GDUFA Regulatory Science Priority Initiatives for Fiscal Year 2019

FDA prepares a yearly list of regulatory science priority initiatives for generic drugs as part of a commitment in the Generic Drug User Fee Amendments of 2017 (GDUFA II). These priority initiatives are chosen based on input from FDA, industry and other stakeholders.

GDUFA II regulatory science supports the fulfilment of product-specific guidance development, pre-ANDA meeting, and ANDA submission review commitments. The regulatory science program enables the conduct of research to investigate scientific issues that are encountered during review of regulatory submissions. In addition, research is important for the development of guidances and recommendations that can guide generic product development during the pre-ANDA phase. The GDUFA II commitments provide a new pre-ANDA program designed to accelerate access to generic versions of complex drug products. The pre-ANDA program allows FDA to engage with potential applicants in pre-ANDA meetings that discuss development strategies for complex generic drug products that do not have product-specific guidances or that propose new or alternative development strategies for complex generic drug products. Elements of this program, including the development of product-specific guidances and pre-ANDA meetings, require FDA to constantly build a strong scientific foundation related to complex generic drug products. This scientific foundation supports the development of new and more efficient equivalence methods.

FDA held a public workshop on May 24, 2018, and specifically asked for comments on the 15 scientific priorities posted in FY 2018 to accelerate access to generic drug products. FDA considered comments raised in the workshop discussions as well as comments submitted to the docket. Specifically, 10 post-workshop panelist comments and 8 comments from the docket were received. This feedback did not result in the identification of new priority areas for FY 2019. Almost all comments were directed toward the existing research priorities. Therefore, FDA will continue following FY 2018 GDUFA regulatory science priority initiatives with minor modifications into FY 2019 and will continue to track and report on these priority initiatives during the next four years of GDUFA II. In each year of the 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 and 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 bioequivalence (BE) methods for long-acting injectables 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 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 RLD on the substitutability of complex generic drug-device combination products

D - Tools and methodologies for BE and substitutability 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 non-Q2 (quantitatively inequivalent) formulations
4. Develop methods 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 2018 Public Workshop

After reviewing the public comments, we will consider the following input in the implementation of the FY 2019 research priorities noted above. According to the public comments, FDA should conduct research related to:

- Pharmaceutical equivalence for peptides and oligosaccharides including active pharmaceutical ingredient (API) sameness, impurity characterization and immunogenicity risk assessment [part of A1 and A3]
- Pharmaceutical equivalence for extended-release parenteral products (e.g., microspheres and suspension) including the development of tools or approaches for immunogenicity risk assessment [part of A3 and A4]
- In vitro Q3 approaches to support therapeutic equivalence of complex formulations and dosage forms (e.g., topical, transdermal, inhalation, and ophthalmic products) [part of B2, B3, B4, and B5]
- Determining the CQAs of complex products; linking CQAs to clinical relevance to establish therapeutic equivalence of complex products through in vitro and/or ex vivo approaches [part of A4, B2, B3, B4, and B5]
- Biorelevant and novel in vitro release methods for solid oral dosage forms [part of D2]
- Modeling and simulations on meta-data to determine the most sensitive study design, alternative endpoints or bioequivalence margin for clinical endpoint bioequivalence studies [part of D1]
- Developing a model-based equivalence assessment methodology for longitudinal efficacy data in comparative clinical endpoint bioequivalence studies [part of D1]
- Physiological data to support PBPK models, specifically, the parameters that would define different tissues in the body, differences of these parameters in different populations and disease states, and how these parameters fluctuate not only across a population but within a variable (this final point is of particularly important to virtual BE study simulations) [part of B1]
- Mechanistically understanding formulation factors for their incorporation into PBPK models, specifically, how formulation factors/CQA impact BE (whether systemic or local) and what is the impact of different excipients (i.e., non-Q2) [part of B1, B2, B2, B4, B5, and D2]
- Using PBPK modeling to evaluate bioequivalence in all conditions (such as administration with food) and populations in which a generic product may be used [part of D2]
- A quantitative and integrative approach that will separate post-marketing “signals from noise” to discern whether post-marketing complaints should be prioritized for further investigation [part of D4]
- Determining the CQAs of complex products and ensuring the most efficient and relevant techniques and methodologies are recommend for in vitro-only approaches to assess bioequivalence [part of A4, B2, B3, B4, and B5]
- Ensure that as new BE approaches are developed that the analytical and computational methods are practical and implementable by generic drug developers in addition to providing sufficient evidence of bioequivalence [part of A4, B1, B2, B3, B4, B5, D1, and D2]
- Explore how to increase transparency and engagement with interested parties, including establishing processes for making research data more publicly accessible [relevant to all areas]