GDUFA Regulatory Science Priorities for Fiscal Year 2016

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. To comply with this GDUFA requirement, the FDA Office of Generic Drugs developed the following fiscal year (FY) 2016 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). Based on public and FDA input, FY 2016 research priorities include evaluating modified release formulations, such as those for anti-epileptic drugs and identifying the role replicate design studies may add to bioequivalence determinations. New FY 2016 priorities include 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. New FY 2016 priorities include transdermal irritation studies and research into 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. New FY 2016 priorities include BE approaches for non-Q1 and Q2 nasal and MDI formulations.

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 for abuse-deterrent formulations, narrow therapeutic index (NTI) drugs, and equivalence of modified release solid oral dosage forms. Developing the pathway for generic versions of abuse-deterrent formulations requires tools for evaluating antagonist/agonist combinations and technologies to deter nasal abuse. Based on the significant clinical impact of small variations in drug exposure, generic versions of NTI drugs require risk-based review that includes identifying NTI drug methods, adjusting bioequivalence standards, and improving manufacturing quality through advances in process control, continuous manufacturing and quality metrics. Modified release solid oral dosage forms have more failure modes than immediate release products; therefore, research into improving review standards for equivalence of modified release products is critical. New FY 2016 research priorities include the interpretation of fully replicate design BE studies to identify more precisely when they add value to the ANDA review of modified release products, research to support improved consistency of the manufacturing of modified release products (including analytical characterization of the release mechanism, improvement to IVIVC/dissolution methods, and use of quality metrics), and research to improve the evaluation of excipients both for safety and for their impact on BCS class III biowaivers.

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. New FY 2016 research priorities include investigating 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.

Public Input

The FY 2016 research priorities list was prepared based on comments received at the June 5, 2015 public meeting,[1] comments submitted to the public docket, scientific issues raised in citizen petitions, meeting request and controlled correspondence topics, tracked safety issues, and discussions within FDA's Center for Drug Evaluation and Research.

Public input, as described above, included the following recommendations:

- Equivalence methods for complex and locally acting drugs
    - Improve in vitro release for ophthalmic drugs
    - Develop bioequivalent topical products, implants, and long-acting injectables; fund studies on in vitro bioequivalence and nanomaterial generics, such as liposomes and nanocolloids; and clarify standards for equivalence of drug/device combinations
    - Nanomedicine fractionation methods to determine bioequivalence and facilitate generic development
    - Development of precise, well-defined in vitro methodologies to replace the need for clinical endpoint studies for nontraditionally absorbed drug products. New methodologies must be carefully evaluated before it can be relied upon by patients and regulators.
    - Methods to evaluate physicochemical properties for monitoring and control of manufacturing process of complex drugs
- Post-market surveillance and evaluation of generic drugs
    - Better, systematic approach to monitoring appropriate prescribing of generic drugs and responding to issues about generic drug safety is a national, public health need
    - Consider the substitution of generic products in pediatric populations and identify any addition factors that may impact successful substitution
    - Evaluate regional use of generic medications (regional market penetration) using claims databases
    - Evaluate characteristics of patients who receive branded versus generic formulations of specific medications
- Therapeutic equivalence evaluation and standards
    - Tighter standards for NTI drugs especially anti-epileptic drugs (AEDs) and consideration of substitution in pediatric and geriatric populations
    - Further research into variability of excipients, particularly on how they may affect clinical performance, even if finished product meets normal specifications and improvements in availability of information about excipients to aid product development
    - Research into approaches to evaluate significance of shape differences relative to the RLD
    - Advancements in in vitro/in vivo dissolution methods to predict in vivo performance
    - Research into establishment of quality metrics

[1] http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm387358.htm