Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year (FY) 2024

Consistent with FDA's commitment reflected in the GDUFA Reauthorization Performance Goals And Program Enhancements Fiscal Years 2023-2027 (GDUFA III Commitment Letter), FDA held a public workshop on May 11th and 12th, 2023, to obtain input on GDUFA science and research priorities.

FDA relies, in part, upon this public input to identify science and research priorities that can help expand and accelerate patient access to generic drug products. FDA considered the public input, along with comments provided in the workshop discussions, and comments submitted to the docket. This feedback, collectively, supported the advancement of research in eight priority areas for the GDUFA science and research program.

These eight areas encompass scientific challenges that the generic industry and FDA's generic drug program identify as being significant over the coming years, and they also represent opportunities for scientific advances to accelerate access to generic versions of complex products and make the development of generic drugs more efficient and globally harmonized. Scientific advancements in these areas would maximize the use of the generic drug process to supply needed medications, modernizing the generic drug program to use advances in data science and models in application assessments.

Specific research priorities for FY 2024 were identified within each of the eight research areas enumerated below. The numbering of the eight research areas does not reflect any relative prioritization among the research areas.

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. FY 2024 science and research priorities specifically include:

A. 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

B. Developing analytical methods, and approaches using orthogonal methods, for the identification and quantitation of nitrosating species in ingredients, including considerations for the distribution of nitrosating species in an ingredient or drug product
C. Elucidating the reactivity of different functional groups in APIs (e.g., tertiary amines beyond secondary amines) or other factors that may improve the ability to predict formation of NDSRIs or small molecule nitrosamines and the risks of their formation under relevant conditions for pharmaceuticals
D. Estimating acceptable intake amounts for impurities such as nitrosamine adducts (e.g., NDSRIs) using certain mutagenicity evaluations (involving in vitro, in silico or in vivo (animal) models) or using quantitative structure activity relationship modeling

2. Enhance the Efficiency of Equivalence 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. FY 2024 science and research priorities specifically include:

A. 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
B. Improving and standardizing in vitro methods for assessing the immunogenicity of peptide or oligonucleotide products, including associated impurities

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. FY 2024 science and research priorities specifically include:

A. 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
B. Improving characterization tools for polymeric ingredients and related complex formulations to support assessments of qualitative sameness

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. FY 2024 science and research priorities specifically include:

A. 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
B. Developing efficient BE methods for topical drug products (applied to skin or other areas for local action) that may contain compositional differences relative to the reference standard
C. Improving comparative in vitro permeation test (IVPT) and in vivo cutaneous pharmacokinetics (PK)-based study designs and data analysis techniques that help to resolve practical challenges with implementing these methodologies to support a demonstration of BE for topical drug products

5. Enhance the Efficiency of Equivalence 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. FY 2024 science and research priorities specifically include:

A. Improving data analysis approaches for assessing comparative task analysis and comparative use human factors study results
B. Developing improved criteria for comparative device performance assessments that would support a demonstration of BE by in vitro methods (e.g., predictive adhesion performance of transdermal delivery systems or anthropometric evaluation of device design changes for injectable and inhaled drug products) to eliminate the need for certain in vivo studies
C. Developing efficient approaches to support transitions by generic products to utilize more environmentally friendly propellants

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

This research area focuses on understanding of how ingredients in oral and parenteral drug products may modulate bioavailability, and on improving biorelevant dissolution methods as well as in silico models to support the expansion of biowaivers and to support global harmonization under ICH M13A[1]. This includes developing evidence to support the feasibility of biowaivers for immediate release (IR) oral drug products with differences in formulations larger than currently recommended in FDA guidance, or for IR oral drug products that do not demonstrate comparable dissolution profiles across strengths. It also includes establishing approaches to manage potential risks related to subject safety more consistently when developing clinical BE study recommendations and elucidating potential

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Draft Guideline M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

failure modes for BE with special populations (e.g., pediatric, or geriatric patients) to improve tools and methodologies that can be incorporated into BE study recommendations which ensure the equivalence of therapeutic outcomes in diverse populations. FY 2024 science and research priorities specifically include:

A. Utilizing oral physiologically based PK (PBPK) modeling to identify risk factors for food effects and formulation dependent drug interactions (e.g., proton pump inhibitors) to support global harmonization of the most efficient BE approaches for these products
B. 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
C. 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 area 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. For example, while it may not be feasible to adequately characterize the long-term bioavailability of drugs from LAI products using in vivo or in vitro methods alone, it may be feasible to integrate limited in vivo and in vitro data with PBPK models that generate the remaining evidence needed to support a demonstration of BE. This area includes research on the use of MIE to evaluate failure modes for BE and to optimize the design of BE studies. FY 2024 science and research priorities specifically include:

A. 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
B. Establishing best practices for model standardization, validation, acceptance, and sharing (e.g., using model master files) that improve the reproducibility and reusability of quantitative pharmacology information used in BE study simulations

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. FY 2024 science and research priorities specifically include:

A. 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
B. Integrating AI/ML tools with FDA information and data to support quantitative analyses and modeling approaches that facilitate regulatory assessments, and identifying strategies to optimize the reliability of outcomes produced by these tools
C. Exploring the capability of AI/ML tools for a prospective applicant to be able to efficiently assess the completeness of its ANDA prior to submission, and to enhance the efficiency, consistency, and quality of regulatory assessments once ANDAs are submitted