EPILEPSY FOUNDATION

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Testimony before the Advisory Committee for Pharmaceutical Science

Food and Drug Administration

Rockville, Maryland

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Good afternoon.

First, I would like to briefly introduce myself. I am here today on behalf of the Epilepsy Foundation. I serve on the Board of Directors at the Foundation and am the Chair of their Professional Advisory Board. I am a neurologist specializing in epilepsy at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. I am also an Associate Professor of Neurology at Harvard Medical School. I serve on the Board of Directors of the Epilepsy Foundation of Massachusetts and Rhode Island and am a former President. Above all, I am an advocate for patients with epilepsy, including the nearly 1,500 patients under my care.

In addition to these perspectives, I have also been the principal investigator on over 60 studies of new antiepileptic drugs and devices and have long admired the Food and Drug Administration (FDA) for their role in regulating the testing, approval and use of seizure therapies.

My discussion will focus on a group of patients whose health and well-being are dependent to a great extent on their seizure medications and for whom relatively minor fluctuations in serum concentration may have devastating social and medical consequences. For these patients, it is critical to distinguish between bioequivalence and clinical equivalence with regard to their medications and generic counterparts.

Epilepsy is a condition characterized by seizures that affects 2.3 million Americans of all ages. Approximately 181,000 new cases of epilepsy occur each year; 10% of the American population will experience a seizure in their lifetimes; 3% will develop epilepsy by age 75. The estimated annual cost of epilepsy is $12.5 billion. Of these, $1.7 billion (14%) are direct medical costs; $10.8 billion (86%) are indirect costs. A single seizure can have serious ramifications on employment, driving privileges, social interactions and self-image. Individual seizures can cause injuries ranging from broken bones to burns to death.

Not all people with epilepsy are the same. For many patients, seizure control is easy to obtain. A number of studies of new-onset seizures show a seizure free rate of 60% to 70%. In this group of patients, varying serum concentrations of seizure medications are not critical to seizure control or the development of side effects. They have a wide therapeutic window. Studies of therapeutic bioequivalence that draw predominantly on patients in this group will likely show no clinical difference between brand and a generic, or between generics.

However, there is another group of patients, relatively small compared to the other group, for whom seizure control and avoidance of side effects occurs within a much narrower range of serum concentrations. In fact, the range that their blood levels must be restricted to is narrower than the range defined as "bioequivalent" by the FDA. This characteristic is typical for many of the patients that I treat at our epilepsy referral center and these are the patients that generate the anecdotal reports of seizure breakthrough

when switched from branded seizure medications and their generic equivalents. In my opinion, studies of therapeutic bioequivalence that draw predominantly on patients in this group are more likely to show that bioequivalence does not necessarily equal therapeutic equivalence for certain seizure medications.

As you know, the bioequivalent rule is the guide by which the FDA approves generics. The FDA states that two formulations whose rate and extent of absorption in healthy subjects differ by –20% to +25% compared to the brand name are generally considered bioequivalent. As noted above, this variability exceeds what is safe for some people with epilepsy. That is why the Epilepsy Foundation has taken the position that prior expressed permission of the treating physician and the patient be obtained before one formulation of an antiseizure medication is switched to another.

The Foundation's view, however, is often at odds with those of insurance companies, formulary committees and state legislative bodies. These groups often make the assumption that the FDA's definition of bioequivalence means that two bioequivalent drugs are clinically equivalent, that is, completely interchangeable without any clinical consequences for every patient.

There are many different seizure medications. The three front-line medications are carbamazepine, phenytoin, and valproic acid. Each is available both as brand name and as generics and each is classified as a narrow therapeutic index drug. There are at

least six different companies that make generic carbamazepine, three that make generic phenytoin, and six that make generic valproic acid.

Let's focus on phenytoin and a typical example of this problem. Suppose that a patient needs a minimum blood level of 10 to control seizures and cannot have a level over 15 in order to avoid disabling side effects. Let's say this patient is on Dilantin, which is the brand name phenytoin. On three Dilantin a day, the patient has a level of 10. Everything is fine. The patient is then switched to a generic version and her blood level drops to 8, resulting in seizures. This generic was approved by the FDA because it fell within the –20% to +25% rule of the FDA. The doctor checks a blood test, verifies that the level has dropped, and then increases the daily dose to bring the level back up to 10. Again, everything was fine. Two months later, the pharmacy fills the prescription with another company's generic phenytoin, and now the level goes up to 20. Now the patient complains of side effects, and another blood test, doctor's visit, and possibly an emergency room visit result. This other generic was also approved by the FDA. An additional change in dose is made and the cycle repeats.

The economic costs of therapeutic nonequivalence may outweigh the potential savings in costs from generic substitution. Let me give you the financial impact of one actual patient. He was switched by the pharmacy from brand name Dilantin to one of the generic versions. Neither the patient nor the physician was notified. As a result of the switch, the patient had seizures that required hospitalization. The bill for the hospitalization was nearly $4,000. What is the monthly difference in cost between the

brand and the generic? According to the pharmacy that dispensed the generic, it is $4. In other words, it will now take 83 years to recoup the costs of the hospitalization with the less expensive product.

How frequently does this happen? Quite often, as demonstrated by a survey conducted by the Professional Advisory Board of the Epilepsy Foundation and presented to the Office of Generic Drugs at the Food and Drug Administration in January.

As you can see, the consequences of a recurrence of symptoms of epilepsy, i. e. seizures, can be far more devastating to an individual's health, their productivity and to the cost of their illness to society than the recurrence of symptoms of other medical conditions.

The Foundation, like the FDA, is committed to enhancing patient safety, avoiding unnecessary medical and social costs, and increasing the safe and effective utilization of generic medications.

To this end, I strongly recommend that this committee urge the FDA to investigate whether there are patients with epilepsy for whom bioequivalence does not perfectly predict clinical equivalence. The results of such an investigation will be most helpful in shaping future policies on the interchangeability of anti-convulsants and their generic counterparts.

I look forward to the opportunity to work with you. Thank you for the opportunity to speak to you today.

Steven C. Schachter, MD

EXECUTIVE SUMMARY

Epilepsy Foundation Survey of Patients Concerning Generic Drugs

November 10, 1998

In correspondence reviewed by the Epilepsy Foundation, Dr. Stuart L. Nightingale of the Food and Drug Administration wrote that brand name antiepileptic drugs (AEDs) and their generic counterparts were completely interchangeable. He maintained that there were no documented instances of patients who experienced problems when switched from the brand to generic version of an AED. This opinion gave support to regulations that allow pharmacists to substitute generic AEDs for brand name AEDs without the express permission or knowledge of the patient or the prescribing physician.

In response to Dr. Nightingale's statement, members of the Professional Advisory Board (PAB) of the Epilepsy Foundation decided to survey patients attending epilepsy clinics to determine whether there existed any patient-perceived complications of generic substitution of brand name AEDs. Several members of the PAB created a questionnaire for patients to complete in the doctor's office (see Appendix A). Patients attending epilepsy clinics in Boston, New Haven, New York, and Phoenix completed a total of 123 questionnaires.

Overall, 30% of patients completing the questionnaires had previously been given generic rather than brand name AEDs by their pharmacist. Of this group (N=37), 41% stated that their seizure control worsened and 32% said that side effects developed or worsened while taking the generic drugs. Because of seizures and/or side effects, 46% of these patients were placed back on brand name AEDs.

Twelve percent of the total group was switched in the past from a generic AED to the brand name version. Of this group (N=15), 20% stated that their seizure control worsened and 7% said that side effects developed or worsened.

Based on the results of the questionnaire survey, it appears that seizure breakthrough and side effects commonly occur from interchanging brand name AEDs and their generic counterparts. Notably, over 10% of all surveyed patients indicated that their seizures worsened when they were switched to a generic AED.

These unacceptable outcomes can only be minimized if the physician and patient have full control over which version of a drug is prescribed and dispensed. This is a position strongly articulated by the Epilepsy Foundation.

Prepared by Steven C. Schachter, MD, Chair, Advocacy Committee, Professional Advisory Board, Epilepsy Foundation.

Appendix A

Questionnaire about Generic Medications and Epilepsy
(with results shown in the "Yes" and "No" columns)

YES	NO	
30% 37/123	70% 86/123	1. Was your prescription for a brand name seizure medication ever filled by the pharmacist with a generic version? If no, skip to question #5.
41% 15/37	59% 22/37	2. Did your seizure control worsen while you took the generic seizure drug?
32% 12/37	68% 25/37	3. Did side effects develop or get worse within a month of this switch to the generic seizure drug?
46% 17/37	54% 20/37	4. Did your doctor put you back on the brand name medication because of seizures or side effects that you had while on the generic seizure drug?
12% 15/123	88% 108/123	5. Have you ever been switched from a generic seizure medication to a brand name seizure medication? If no, skip to the end.
20% 3/15	80% 12/15	6. Did your seizure control worsen within a month of this switch from a generic seizure medication to a brand name seizure medication?
7% 1/15	93% 14/15	7. Did side effects develop or worsen when the generic seizure medication was switched to the brand name seizure medication?