GDUFA Regulatory Science Priorities for Fiscal Year 2015

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) 2015 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 researching 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 2015 research priorities include evaluating extended release formulations, such as those for anti-epileptic drugs and attention deficit hyperactivity disorder drugs.

Equivalence of complex drug products includes research into making generic versions available in all product categories, including complex drugs with unique characteristics. FDA's Office of Generic Drugs 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.

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, gastro-intestinal, and optic drug products. This research priority includes re-evaluating statistical methodologies for topical and transdermal product irritation and investigating in vitro alternatives to clinical endpoint bioequivalence studies.

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’s research priorities are as follows: 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 and continuous manufacturing. Further, 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 approaches to bioequivalence study analysis for modified release solid oral dosage forms such as partial area under the curve, in vitro/in vivo correlation, or predictive dissolution will enable risk-based review based on dosage form complexity.

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. At the interface between methods and modeling are statistical methodologies for evaluating in vitro equivalence, including methods for in vitro bioequivalence of cascade impactor data. Investment in data warehouse infrastructure is needed to further enable computational tools for research and regulatory review.

Public Input

The FY 2015 research priorities list was prepared based on comments received at the May 16, 2014 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:

- Post-market surveillance and evaluation of generic drugs
    - Leverage the rapid proliferation of public and private data to utilize enormous population data sets for systemic adverse-event surveillance, and formulate enhanced, systematic approaches for monitoring and responding to issues regarding generic drug safety.
- Bioequivalence of complex and locally-acting products
    - 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.
- Therapeutic equivalence evaluation and standards
    - Control raw materials in manufacturing; improve blend uniformity testing; enhance facility and manufacturing processes and technologies; define standard quality metrics for evaluation of manufacturing processes; set clinically relevant specifications; provide guidance on size and shape requirements; evaluate abuse-deterrant technologies; develop in vivo predictive dissolution methods; and expand biopharmaceutics classification system biowaiver-based approvals.
- Computational and analytical tools
    - Improve inactive ingredient databases; develop predictive risk models to reduce drug shortages; and enhance models for robust risk assessment.
- Timeliness and Priorities
    - Provide timely responses to pre-ANDA complex drug meetings, and prioritize efforts so as to accelerate the availability of new generic medicines, medicines that lack significant generic competition, and medicines that play a particularly important role in public health.

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