. This research will characterize attributes such as API type and state and its effect on the viscosity and syringeability of an in situ forming implant (ISFI), formulation solidification, water uptake, microstructure, degradation, and drug release in vitro as well as in vivo. A key aim of the research is to develop and evaluate in vitro release test (IVRT) methods that incorporate an adapter (in which an implant is formed) and a dissolvable polyvinyl alcohol (PVA) film (that can emulate the burst release of the drug that occurs in vivo) potentially supporting the establishment of in vitro-in vivo correlations (IVIVCs). The outcomes of this research are expected to establish a comprehensive profiling of CQAs for PLGA polymer based ISFIs with APIs such as risperidone and leuprolide acetate, which can facilitate the development and assessment of generic ISFIs and inform recommendations for efficient BE approaches for these products. This research addresses FY 2023 GDUFA Science and Research Priorities 3A and 3B.

- **In Vitro and In Vivo Assessment of Buprenorphine Extended-Release Injections for Supporting Generic Product Equivalence (75F40123C00196)**

  A contract awarded to the Virginia Commonwealth University focuses on 1) characterizing the physicochemical properties of an reference listed drug (RLD), SUBLOCADE® buprenorphine extended-release injectable solution product; 2) formulating and characterizing a test buprenorphine extended-release injectable solution with the same components and composition; 3) developing a reproducible and discriminating IVRT method to assess the equivalence of drug release rates between the

test and RLD products; and 4) evaluating the correlation between in vitro and in vivo studies of this buprenorphine extended-release injection. This research will establish a comprehensive understanding of polymer and drug product CQAs and of how these attributes affect drug release. The outcomes of this research are expected to support the development of efficient, characterization-based BE approaches for poly PLGA-based in situ forming depot products. This research addresses FY 2023 GDUFA Science and Research Priorities 3A and 3B.

- **New PLGA Analytical Methods for Mini-Size Complex Long-Acting Injectable Formulations (75F40123C00192)**

  A contract awarded to Akina Inc. focuses on developing and validating new analytical methods to characterize individual PLGA polymers in complex mini-size long-acting injectable, insertable, or implantable (collectively LAI) formulations. These drug products have a very small quantity of PLGA available for assay, which makes it challenging to analyze the polymers using conventional approaches. This research will validate the new analytical methods using OZURDEX® (dexamethasone) intravitreal implants as a model product and utilizing these methods to characterize the PLGA components in DURYSTA® (bimatoprost) intracameral implants. The outcomes of this research are expected to establish new analytical methods that can separate mixtures of PLGA polymers, even when they are used as a relatively small component of a complex formulation. This research addresses FY 2023 GDUFA Science and Research Priority 3B.

4. Enhance the Efficiency of BE Approaches for Complex Routes of Delivery:

This research initiative focuses on understanding how ingredients and other aspects of a formulation influence drug absorption via complex routes of delivery, building in vivo predictive models, and identifying corresponding failure modes for BE, to support the development of efficient BE approaches for these products.

- **Development of a Laser-Based Testing Platform for Generic Dry Powder Inhaler (DPI) Evaluation and In Silico Model Validation (75F40123C00201)**

  A contract awarded to the University of Sydney focuses on developing a DPI drug testing platform, instrumented with modern laser and optical diagnostics techniques, that could assess the aerosol performance of drug formulations and device designs more rapidly than the current technology. This research will use those diagnostic results to develop a centralized data set that can be accessed by computational fluid dynamics (CFD) modelers globally as part of a coordinated effort to provide better high resolution and dynamically resolved data for in-silico model validation of DPI devices. The outcomes of this research are expected to help develop more accurate and efficient in vitro tests that could be utilized to support a demonstration of BE, in lieu of comparative clinical endpoint BE studies. The data generated could also improve in silico modeling to predict the regional deposition of drug particles more accurately than is currently possible. This research addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

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

  A grant awarded to the University of Florida focuses on leveraging modeling and simulation techniques to address challenges related to establishing BE for complex

orally inhaled drug products (OIDPs). This research will use population pharmacokinetics (PK) models to assess formulation differences in regional lung exposure based on systemic PK concentration data. By creating mechanistic lung models, the project seeks to simulate various scenarios considering factors like lung regions, deposition patterns, absorption rates, and more. The outcomes of this research are expected to support the development of efficient BE approaches for locally acting OIDPs, supported by PK modeling, as alternatives to comparative clinical endpoint or pharmacodynamic BE studies. This research addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

- **A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods (U01FD007987)**

  A grant awarded to Fluidda Inc. focuses on conducting an in vivo nuclear imaging deposition study in human lungs that will produce high resolution branch-level deposition observations that may be used to validate future in silico regional lung deposition predictions. This research involves an in vivo study that will be conducted using an OIDP indicated for the treatment of both asthma and chronic obstructive pulmonary disease (COPD) using either single photon emission computed tomography (SPECT)/ computed tomography (CT) or, if feasible, positron emission tomography (PET)/CT. A key aim of this research is to estimate drug deposition in the small branches of the lung by applying an optimized protocol and using CT scan data from patient-specific anatomic regions. The outcomes of this research are expected to help establish a detailed three-dimensional map showing how the drug in an OIDP travels after it is inhaled, and where it ends up. These results will provide a frame of reference against which it will be possible to compare the predictions of regional lung deposition produced by computational models, so that the accuracy of the modeled predictions can be evaluated and improved sufficiently to support the development of efficient BE approaches for OIDPs. This research addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

- **In Vitro Tests to Support Bioequivalence Determination When Generic Dermatological Formulation has Differences from the Brand Product Formulation (75F40123C00204)**

- **Role of Excipients and Excipient Substitution in Topical Semi-Solid Formulations and Their Effect on Product Performance and Quality (75F40123C00213)**

  Two complementary contracts awarded to Mercer University (75F40123C00204) and Rutgers University (75F40123C00213), respectively focus on evaluating the impact of differences in the components and composition of topical formulations on their physicochemical and structural (Q3) attributes and product performance. The research at Mercer University will evaluate how differences in specific types of formulation components, such as among different carbomers that serve as gelling agents, may influence Q3 attributes in different semisolid dosage forms with different model drugs. The research at Rutgers University will systematically investigate the impact of a series of quantitative differences in inactive ingredients (including different sources and excipient grades) on product quality and performance for different semisolid dosage forms with different model drugs. The outcomes of research supported by these two contracts are expected to enhance our understanding of how compositional differences in topical formulations may influence bioavailability (BA), and to identify what evidence could mitigate the risk of failure modes for BE with prospective topical generic products that may contain compositional differences relative to their respective reference standard

(RS) products, thereby supporting the development of efficient characterization-based BE approaches for such products. This research addresses FY 2023 GDUFA Science and Research Priority 4B.

- **Understanding Preservative Effects on Bioequivalence of Topical Ocular Products (75F40123C00205)**

  A contract awarded to the University of Eastern Finland focuses on understanding how formulation properties of topical ophthalmic solutions influence their interactions with physiological features of the eye and, thereby, influence product performance, as well as on understanding how compositional differences in components such as preservatives may impact drug BA or BE. This research will elucidate how preservatives affect ophthalmic drug absorption from topically administered eye drops. The outcomes of this research are expected to support the development of efficient, evidence based, BE approaches for ophthalmic solution generic products that may contain a different preservative than the RLD product. This research addresses FY 2023 GDUFA Science and Research Priority 4B.

- **A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs (75F40123C00072)**

  A contract awarded to CFD Research Corp. focuses on developing and validating a modeling approach that integrates CFD and physiologically based PK (PBPK) to predict drug kinetics in the eye following topical administration of ophthalmic drug products. This research will integrate a two-dimensional CFD model and a compartmental dynamic blinking model to improve the representation of fluid flow and drug transport, distribution, and excretion in rabbit and human eyes. A key aim of the research is to conduct in vitro, ex vivo and in vivo rabbit studies that will provide a reference for validation of the hybrid CFD-PBPK model, and to inform the development of an interspecies model extrapolation. The outcomes of this research are expected to enhance our understanding of the interactions between topical ophthalmic dosage forms and the physiology of the eye, and to provide a web-based opensource framework that can inform generic product development and assessment, as well as supporting the development of efficient characterization-based BE approaches for topical ophthalmic products. This research addresses FY 2023 GDUFA Science and Research Priorities 4B and 7A.

- **Development and Validation of a Multi-functional, Multi-purpose Quantitative Tool for Dermal Physiologically Based Pharmacokinetic Modeling (U01FD007957)**

- **Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis, and Influence of Excipients (U01FD007954)**

  Two complementary grants awarded to the University of Bath (U01FD007957) and Certara UK Ltd. (U01FD007954), respectively focus on developing and validating mechanistic PBPK models for topical drug products. These models would predict how compositional differences in product formulations may impact product performance while accounting for product metamorphosis as well as Q3 and thermodynamic changes that occur following dose administration on the skin. The research at the University of Bath will leverage information from in vitro product quality and performance test methods to develop and validate a mechanistic PBPK model of topical drug permeation. The research at Certara UK Ltd. will elucidate how the components and composition of a topical formulation can modulate drug delivery into the skin. In vitro permeation test studies and in vivo cutaneous PK studies will be utilized to validate model predictions for

topical formulations with variations in drug product attributes. The outcomes of research supported by these two grants are expected to facilitate the development of efficient model-integrated evidence approaches that incorporate modeling and simulation to support a demonstration of BE for topical products, including those that may contain compositional differences relative to the RS product. This research addresses FY 2023 GDUFA Science and Research Priorities 4B and 7A.

5. Enhance the Efficiency of BE Approaches for Complex Drug-Device Combination Products:

This research initiative focuses on evaluating the impact of identified differences in the user interfaces, hardware, software, or propellants between prospective generic and the RLD on the BE, therapeutic equivalence, or post-marketing safety of generic drug-device combination products.

- **Comparative Use Human Factors Studies to Assess the Impact of Differences in the User Interface of Generic Drug-Device Combination Products as Compared to the Reference Listed Drug (75F40123D00028-75F40123F19001)**

  A contract awarded to Core Human Factors, Inc. focuses on understanding how particular types of user interface differences of drug-device combination products (DDCPs) impact use error rates. This research will involve the conduct of comparative analyses and comparative use human factors studies to evaluate DDCPs in different user groups (e.g., patients, caregivers, healthcare providers) and use environments (e.g., hospital, home, public use), and will evaluate ways to improve the analysis of data from such studies. The outcomes of this research are expected to inform and support the establishment of best practices and efficient approaches for generic DDCP development and assessment by clarifying how, and in what situations, differences in the user interface of a DDCP may lead to use errors that may impact the substitutability of a prospective generic DDCP. This research addresses FY 2023 GDUFA Science and Research Priority 5A.

- **Toolkit to Assess Adhesion Performance of Topical and Transdermal Delivery Systems (TDS) In Vitro – Grant Expansion Awarded to the Center for Research on Complex Generics (CRCG) (1U18FD007054)**

  A grant expansion awarded to the CRCG that funds collaborative research with the University of Queensland focuses on developing improved in vitro adhesion tests for transdermal and topical delivery systems (collectively, TDS) that are predictive of the adhesion performance of TDS in vivo. This research will establish test methods that subject TDS to conditions encountered in vivo during product wear, making it possible to compare TDS and distinguish clinically meaningful differences in adhesion performance. The outcomes of this research are expected to develop improved criteria and more efficient approaches for evaluating potential failure modes related to TDS adhesion in vitro, during the development and assessment of prospective generic TDS (and over the life cycle of the drug product). This research addresses FY 2023 GDUFA Science and Research Priority 5B.

- **Research Challenges Related to Environmentally Friendly Propellants in Metered Dose Inhalers (75F40123C00186)**

  A contract awarded to the Aptar Pharma Rx focuses on investigating the product design space for metered dose inhalers (MDIs) utilizing alternative low global warming potential

(GWP) propellants such as hydrofluoroalkane (HFA) 152a and hydrofluoroolefin (HFO) 1234ze. This research will elucidate how an MDI reformulation with a low GWP propellant may influence key product quality and performance attributes, and what types of changes to the formulation and/or device can be made to address any performance differences that may affect BE with approved MDIs. The outcomes of this research will facilitate evidence-based decisions relating to generic product development (including post-approval reformulations) and support regulatory recommendations to help guide generic product transitions to low GWP propellants. This research addresses FY 2023 GDUFA Science and Research Priority 5C.

6. Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products:

This research initiative focuses on understanding of how ingredients in oral and parenteral drug products may modulate BA, and on improving biorelevant dissolution methods as well as in silico models to support the expansion of biowaivers and to support global harmonization.

- **Evaluation of Oral Extended-Release Tablets to Support a Demonstration of Bioequivalence for Additional Strengths (U01FD007959)**

  A grant awarded to Northeastern University focuses on understanding how formulation variables (e.g., drug and excipient attributes) across multiple strengths of an extended release (ER) oral drug product influence drug release. This research will develop mechanistic models parameterized with dissolution data to compare oral ER generic drug products and their corresponding RS products across multiple strengths to establish dissolution safe spaces. A key aim of this research is to construct a “proof-of-concept” model of complex oral ER drug products to identify key variables that affect drug release mechanisms for different formulation design strategies. The outcomes of this research are expected to establish a body of evidence that supports efficient approaches to demonstrate the BE of oral ER drug products with multiple strengths, thereby, facilitating product development and regulatory assessment for multiple strengths of relevant oral ER generic products. This research addresses FY 2023 GDUFA Science and Research Priority 6B.

7. Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of BE:

This research initiative focuses on developing tools and advancing approaches to integrate complementary in silico (modeling), in vivo and in vitro evidence in ways that collectively mitigate the risk of failure modes for BE and support a framework for virtual BE studies. This initiative includes research on the use of MIE to evaluate failure modes for BE and to optimize the design of BE studies.

- **Development of a Laser-Based Testing Platform for Generic Dry Powder Inhaler (DPI) Evaluation and In Silico Model Validation (75F40123C00201)**

  Please refer to Section 4, above, for a description of this research contract awarded to the University of Sydney, which addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

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

  Please refer to Section 4, above, for a description of this research grant awarded to the University of Florida, which addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

- **A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods (U01FD007987)**

  Please refer to Section 4, above, for a description of this research grant awarded to Fluidda Inc., which addresses FY 2023 GDUFA Science and Research Priorities 4A and 7A.

- **A CFD-PBPK Framework for Supporting Bioequivalence Evaluation of Ophthalmic Drugs (75F40123C00072)**

  Please refer to Section 4, above, for a description of this research contract awarded to CFD Research Corp., which addresses FY 2023 GDUFA Science and Research Priorities 4B and 7A.

- **Development and Validation of a Multi-functional, Multi-purpose Quantitative Tool for Dermal Physiologically Based Pharmacokinetic Modeling (U01FD007957)**

  Please refer to Section 4, above, for a description of this research grant awarded to the University of Bath, which addresses FY 2023 GDUFA Science and Research Priorities 4B and 7A.

- **Formulation Toolbox for Topically Applied Drugs to Account for Physical Parameters, Dynamic Metamorphosis, and Influence of Excipients (U01FD007954)**

  Please refer to Section 4, above, for a description of this research grant awarded to Certara UK Ltd., which addresses FY 2023 GDUFA Science and Research Priorities 4B and 7A.

- **A State-of-the-Art Virtual Bioequivalence Platform and Case Studies on Complex Formulations, Systemic and Local Concentration-based Bioequivalence (U01FD007904)**

  A grant awarded to Certara UK Ltd. focuses on developing a tool that could automate virtual BE assessments under a variety of study designs by leveraging sufficiently validated mechanistic PBPK models. This research will be developed using case studies of orally administered and LAI drug products to establish a rational framework which addresses relevant considerations for designing an efficient virtual BE study. The outcomes of this research are expected to advance efficient, model-integrated BE approaches by helping to establish best practices for model standardization and validation. This research addresses FY 2023 GDUFA Science and Research Priorities 7A and 7B.

- **Development and Validation of a Workflow to Conduct Virtual Bioequivalence Studies Using PBPK Models (U01FD007906)**

  A grant awarded to Simulations Plus, Inc. focuses on identifying best practices and developing a proposed workflow for the design and conduct of virtual BE studies for

orally administered drug products. This research will leverage in vitro and in vivo data for selected drug products to develop mechanistic oral absorption PBPK models with biopharmaceutics integration that generate realistic population predictions by accounting for various sources of inter-subject and intra-subject variability; the research will also evaluate their generalizability across more than one modeling platform. The outcomes of this research will support the development and validation of a workflow that encompasses all relevant considerations when designing a virtual BE study using mechanistic oral absorption PBPK models, and are expected to advance efficient, model-integrated BE approaches by establishing best practices for model standardization and validation. This research addresses FY 2023 GDUFA Science and Research Priorities 7A and 7B.

8. Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools:

This research initiative focuses on building systems and infrastructure that support the functionality of AI/ML tools which FDA can use to improve the efficiency and consistency of scientific assessments and advice. This includes using AI/ML tools such as natural language processing (NLP) that automate the assembly of key information routinely assessed during the development of recommendations in product-specific guidances (PSGs), or during the assessment of ANDAs, as well as AI/ML tools that facilitate planning and resource allocation to support GDUFA commitments.

- **Large Language Models to Support BE Evaluation (U01FD005978-08)**

  A grant awarded to the University of California, San Francisco (UCSF) - Stanford Center of Excellence in Regulatory Science and Innovation (CERSI) focuses on facilitating ANDA assessment by developing an interactive expert assistant system for FDA assessors that is based on large language models (LLMs). The system would be trained/tuned using information and data in the public domain (e.g., drug labeling and ANDA assessment information that is publicly available through Drugs@FDA). In addition, the system would be able to extract and organize information from text as well as images (e.g., chromatograms) in a variety of file formats. The outcomes of this research are expected to improve the efficiency of ANDA assessment by integrating AI tools with information and data available to FDA and identifying strategies to optimize the reliability of outcomes produced by these tools (e.g., by helping an assessor to efficiently identify/reconcile discrepancies across the data and information submitted in an ANDA). This research addresses FY 2023 GDUFA Science and Research Priority 8B.