Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year 2021

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 May 4, 2020, and specifically asked for comments on the 15 scientific priorities posted in FY 2020 to accelerate access to generic drug products in order to identify priorities for FY 2021. FDA considered comments provided in the workshop discussions as well as comments submitted to the docket. This feedback resulted in the revision of several priority areas for FY 2021 as well as new priorities that reflect the current landscape of regulatory science needs. For example, the research priority initiative to develop better methods for evaluating abuse deterrence of opioid products that was included in the FY 2020 priorities was removed from the FY 2021 priorities as FDA's ongoing research in this area is sufficient to address the identified needs. The success of our research programs on alternative bioequivalence (BE) methods for topical and ophthalmic products has led to the completion of these priorities and a new focus on expanding alternative BE methods to a larger space of formulation differences. For inhalation drug products, the success of previous research activities has changed the focus from development of new BE approaches to implementation of new BE approaches. Research priorities to optimize BE study design and methodologies to evaluate modified study designs have been proposed for FY 2021 as a response to the ongoing COVID-19 pandemic. A new focus of our modeling and simulation research for oral products will support ongoing global harmonization of BE standards via the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) process. FDA will continue to track and report on these priority initiatives during the next 2 years of GDUFA II. In each year of GDUFA II, FDA may revise the list and indicate when the priority initiatives are complete.

The priority initiatives below 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 in 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 BE approaches

B - Complex routes of delivery

1. Improve Physiologically Based Pharmacokinetic (PBPK) 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 excipients on 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 alternative 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 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

D - Tools and methodologies for BE and therapeutic equivalence evaluation

1. Improve quantitative pharmacology and BE trial simulation to optimize design of BE studies for generic drug products and establish a foundation for model-based BE study designs
2. Integrate predictive dissolution, PBPK, Pharmacokinetic/Pharmacodynamic (PK/PD) models and machine learning to evaluate in vitro BE options for orally administered drug products and support global harmonization of the most efficient BE recommendations
3. Expand the scientific understanding of the role of excipients in generic drug products 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 large data sets (e.g., BE study submissions, electronic health records, substitution/utilization patterns, drug safety data, and drug quality data) to support regulatory decisions and improve post-market surveillance of generic drug substitution