Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year (FY) 2022

Consistent with FDA's commitment reflected in the GDUFA Reauthorization Performance Goals And Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter), FDA held a public workshop on June 23, 2021, and specifically asked for comments on the 15 scientific priorities posted in FY 2021. At this workshop, FDA also sought input on topics identified in the March 24, 2021 Federal Register notice announcing the FY 2021 public workshop. FDA relies, in part, upon this public input to identify science and research priorities for FY 2022 that can help accelerate access to generic drug products. FDA considered the aforementioned public input, along with comments provided in the workshop discussions, and comments submitted to the docket. This feedback, collectively, resulted in the revision of several priority areas for FY 2022.

For example, FDA received general feedback that research to support global harmonization of the most efficient BE standards should be prioritized. In addition, several generic industry stakeholders emphasized the need for research on harmful impurities such as nitrosamines, potentially related to their formation or mitigation, the development of computational toxicology tools, and the assessment of human exposure risks. The scientific considerations associated with harmful impurities such as nitrosamines are not specific to generic products, but, given the number of prescriptions filled by generic medications, this is a high priority for generic product manufacturers. This feedback was incorporated into revisions to the FY 2022 science and research priorities D2, D3 and D5.

FDA also received feedback about the need for tools to facilitate the prediction of both lung tissue concentrations and systemic concentrations of orally inhaled products, suggesting a need for research to link validated computational fluid dynamics (CFD) models to mechanistic physiologically based pharmacokinetic (PBPK) models; this feedback also suggested a need for research utilizing CFD modeling to explore the relationship between aerodynamic particle size distribution (APSD) and regional lung deposition for various orally inhaled products, and to calibrate the cascade impactor studies that are used to derive APSDs. Based upon this feedback, the FY 2022 science and research priority B1 has been revised to encompass improvements to not only PBPK models but also to CFD models, which can support alternative approaches by which to demonstrate bioequivalence (BE) for orally inhaled products.

In addition, FDA received specific feedback that results from dissolution tests may have limitations for informing PBPK and pharmacokinetic/ pharmacodynamic (PK/PD) models that are intended to support a demonstration of BE, and that research is needed to potentially also integrate the results from permeability studies into these models. Therefore, the FY 2022 science and research priority D2 has been revised to prioritize the development of tools and methodologies for BE and therapeutic equivalence evaluation that integrate predictive dissolution as well as permeability test results with PBPK and PK/PD models, as well as machine learning, to evaluate in vitro BE options for

orally administered drug products and to support global harmonization of the most efficient BE recommendations.

Another area where FDA received specific feedback related to prioritizing research into the utilization of artificial intelligence (AI) to enhance and expedite the development and assessment of generic drugs. Discussions during the FY 2021 public workshop illustrated that AI tools are already utilized by certain generic industry stakeholders, who confirmed the current utility and future potential of AI to support generic drug development and assessment. Further research was recommended to establish how AI can support the assessment of prospective generic drugs, and based upon this feedback the FY 2022 science and research priority D5 has been revised to prioritize the development of methods and integrated technological solutions that will allow FDA to leverage AI to support regulatory decisions and improve post-market surveillance of generic drug substitution. Potential research in this area may include an assessment of opportunities for AI to improve modeling approaches by the inclusion of appropriate domain knowledge, assist with the interpretation of comparative product characterization data and performance results, and facilitate expeditious access to information in FDA's databases to support the consistency and comprehensiveness of ANDA assessments.

The priority initiatives are organized according to the categories of complex generic drug products described in the GDUFA II Commitment Letter, followed by a category addressing topics related to tools and methodologies for evaluating bioequivalence and therapeutic equivalence more generally. These initiatives are based on the need to develop efficient and modern generic drug research, development and review tools:

A - Complex active ingredients, formulations, or dosage forms

1. Improve advanced orthogonal methods for characterization of chemical compositions, molecular structures, and distributions of complex active ingredients
2. Improve particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products
3. Establish predictive in silico, in vitro, and animal models to evaluate immunogenicity risk of formulation or impurity differences in generic products
4. Develop predictive in vitro BE methods for long-acting injectable drug products including the identification of the critical quality attributes (CQA) and drug release mechanisms for these products
5. Advance characterization tools for polymeric excipients and related complex formulations to provide product-specific guidance on qualitative sameness assessment and explore alternative bioequivalence approaches.

B - Complex routes of delivery

1. Improve physiologically based pharmacokinetic (PBPK) and computational fluid dynamics (CFD) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic) to allow their use in supporting alternative BE approaches
2. Enhance understanding of the role of excipients in topical drug absorption to evaluate in vitro BE methods for non-Q1/Q2 topical drug products applied to skin or other local areas

3. Implement in vitro methods together with PK and certain other methods as alternatives to the use of comparative clinical endpoint BE studies for nasal and inhaled drug products

C - Complex drug-device combination products

1. Evaluate the impact of identified differences in the user-interface from the reference listed drug (RLD) on the therapeutic equivalence and post-marketing safety of complex generic drug-device combination products
2. Develop criteria for device performance comparisons that would support a BE demonstration by in vitro methods and eliminate the need for in vivo BE studies.

D - Tools and methodologies for BE and therapeutic equivalence evaluation

1. Improve quantitative pharmacology and BE trial simulation to optimize the design of BE studies for generic drug products and establish a foundation for model-based BE study designs
2. Integrate predictive dissolution and permeability test results, PBPK models, (PK/PD) models and machine learning to evaluate in vitro BE options for orally administered drug products, support global harmonization of the most efficient BE recommendations, or assess the risk of human exposure to harmful impurities such as nitrosamines
3. Expand the scientific understanding of the role of excipients in generic drug products, either related to the formation or mitigation of harmful impurities such as nitrosamines, or to support the expansion of the Biopharmaceutics Classification System (BCS) Class 3 biowaivers to drug products with differences in formulations larger than currently recommended in FDA guidance
4. Develop alternative BE approaches to account for unexpected events such as COVID-19-related study interruptions and protocol deviations
5. Develop methods and integrated technological solutions that will allow FDA to leverage AI tools and large data sets (such as the development of models and data to support quantitative structure-activity relationship (QSAR)-based methods for harmful impurities such as nitrosamines, bioequivalence study submissions, electronic health records, substitution/utilization patterns, drug safety data, and drug quality data) to support regulatory decisions and to improve post-market surveillance of generic drug substitution

The feedback provided to FDA during the FY 2021 public workshop, along with comments received to the docket, also emphasized the continued need to prioritize science and research in the specific areas already described in the 15 scientific priorities posted in FY 2021. Therefore, FDA will continue to advance research initiatives consistent with these priorities for FY 2022, and will track and report on these priority initiatives during this last year of GDUFA II. Examples of potential new science and research initiatives for FY 2022 that support the continuing priority areas from FY 2021 include the following:

A. **Complex active ingredients, formulations, or dosage forms**: Under priority A1, research to improve advanced orthogonal methods for the characterization of chemical compositions, molecular structures, and distributions of complex active ingredients may focus on new methodologies that have the potential to support a demonstration of BE for generic versions of oligonucleotide drug products.

B. **Complex routes of delivery**: Under priority B1, research to improve PBPK and CFD models of drug absorption via an inhaled route of delivery may focus on new tools that can support alternative BE approaches, potentially related to elucidating mechanisms that may drive slow regional absorption of drugs in the lung, expanding human airway models to account for population variation and disease states, enhancing the modeling of receptor dissociation for inhalation PBPK models, and optimizing the prediction of metered dose inhaler atomization to provide complete model characterizations of device and formulation behavior, as well as the development of tools like lung on a chip or whole lung in vitro models for measuring regional deposition.

C. **Complex drug-device combination products**: Under priority C1, research to evaluate the impact on therapeutic equivalence of identified differences between the user-interfaces of proposed generic combination products and their reference listed drug products may focus on evaluating how factors like age, comorbidities, education, race, ethnicity, socioeconomic level, and geographic location may influence study outcomes when comparing user interfaces, or may influence the potential for medication errors.

D. **Tools and methodologies for BE and therapeutic equivalence evaluation**: Under priority D1, research to improve quantitative pharmacology and BE trial simulation to optimize the design of BE studies for generic drug products and establish a foundation for model-based BE study designs may focus on new approaches to support waivers for additional strengths, to assess when fed PK BE studies may potentially be waived, and to explore the feasibility of potential alternatives to the use of vehicle placebo treatment arms in comparative clinical endpoint BE studies for topical products.