GDUFA Regulatory Science Priorities for Fiscal Year 2017

In the Generic Drug User Fee Amendments (GDUFA) of 2012, FDA committed to prepare a yearly list of regulatory science priorities for generic drugs based on input from industry and other stakeholders. Our focus in the final year of GDUFA I is to complete research activities identified in prior years rather than initiate new priorities. Therefore, FDA Office of Generic Drugs developed the following fiscal year (FY) 2017 regulatory science priorities for generic drugs:

- **Post-market evaluation of generic drugs**
- **Equivalence of complex products**
- **Equivalence of locally-acting products**
- **Therapeutic equivalence evaluation and standards**
- **Computational and analytical tools**

Post-market evaluation of generic drugs includes research into monitoring methods, understanding patient perceptions of generic drug quality and effectiveness, and verifying therapeutic equivalence via patient brand-to-generic switching studies. These investigations provide additional data in therapeutic areas where concern exists about the substitutability of generic drugs and allow FDA to verify that generic drugs are fully interchangeable, safe, and effective in comparison to their reference listed drug (RLD). Ongoing activities include evaluating modified release formulations, identifying the role replicate design studies may add to bioequivalence determinations, and piloting surveillance methodologies for generic drugs within FDA's Sentinel program.

Equivalence of complex drug products includes research into making generic versions available in all product categories, including complex drugs with unique characteristics. FDA spends an increasing amount of time reviewing and developing policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs. This scientific research supports the development of guidance and policy that clarifies the Abbreviated New Drug Application (ANDA) pathway for complex products, such as drug-device combinations, transdermal systems, implants and parenteral microspheres, nanomaterials (e.g. liposomes and iron colloids), and products that contain complex mixtures and peptides. Research continues into new guidance for transdermal irritation studies and for human factors studies that will aid in evaluation of product substitutability and robustness for drug-device combinations.

Equivalence of locally-acting products includes research into new bioequivalence methods and pathways for locally-acting drugs. To date, the lack of efficient bioequivalence pathways for locally-acting drug products has limited the availability of generic drugs in this category, which includes inhalation, topical dermatological, nasal, ophthalmic, gastrointestinal, and otic drug products. This research priority includes evaluating in vitro alternatives to clinical endpoint bioequivalence studies. Often these in vitro alternatives are based on microstructure characterization (Q3 equivalence) for

products that are qualitatively (Q1) and quantitatively (Q2) similar in formulation, with a research goal of guidance for Q3 bioequivalence approaches. To provide access to generic products for which a Q3 approach is not sufficient, research continues into BE approaches for non-Q1 and Q2 complex formulations for nasal, inhalation and dermal products.

Therapeutic Equivalence Evaluation and Standards research supports the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery. FDA continues to prioritize research that supports a pathway for generic versions of abuse-deterrent formulations, improves the evaluation of excipients both for safety and for their impact on BCS class III biowaivers, increases our understanding of solid dispersions of low solubility drugs and supports equivalence of modified release solid oral dosage forms. Many of these goals include research related to improving manufacturing quality through advances in process control, continuous manufacturing and quality metrics, advancing analytical characterization of the release or abuse-deterrent mechanisms and improvement to IVIVC/dissolution methods.

Computational and Analytical Tools impact the other four GDUFA regulatory science priority areas and are essential to modernizing the ANDA review process. Modeling and simulation tools that FDA will investigate include physiologically-based pharmacokinetic or absorption models; pharmacodynamic models or clinical trial simulation; systems biology; and quantitative risk modeling. Research priorities for advanced analytical methods include developing methods that characterize peptides and other complex mixtures and that evaluate particle size, surface chemistry, and gene expression for impurities or immunogenicity. Investment in data warehouse infrastructure is needed to further enable computational tools for research and regulatory review, risk assessment and fraud/outlier detection. Research continues in the use of modeling and simulation tools to address questions of substitutability outside the range of traditional bioequivalence studies such as pediatric and geriatric populations or patients taking proton-pump inhibitors and generalization of statistical methods for evaluating in vitro equivalence.