July 19, 2013

Margaret Hamburg, Commissioner
Food and Drug Administration
Attn: Division of Dockets Management (HFA–305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives Public Hearing; Request for Comments (Document ID FDA-2013-N-0402-0001)

Dear Commissioner Hamburg:

The Epilepsy Foundation appreciates the opportunity to comment on the Generic Drug User Fee Amendments of 2012 (GDUFA) and support the agency’s goals under this act to enhance public access to safe, high-quality generic drugs. We appreciate the efforts that the agency has undertaken in its regulatory science plan, especially for the leadership and attention related to bioequivalence and epilepsy drugs.

The Epilepsy Foundation is grateful for the opportunity to join in a collaborative dialogue with the FDA, NIH, and the American Epilepsy Society to collaborate on research that can help address safety, efficacy, and quality concerns on generic AED substitution. We strongly believe that continued work by our joint leadership can provide the best standards and improve public confidence in the prescription drug marketplace. The Epilepsy Foundation believes this was a strong step by the FDA, and we urge the agency to continue to address this important public health concern for the epilepsy community. We believe it is imperative that the pharmacokinetic studies and evaluation of antiepileptic drugs remain the agency’s GDUFA Regulatory Science Plan and is a priority for 2014.

The Epilepsy Foundation emphasizes past comments made to the agency, and provides this background to the GDUFA committee as many comments at the June public hearing focused on sharing information from current research literature. As we have shared with FDA leadership, members of the epilepsy community have for years reported experiencing seizures and other harmful side effects after switching from one version of an antiepileptic drug (AED) to another, whether the switch was brand-to-generic, generic-to-brand, or generic-to-generic. Based on evidence in the clinical literature as well as reports from physicians and patients, the Epilepsy Foundation has developed serious concerns about policies that permit or require AED substitutions without the consent of the doctor and patient. In fact, the results of the Epilepsy Foundation's survey, 'In Their Own Words: Epilepsy Patients' Experiences Changing the Formulation of the Drugs They Use to Prevent Seizures,' (attached to these comments) demonstrate that for many patients with epilepsy, AED substitutions have not been neither effective nor safe. The Epilepsy Foundation survey is attached to these comments as an Appendix.
There is growing evidence that these variations, however slight, can mean the difference between controlled epilepsy and breakthrough seizures or other negative consequences. Patients today are most typically switched from brand-name drugs to generics, or from one generic drug to another, for a single, non-clinical reason: pressure to reduce costs. In most states, unless a physician explicitly writes "dispense as written" or "no substitution," pharmacists can switch a patient to a lower-cost generic drug without the consent or knowledge of either the patient or the physician. The Epilepsy Foundation appreciates that cost-control is a worthy goal and, in general, it enthusiastically supports providing patients with greater access to generic medications. The Foundation is committed to the welfare of people with epilepsy and their families, and the high cost of many name-brand medications is a particularly significant issue for people with epilepsy, many of whom will take medication on a daily basis for the remainder of their lives. The Foundation welcomes the opportunity that generic medications present to lower the overall costs of delivering effective healthcare to individuals and society; we believe equally that short-sighted cost considerations should never be allowed to trump efficacy or take precedence over patient welfare. Indeed, if a patient is switched off of a well-functioning drug to avoid costs, the direct economic consequences borne by society if the cheaper drug fails—whether incurred in the form of increased ambulance rides and emergency-room admissions, greater numbers of in-patient doctor visits, or lost worker-productivity—will quickly eliminate any short-term savings occasioned by the switch. Meanwhile, the concurrent human costs borne by patients and their families can be immeasurable.

Based on evidence in the clinical literature (see Appendix) as well as reports from physicians and patients, the Epilepsy Foundation has developed serious concerns about policies that permit or require AED substitutions without the consent of the doctor and patient. A study in the journal Neurology by David Labiner et al, based upon health insurance claims from over 90 health plans, found that generic substitution in five common AEDs in the U.S. was associated with significantly greater use of medical resources and risk of epilepsy-related medical events, including injury, compared to brand use. We believe that studies demonstrate that for many patients with epilepsy, AED substitutions have been neither effective nor safe. In addition, the scientific literature now contains:

- **clinical confirmation** that switching between "equivalent formulations of the same anti-epileptic drug, whose differing effects in the body are not considered "significant" by the FDA, caused serious adverse consequences in patients
- **case studies** affirmatively establishing that switching between "equivalent" AEDs can lead to breakthrough seizures
- **statistical analysis** showing that persons with epilepsy who recently switched between "equivalent" AEDs sought more in-patient and emergency care than those who did not,
- **case studies** documenting that epilepsy patients on the brand name and generic versions of "equivalent" AED medications had different levels of therapeutic medication in their blood, and
- **population data** revealing that epilepsy patients have "switch[ed] back" to brand-name medication at significantly higher rates than patients who have switched to generic drugs to treat other long-term conditions.

As was expressed at the GDUFA June public meeting by presenters, there are distinguishing features of epilepsy that further suggest that AED-switching should be approached with special caution. First, seizure control can be an all-or-nothing proposition. Slight changes in the amount of medication received by a person with epilepsy can mean the difference between a fully controlled condition and breakthrough seizures. In some patients, there may be correspondingly little room for error when
changing the patient's dosage or prescription. Second, the consequences of a breakdown in a well-functioning seizure-control regimen can be catastrophic. The consequences of a breakthrough seizure can be extreme: seizures increase the likelihood of serious bodily injury and death, and, even when no physical injury occurs, seizures often result in significant social, legal and developmental consequences, including loss of the patient's driver's license, loss of employment, and loss of self-esteem.

The Epilepsy Foundation strongly supports a GDUFA research investment that can contribute to the best standards for bioequivalence and epilepsy treatments. It is important for the FDA to recognize that without administrative action, patients will remain in danger of the consequences or harm due to breakthrough seizures. We renew a call that the FDA consider issuing a limited advisory to patients and physicians regarding potential problems with switching between different medication formulations (whether generic to generic or generic to brand) for some people with epilepsy. This could be limited to patients who have experienced problems with switching between different manufacturers' formulations of anti-epileptic drugs (AEDs) in the past. Specifically, we hope that the FDA would at least offer an advisory to physicians and this specific category of patients, advising physicians that they should consider monitoring the blood levels of patients before making any subsequent changes in the patient's treatment regimen and that, for these limited patients, no switching should occur except with the oversight, monitoring, and consent of the physician and patient.

The Epilepsy Foundation strongly supports the GDUFA Research Initiative and the recommendations of the FDA Advisory Committee on Pharmaceutical Science & Clinical Pharmacology to provide changes in the bioequivalence standards and consideration of critical dose or narrow therapeutic index drugs. We acknowledge to the agency that research results expected to provide the agency with guidance that would allow for more elevated action, may take several years. In comparison to many western and European nations where substitution is not permitted without patient and physician consent, a limited advisory would be a modest step and a positive interim measure that would serve patients’ interest and safety.

The Foundation presents the following recommendations for the FDA: The FDA should adopt the Advisory Committee recommendations as they relate to revising the bioequivalence approaches for NTI/CD drugs by recognizing that NTI/CD drugs are a distinct group of products.

- Develop a listing of such NTI/CD drugs and include AEDs on such a list. Include a process for products already on the market to fall under these consumer safety standards.
- Establish a process and convene a committee to address bioequivalence standards for NTI/CD drugs and develop new requirements for confidence intervals.
- Ensure that committee includes experts, clinicians, and researchers from communities that are currently experiencing problems with medication switching.

The Epilepsy Foundation and our medical experts are looking to the FDA, as the agency that ensures the safety and efficacy of all medications for people in this country, to help protect consumers. The Foundation recognizes that patients as consumers are tied to the health insurance plan provisions that may mandate medication switches; however the health plan provides no support or requirements for the supply of generic medications through a consistent manufacturer. It should not be left to a patient or caregiver to negotiate with pharmacies, as ultimately consumers may not be equipped or successful in securing a stable manufacturer of their generic medication from the pharmacy that their health insurer covers. We believe that the FDA has the authority and direction from the recent advisory committee
recommendations to address these patient and physician concerns and provide a pathway for more
stability in the generic product marketplace for epilepsy patients.

We look forward to continuing to work with you to address these issues. Should you have immediate
questions, please contact Angela Ostrom, Epilepsy Foundation Vice President Public Policy & Advocacy
at aostrom@efa.org. Thank you for your consideration and leadership on this issue.

Sincerely,

Philip M. Gattone, M.Ed.
President & CEO
Appendix


- Andermann, F., et al, **Compulsory generic switching of antiepileptic drugs: Higher switchback rates to branded compounds compared with other drug classes.** *Epilepsia*, 48(3); 464-469 (2007).


- Burkhardt, R.T., PharmD, et al., **Lower phenytoin serum levels in persons switched from brand to generic phenytoin.** *Neurology* 63 (2004).


- Helmers, Sandra, et al., **Economic burden associated with the use of generic antiepileptic drugs in the United States.** *Epilepsy & Behavior* 18; 437-444 (2010).


- Zachry, W.M. III., et al., **Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes.** *Epilepsia*, 50 (3); 493-500 (2009).