June 2, 2017
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2013-N-0402-0029, Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives; Public Workshop; Request for Comments

To Whom It May Concern:

An important public hearing was held at the Food and Drug Administration (FDA) in early May 2017 related to setting a research agenda for the FDA Office of Generic Drugs under the Generic Drug User Fee Act. We commend the agency for seeking input through this process and would like to highlight what we believe are some of the key priorities related to generic drug approval and optimal clinical use of generic drugs.

A competitive generic drug market consisting of sufficient numbers of independent manufacturers making high quality products is essential to the US health care system and to all aspects of clinical care, given the ubiquity of generic drug use. At the same time, we must ensure that there is sufficient physician and patient confidence in the generic drugs that they take to reduce waste and promote better adherence and patient outcomes. There are two main types of studies that can help reach these goals: (1) research on strategies that delay timely availability of generic drugs, and (2) research on outcomes from post-approval use of generic drugs.

(1) Ensuring timely availability of generic drugs

There are many issues that can block the appropriate development of a competitive generic drug market. For example, pharmaceutical manufacturers obtain a portfolio of secondary patents on their marketed drugs, seeking to extend the duration of its patent exclusivity far beyond that of the originator product (small molecule, biologic, or otherwise).1 We looked at two HIV drugs, ritonavir and lopinavir/ritonavir, identifying 108 patents that could have been used to delay competition for an additional 12 years beyond base compound patents.2 Many of these patents covered related chemical structures, manufacturing processes, and methods of treatment. When these patents are listed in the FDA Orange Book, generic

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drug manufacturers must figure out a way to design around them or get them overturned in court. This process is extremely prevalent in the pharmaceutical industry, adding between 6 and 7 years of additional exclusivity for Orange Book listed drugs from 1988 to 2005. We therefore recommend that the Office of Generic Drugs study the listing process for patents in the Orange Book, including the types of patents listed, the outcomes of those patents in subsequent litigation, and the relationship between the types of patents listed in the Orange Book and the number and quality of generic drug applications.

Delays in the generic drug approval process can also come from outside the Orange Book system. For a generic drug manufacturer to undertake studies for ANDA approval, it must obtain a sample of the reference product. Some companies have successfully delayed market entry of generic drugs by refusing to provide samples. The FDA could study alternative approaches that could help prevent such anticompetitive business strategies, such as the possibility that the FDA might act as a sample repository for reference brand-name drugs.

Finally, we recommend that the FDA undertake formal, independent evaluation of the mechanics of its review processes. For example, while OGD has reduced its time for approving ANDA applications since 2012, remaining challenges include poor quality of initial ANDA submissions by generic manufacturers that require multiple review cycles to approve. We therefore suggest that the OGD study the quality of ANDA applications and the potential impact of greater transparency of the ANDA queue, as detailed in a recent report from Sharfstein et al. Similarly, a recent study has highlighted the prevalence of Citizen Petitions from brand-manufacturers, aimed at influencing the ANDA approval process. The FDA has often denied late-filed Citizen Petitions as ANDA applications are approved, but the agency could undertake a study of the characteristics of such late-filed petitions and how they affected generic uptake.

(2) Post-approval use of generic drugs and its outcomes

A vibrant, competitive marketplace of high quality generic drugs requires attention to ensure that there are appropriate numbers of generic drug manufacturers on the market and to the products that they are selling. Notable examples have occurred in recent years of companies that have cornered the market on an off-patent product and reduced patient access to it by increasing prices or reducing the supply. The FDA OGD should study how it can respond to such cases and evaluate the various options potentially available to facilitate market entry of generics by, for example, allowing importation of generic drugs approved in other well-regulated settings or prioritizing ANDA applications aimed at products that would compete in this space.

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The OGD should also take the lead in ensuring active oversight of the safety of generic drugs. Three important Supreme Court cases have excluded generic manufacturers from liability for safety issues that arise among drugs that no longer have regulatory or patent protection. The FDA has proposed a rule allowing generic manufacturers to update drug labels when new safety data are discovered, but even if this rule is taken up, the FDA is in a better position than small individual generic manufacturers to review the safety of generic drugs. OGD should therefore study different approaches to active postmarket safety surveillance of generic drugs that would allow FDA to continue to learn about a drug’s effectiveness and safety after generic entry.

Finally, we believe OGD should continue to study prescriber and patient attitudes about generic drugs. For example, prescribers remain an obstacle to widespread adoption of automatic substitution practices. Despite numerous studies showing the therapeutic equivalence of brand and generic drugs, dispense-as-written prescriptions remain common. In addition, too many patients are skeptical of the safety of drugs labeled as “generic.” OGD should evaluate barriers to generic use and prescribing, and examine how to communicate information to providers or patients to address unfounded concerns about generic drugs.

We thank you for allowing us to share these ideas with you, and hope to continue a dialogue as the FDA works toward setting its generic drug regulatory science research agenda.

Sincerely,

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