Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year 2020

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 1, 2019, and specifically asked for comments on the 15 scientific priorities posted in FY 2019 to accelerate access to generic drug products in order to identify priorities for FY 2020. FDA considered comments provided in the workshop discussions as well as comments submitted to the docket. This feedback did not result in the identification of new priority areas for FY 2020, as almost all comments were directed toward the existing research priorities. Therefore, FDA will continue following FY 2019 GDUFA Science and Research priority initiatives with minor modifications into FY 2020 and will continue to track and report on these priority initiatives during the next 3 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 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 (BE) 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 analytics 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) for these products
5. Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

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)
2. Expand characterization-based BE methods across all topical dermatological products
3. Expand characterization-based BE methods across all non-solution ophthalmic products
4. Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) comparative clinical endpoint BE studies for inhaled corticosteroids
5. Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products that are more predictive of and sensitive to differences in local delivery

C - Complex drug-device combinations

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 complex generic drug products

2. Integrate predictive dissolution, PBPK and Pharmacokinetic/Pharmacodynamic (PK/PD) models establishing generic drug bioequivalence standards

3. Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System (BCS) of Class 3 biowaivers to drug products with differences in formulations larger than currently recommended in FDA guidance

4. Develop methods and integrated technological solutions that will allow FDA to leverage large data sets (such as bioequivalence 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

Discussions and Comments at the FY 2019 Public Workshop

According to the public comments and discussion with internal stakeholders, FDA should conduct research related to:

1. Characterization of new classes of complex APIs, such as oligonucleotides to inform development of monograph standards and specifications and provide more clarity on the number of batches that need to be characterized [A1].
2. Characterization studies to ensure drug product sameness for complex injectables [A4] and API sameness for complex mixtures and peptides [A1].
3. Particle size measurement and methods for statistical evaluation to support the use of in vitro BE methods for simple [drug] suspensions, such as ophthalmic suspensions and parenteral suspensions [A2].
4. Utility of animal models in supporting in vitro-in vivo correlation (IVIVC) development and in vitro/in vivo bridging [A4, B3].
5. Development and validation of PBPK models by the Agency for locally-acting drugs to support in vitro BE methods and establish relationships between local and systemic exposures [B1].
6. How to handle below the limit of quantification (BLOQ) values, outliers, and missing or unbalanced data (due to device malfunction) in in vitro permeation tests (IVPT) [B2].
7. Design of appropriate comparative human factors studies that support evaluating differences in user interface design [C1].
8. Model effects of transdermal patch adhesion on PK profile [D1].
9. Developing alternative approaches to multi-dose BE studies that require steady state, especially for long acting injectable products [D1, A4].
10. Use of biorelevant tools to expand alternative dissolution methods for BE [D2].
11. Use of quantitative models for endogenous compounds to establish whether the level of change from baseline can potentially confound BE determination and optimize BE study design [D2].
12. Improving quantitative models to better predict the impact of sugar alcohols on solution bioequivalence [D2].
13. Avoiding use of fed BE studies for high solubility IR drug products, including modeling to improve prediction of fed studies and analysis of FDA and industry datasets [D2].
14. Investigating in vitro alternatives to in vivo sprinkle BE studies [D2].
15. Methods to support bridging studies (intended to establish the degree of similarity between U.S. and foreign products), particularly in cases when U.S. samples are only sufficient for bridging studies but not for pivotal studies [D2].
16. Expanding scientific understanding of role of excipients and approaches to support Class 3 biowaivers for drug products that do not contain the same formulations qualitatively or quantitatively (non-Q1/Q2), including modeling approaches to improve the understanding of the interplay between excipients and the physiological environment of the GI tract on drug luminal concentrations, transit, gut metabolism, and gut wall permeability (including the impact of high or low permeability values on BE risk) [D3].
17. Investigating range of grades for commonly used excipient families for toxicological effects to support bridging studies [D3].
18. Mining un-submitted BE datasets (obtained via collaboration with the generic industry) to gain understanding of RLD lot-to-lot variability and handling outliers [D4].

19. Development of alternative approaches to address outliers in clinical BE studies when the causes are not related to the test formulation [D4].
20. Application of Bayesian approach in facilitating generic drug development [D4].