Fiscal Year (FY) 2024 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 2024. 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 2024. 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 2024. They are organized based on the GDUFA III priority initiative(s) they address, and thereafter, sorted alphanumerically by the specific FY 2024 GDUFA research priorities they address (e.g., 4A, 4B, etc.).

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

This research area 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.

- **Construction of a Database Containing Drug Biopharmaceutics Classification System (BCS) Class Information (75F40124P00142)**

  A contract awarded to Drexel University will leverage large language models to i) search and extract BCS classification information from relevant data sources, ii) automatically designate the BCS class of a drug substance, and iii) construct a BCS database that contains the BCS class of drug substances for products that are reformulated to mitigate the risk of nitrosamine impurities. The outcomes of this research are expected to establish a BCS database that provides the FDA with a critical tool to help determine appropriate regulatory pathways for such reformulated products.

  This research addresses FY 2024 GDUFA Research Priority 1A: Evaluating practical strategies that may mitigate the potential risks of harmful impurities such as nitrosamine adducts (e.g., NDSRIs), and evaluating the effect of these strategies on the absorption

and/or the bioavailability of active pharmaceutical ingredients (APIs), including utilizing modeling and simulation approaches to assess the risk of altering the performance of a generic product in the event of a reformulation.

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

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

- **Comprehensive Assessment of the Diastereomer Composition of LEQVIO (Inclisiran) to Determine How Chemical Synthesis Impacts Biological Activity (U01FD008322)**

  A grant awarded to the University of Maryland, Baltimore, will synthesize and evaluate the biological activity of each of the diastereomers identified in the GalNAc-conjugated siRNA drug Leqvio (inclisiran), and assess the contribution to the pharmacological effect from each individual diastereomer. The grant will also evaluate the lot-to-lot variability in diastereomeric composition of different lots of Leqvio. The outcomes of this research are expected to develop new methods for the synthesis and biological evaluation of each of the diastereomers of the siRNA drug inclisiran and provide scientific insights that facilitate the generic siRNA product development and assessment.

  This research addresses FY 2024 GDUFA Research Priority 2A: Developing novel analytical methods, as well as improving and standardizing existing methods, to characterize components (including impurities) that can support a demonstration of sameness for oligonucleotide APIs.

- **Developing Universal Control Peptides for T cell Assays Supporting Immunogenicity Assessments for Regulatory Filings (75F40124C00094)**

  A contract awarded to CUBRC, Inc. will develop and validate sets of peptides as candidates for universal positive and negative controls for adaptive immunogenicity assessment assays, such as for class II HLA binding assays and CD4+ T cell assays. The control peptides would be developed based on four peptides that are known to be immunogenic (salmon calcitonin, teriparatide, tirzepatide and exenatide). The outcomes of this research are expected to identify suitable positive and negative control standards that would help confirm the accuracy, sensitivity and reproducibility of assays utilized to evaluate the adaptive immunogenicity of peptide related impurities in prospective generic products, thereby facilitating the development and assessment of certain generic peptide products.

This research addresses FY 2024 GDUFA Research Priority 2A: Developing novel analytical methods, as well as improving and standardizing existing methods, to characterize components (including impurities) that can support a demonstration of sameness for oligonucleotide APIs.

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

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

- **3D Microscopy, Artificial Intelligence-Based Quantification, and Modeling for Non-Clinical Evaluation and Regulatory Support of Complex Injectable and Insertable Drug Products (75F40124D00022-75F40124F19001)**

  A contract awarded to DigiM Solution LLC will provide advanced structural imaging of drug products, combined with models that may correlate these structural attributes with product performance. These advanced product characterization tools will enable sophisticated comparisons of the structure and function of prospective generic products and their RLD. The outcomes of this research are expected to provide key scientific insights that improve our understanding of how variations in formulation composition or differences in manufacturing parameters might modulate product performance. These outcomes are also expected to support generic product development and assessment, potentially by mitigating the risk of failure modes for BE that could arise from differences between a prospective generic drug product and its RLD.

  This research addresses FY 2024 GDUFA Research Priority 3A: Elucidating drug release mechanisms, CQAs, and characterization test methods for long-acting injectable, insertable, or implantable (collectively, LAI) products with the goal of predicting in vivo performance.

- **Development of PBPK Model-Based Mechanistic IVIVCs for Long-Acting Injectable Suspensions (U01FD008304)**

  A grant awarded to the University of Connecticut, Storrs, will develop a physiologically based pharmacokinetics (PBPK) model to predict in vivo drug release from long-acting injectable (LAI) suspensions, incorporating an in depth understanding of formulation critical quality attributes (CQAs) and critical process parameters. This research focuses on modeling the complex interplay between LAI suspension formulations and the physiological response at the depot site to accurately predict in vivo drug release using PBPK models. The outcomes of this research are expected to include scientific insights into how Q3 attributes of LAI suspensions modulate their drug release in vitro, and how the local tissue physiology impacts the in vivo drug release, as well as model-based mechanistic in vitro/in vivo correlations (IVIVCs) for selected LAI suspensions in GastroPlus®. These scientific insights and practical modeling tools will make it easier to

design and develop generic LAI suspensions and support the development of efficient BE approaches for these complex products.

This research addresses FY 2024 GDUFA Research Priority 3A: Elucidating drug release mechanisms, CQAs, and characterization test methods for long-acting injectable, insertable, or implantable (collectively, LAI) products with the goal of predicting in vivo performance

This research also addresses FY 2024 GDUFA Research Priority 7A: Advancing complementary approaches using MIE to support an efficient demonstration of BE specifically for locally acting products (e.g., inhalation and topical routes of delivery) as well as for LAI products.

- **Developing PBPK-Model Based Mechanistic IVIVC for PLGA Implants (U01FD008303)**

  A grant awarded to the University of Texas at Austin will develop IVIVCs for a long-acting PLGA-based solid implant using a PBPK modeling approach. The research will study physicochemical properties of drug molecules and polymers, implant-specific properties, critical formulation attributes, and the physiological response at the site of administration to elucidate deposition characteristics and mechanisms of drug release in vivo. The outcomes of this research are expected to include the development of a bio-predictive in vitro release test method based upon an understanding of how compositional and physicochemical properties of LAI products modulate drug release from an implant in vitro and a PBPK modeling approach to build IVIVCs that predict in vivo PK profiles of selected implant drug products from in vitro data.

  This research addresses FY 2024 GDUFA Research Priority 3A: Elucidating drug release mechanisms, CQAs, and characterization test methods for long-acting injectable, insertable, or implantable (collectively, LAI) products with the goal of predicting in vivo performance

  This research also addresses FY 2024 GDUFA Research Priority 7A: Advancing complementary approaches using MIE to support an efficient demonstration of BE specifically for locally acting products (e.g., inhalation and topical routes of delivery) as well as for LAI products.

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

This research area focuses on understanding of 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.

- **ML-CFD-DEM Based Reduced Order Models (ROM) to Quantify Variability in Inhalers, Drugs, and Users for Evaluating Comparability of Generic OIDP Complex Products (U01FD008379)**

A grant awarded to Oklahoma State University, Stillwater, supports the research and development necessary to establish more efficient BE approaches for orally inhaled drug products (OIDPs). This research focuses on alleviating some of the challenges with using computational fluid dynamics (CFD), including computational time, limited grid resolution, pre- and post-processing of large simulation datasets, model parameter estimations, and uncertainty quantifications. The goal of this research is to leverage machine learning (ML) and make it easier for generic OIDP developers to use CFD modeling as part of an efficient BE approach. The outcomes of this research are expected to include the development of a reproducible strategy for integrating ML techniques into a CFD framework, validation of the ML-CFD solution and analyses for realistic OIDP performance, and the public availability of ML training datasets that generic OIDP developers can use to streamline product development and to support efficient demonstrations of BE.

This research addresses FY 2024 GDUFA Research Priority 4A: Implementing characterization-based (in vitro) methods, potentially together with in vivo PK and modeling methods, as alternatives to the use of comparative clinical endpoint BE studies for nasal and inhaled drug products.

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

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

- **Comparative Use Human Factors Study to Assess Whether Certain User Interface Differences Between Combination Products with Different Syringe Designs Affect User Error Rates (75F40123D00028-75F40123F19002)**

  A contract awarded to Core Human Factors, Inc. will support the conduct of a Comparative Use Human Factors (CUHF) study to evaluate the impact of “other” design differences, specifically the unique dose markings on syringes, between the reference listed drug (RLD) and generic drug-device combination products (DDCPs), evaluating the impact of these design differences on use error rates in relevant user populations. The outcomes of this research are expected to improve our understanding of how “other” design differences impact patients, their caregivers, and the risks of medication errors when a generic DDCP is substituted for its RLD. These scientific insights will inform generic DDCP development and assessment, ultimately enhancing patient access to high quality, therapeutically equivalent generic DDCPs.

  This research addresses FY 2024 GDUFA Research Priority 5A: Improving data analysis approaches for assessing comparative task analysis and comparative use human factors study results.

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.

- **From Bench to Bioequivalence: In Vitro Mechanistic Understanding of ASD Drug Products in Simulated Gastrointestinal Conditions (U01FD008388)**

  A grant awarded to Simulations Plus, Inc. will study selected model amorphous solid dispersion (ASD) drug products based on their differences in formulations and manufacturing process and perform experiments using Tiny-TIM (a system of models mimicking the digestive tract) to assess the effect of meal type and gastric pH modifications on drug bioavailability. The goal of this research is to compare the predictions from Tiny-TIM with human clinical PK data and thereby assess its performance and predictive utility for generic drug development and assessment. The outcomes of this research are expected to include a body of evidence that helps define what in vivo studies could support an efficient demonstration of BE for ASD drug products and inform decisions during product development and assessment by mitigating the risk of potential failure modes for BE with these high-risk generic oral drug products.

  This research addresses FY 2024 GDUFA Research Priority 6: Improving the Efficiency of BE Approaches for Oral and Parenteral Generic Products

- **Factors Related to Drug and Formulation Affecting Alcohol Dose Dumping in Modified Release Oral Drug Products (U01FD008305)**

  A grant awarded to Texas A&M University Health Science Center will study formulation-related and drug-related factors that may impact alcohol dose dumping for modified-release (MR) oral drug products. The research will involve manufacturing MR products with different formulations for two high risk drugs and evaluating their drug release in alcoholic media in vitro. The outcomes of this research are expected to provide the scientific basis supporting more specific recommendations about how to efficiently demonstrate that the potential for alcohol dose dumping by a prospective generic MR drug product is acceptable, thereby, helping to enhance patient access to more generic MR products.

  This research addresses FY 2024 GDUFA Research Priority 6B: Elucidating how ingredients commonly used to modify drug release in orally administered modified release (MR) products function, to facilitate the implementation of risk-based approaches to support biowaivers for MR products, and to elucidate BE considerations for special patient populations

- **Characterizing Albumin-bound Nanoparticle Drugs using wNMR (75F40124C00132)**

  A contract awarded to the University of Maryland, Baltimore, will develop noninvasive analytical methods to characterize two albumin-bound nanoparticle drug products: paclitaxel albumin-bound particles for injectable suspension and sirolimus albumin-bound particles for injectable suspension. The research will utilize water-proton nuclear magnetic resonance (wNMR) to study the disintegration kinetics of these products, employing multiple wNMR modalities with sampling frequencies as low as 5-10 seconds, providing a significant advantage for accurately measuring the disintegration and release of albumin-bound nanoparticles. The outcomes of this research are expected to establish novel, real-time, noninvasive methods for characterizing the breakdown and disintegration kinetics of nanoparticles (with minimal sample treatment). These new methods will finally make it possible to characterize and compare the true immediate disintegration kinetics of albumin-bound nanoparticle drug products, establishing tools to evaluate how compositional differences in such drug products may impact their disintegration and drug release, thereby, supporting the development and assessment of generic albumin-bound nanoparticle drug products.

  This research addresses FY 2024 GDUFA Research Priority 6C: Developing evidence to support the feasibility of efficient BE methods for parenteral and ophthalmic drug products that may contain compositional differences relative to the reference listed drug, and to support global harmonization of the most efficient BE approaches for these products

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 PBPK Model-Based Mechanistic IVIVCs for Long-Acting Injectable Suspensions (U01FD008304)**

  Please refer to Priority Area 3, above, for a description of this research contract awarded to the University of Connecticut, Storrs, which addresses FY 2024 GDUFA Science and Research Priorities 3A and 7A.

- **Developing PBPK-Model Based Mechanistic IVIVC for PLGA Implants (U01FD008303)**

  Please refer to Priority Area 3, above, for a description of this research grant awarded to the University of Texas at Austin, which addresses FY 2024 GDUFA Science and Research Priorities 3A and 7A.

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

This research area 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.

- **The Safety of Switching Between Complex Branded and Generic Drugs: Developing a Semi-Automated Sequential Surveillance System Using Tree-Based Scan Statistics (U01FD008316)**

  A grant awarded to Brigham and Women's Hospital will develop a principled, scalable, and semi-automated approach to evaluate drug device combination products (DDCPs) in the post-market setting using real-world data (RWD). This research will build on state-of-the-art methods in pharmacoepidemiology to analyze large longitudinal healthcare datasets in a transparent and replicable fashion, and reusable algorithms and computable phenotypes will be shared with FDA to support post-market surveillance and research activities. The outcome of this research will help FDA monitor the safety and effectiveness of generic DDCPs to ensure their substitutability and facilitate timely regulatory action when necessary. Additionally, this research can provide insights into the use and outcomes of DDCPs in large, diverse populations of patients receiving routine care with a focus on helping FDA understand the potential impact of DDCP’s with design differences from their RLD

  This research addresses FY 2024 GDUFA Research Priority 8A: Improving the use of real-world evidence for post-market surveillance of generic drug substitution and for evaluating the impact of generic drugs on public health.