UCB, Inc. – 1950 Lake Park Drive – Smyrna, Georgia 30080

October 3, 2006

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

UCB, Inc. ("UCB"), the NDA-holder for Keppra® (levetiracetam) submits this petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act" or the "Act") (21 U.S.C. §§ 355 (b) and (j)) and 21 C.F.R. § 10.30. This petition requests that the Commissioner of the Food and Drug Administration ("FDA") take the actions discussed in Part I of this Citizen Petition to ensure the safe and effective use of antiepileptic drugs.

I. Actions Requested

1. Require that the full prescribing information of all antiepileptic drugs contain the following language under "Warnings" or "Warnings and Precautions," as applicable: "Physicians and pharmacists should exercise extreme caution when switching patients who are seizure free or whose seizures are well controlled on a given antiepileptic drug. In general, switches in patients who are well controlled and have achieved stability on a given antiepileptic drug should be undertaken only when medically necessary and with full disclosure to the treating physician and the patient." This warning should also appear in the "Highlights" section, as applicable, for labels subject to FDA's final labeling rule of January 24, 2006 (21 C.F.R. §§ 201.56 and 201.57);

2. Add a discussion of antiepileptic drugs to Section 1.8 (Description of Special Situations) of the Orange Book. This discussion should highlight the

2006P.0405

CP1

particular risks associated with substitution of antiepileptic drugs. It should also recommend against switches of antiepileptic drugs in patients who are seizure free or whose seizures are well controlled; and

3. Narrow FDA's bioequivalence range for generic versions of antiepileptic drugs to require a showing, at the 90% confidence interval, that the lower limit is at least 90% of its reference listed drug.

II. Brief Statement of Grounds

Approximately fifty million people worldwide have epilepsy.[1] With approximately three million people diagnosed in the United States alone, epilepsy remains one of the most common and severe neurological disorders facing Americans today. It is a chronic disorder that frequently requires lifelong treatment.

The primary mode of treatment for many forms of epilepsy is antiepileptic drugs ("AEDs"). Physicians carefully titrate these drugs (many of which have narrow therapeutic indices) in the hope of controlling seizures, ideally by achieving a stable, seizure free state, so that patients can lead normal, healthy lives. Establishing seizure control can be a difficult, arduous process. Physicians frequently must try several different AEDs as either monotherapy or polytherapy before seizures are well controlled or seizure freedom is achieved. Several branded AEDs have been available for many years and FDA and EMEA have approved many new, second generation AEDs, most recently in 2005. FDA has also approved several generic versions of branded first generation AEDs, and the recent expiries of the gabapentin and zonisamide patents have led to several generic approvals being granted for each of their compounds.

Over the past several decades, a substantial body of evidence has accumulated demonstrating significant problems with branded/generic and generic/generic switches of AEDs. Since generic AEDs first became available, many patients whose medication has been switched have experienced breakthrough seizures or other serious side-effects. For example, one 1993 survey showed that almost 50% of

[1] *See* World Health Organization ("WHO") (2001). Fact Sheet No. 165. Epilepsy: aetiology, epidemiology and prognosis, *available at* www.who.int/mediacentre/factsheets/fs165/en/ (last visited Sept. 20, 2006).

patients reported breakthrough seizures or other worsening of their condition after being switched.[2] Reports of these problems have persisted to the present day.

The root cause of these problems has not been conclusively established. Numerous peer-reviewed articles and studies have suggested that FDA's methodology for establishing bioequivalence between branded AEDs and their generic counterparts may be insufficient to ensure therapeutic equivalence for the individual patient.[3] This appears to be particularly true for older, first generation AEDs that are characterized by narrow therapeutic indices, low water solubility, and nonlinear pharmacokinetics. This may also may be true, albeit to a lesser extent, for newer, second generation AEDs. Other contributing factors such as poor patient compliance have also been suggested.

Whatever their cause or causes, the consequences of breakthrough seizure are often devastating for epilepsy patients. Even a single breakthrough seizure can cause significant short-term disruptions in a patient's life, loss of legal rights, severe injury, or even death.

Switching a patient who is well controlled or has already achieved seizure free stability on a given AED constitutes a significant and avoidable risk to that patient and, potentially, to others. The goal of AED therapy is seizure freedom with minimal side effects. Once this state has been established, all steps should be taken to avoid disruptions that could lead to breakthrough seizures. As a result, most epileptologists and epilepsy organizations advise against switching stabilized patients unless it is medically necessary.[4] In addition, several European regulatory agencies have recently taken steps to limit the substitutability of AEDs.

In light of the above, UCB strongly urges FDA to take action to limit switches in patients whose seizures are well controlled or who have achieved seizure freedom. We therefore request that FDA require all AEDs (both branded and generic) to include a new warning in their full prescribing information. This warning would urge physicians, pharmacists, and others associated with dispensing AEDs to exercise extreme caution when switching AEDs in a patient who has achieved seizure control or seizure freedom, and to undertake such switches only when medically necessary and

---

[2] *See* Chappell, B. (1993). *The threat of medicine substitution - the patient's viewpoint.* In Towse, A., ed. Not what the doctor ordered. The threat of medicines substitution. Queen's University, Belfast, pp. 71-80.

[3] *See infra* section III(C).

[4] *See infra* section III(B).

with full disclosure to the treating physician and the patient. FDA should also include a discussion of the risks associated with switching AEDs in the Orange Book under Section 1.8, "Description of Special Situations." Furthermore, in light of the frequently expressed concerns that FDA's general bioequivalence guidelines do not provide an adequate surrogate indicator for therapeutic equivalence in epilepsy, UCB also urges FDA to narrow its bioequivalence range for AEDs and require a showing, to the 90% confidence interval, that is at least 90% equivalent to the reference listed drug at the lower limit.

III. Complete Statement of Grounds

A. Epilepsy and AEDs

Epilepsy is a neurological condition affecting the nervous system and causing seizures.[5] According to the Epilepsy Foundation, epilepsy and seizures affect approximately three million people in the United States with an annual cost of nearly $12.5 billion, making it the second most common neurological condition in the United

---

[5] Epilepsy is a brain disorder in which people experience repeated seizures. Epilepsy can be inherited, but can also result from a birth defect, birth or head injury, brain tumor, or an infection in the brain. For half of people with epilepsy, a cause cannot be found. Epilepsy can begin right after birth or can occur for the first time in old age. A seizure is the abnormal electrical release of cells, called neurons, in the brain. This can cause different symptoms based on the location of the seizure and where the abnormal electrical activity spreads. Not all seizures are the same. They can range from tingling in a finger to grand mal (generalized) seizures, during which people lose consciousness, become stiff, and jerk. Not everything that looks like a seizure is a seizure, and not every seizure is an epileptic seizure. Fainting, collapsing, and confusion can also result from other disorders or even from emotional stress. Withdrawal from alcohol or addicting drugs can also cause seizures. *See* UCB, Epilepsy FAQs, *available at* http://www.keppra.com/pc/epilepsy_facts/epilepsy_faq.asp (last visited Sept. 20, 2006).

Seizures can happen to anyone, depending on the situation. Everyone has their own "seizure threshold"—a level of electrical activity that is needed to cause seizures. In most people this threshold is high, but a powerful trigger, such as injury to the brain, can cause a seizure. In a few people, the threshold is low, allowing seizures to start suddenly. *See* UCB, Causes and facts, *available at* http://www.keppra.com/pc/epilepsy_facts/causes_and_facts.asp (last visited Sept. 20, 2006).

States after migraine headache.[6] Fortunately, epilepsy can often be controlled through medication. The first medication approved for use in the United States for treatment of epilepsy was phenytoin (originally introduced as diphenylhydantoin), marketed under the brand name Dilantin. Over the next 30-40 years, a few other drugs were approved for epilepsy and are collectively referred to as "first generation" AEDs. During the 1990's and as recently as 2005, FDA has approved numerous other branded AEDs, collectively termed "second generation" AEDs. Of these second generation AEDs, gabapentin and zonisamide in the United States, and lamotrigine in Europe, have gone off patent and thus exist in both branded and generic forms.

The goal of patient treatment with AEDs is to achieve seizure freedom while minimizing side-effects.[7] It is critical that stable seizure freedom be established because the consequences of a breakthrough seizure are often catastrophic. In the worst of cases, even a single breakthrough seizure can develop into *status epilepticus* and eventually result in death. Data indicate that the relative risk of sudden unexpected death in epilepsy ("SUDEP") is increased after such breakthrough seizures. In one study the relative risk of SUDEP was 23 times higher in patients who had experienced at least one seizure during the year of observation compared to seizure-free patients.[8] A breakthrough seizure that occurs while the patient is driving can easily result in death or injury to the patient and other bystanders. Other breakthrough seizures can lead to burns, broken bones, or other injuries.[9] Even if no physical injury occurs, breakthrough

---

[6] *See, e.g.*, Epilepsy Foundation, Epilepsy & seizure statistics, *available at* http://www.epilepsyfoundation.org/answerplace/statistics.cfm (last visited Sept. 20, 2006).

[7] *See, e.g.*, Schachter, S.C., The Epilepsy Foundation (2001). Working partners: achieving your treatment goal, *available at* http://www.epilepsyfoundation.org/epilepsyusa/equal.cfm (last visited September20, 2006).

[8] Tomson, T., et al. (2005). *Sudden unexpected death in epilepsy: a review of incidence and risk factors*. Epilepsia; 46(Suppl. 11):54-61, 58.

[9] *See, e.g.*, Feely, M., et al. (2005). *Risk management in epilepsy: generic substitution and continuity of supply*. European J. Hosp. Pharm. Science 11(4):83-86, 84; European Concerted Action and Research in Epilepsy ("EUCARE") (2003). *Epilepsy: safety, excess mortality, and sudden death.* In EUCARE, *European White Paper on Epilepsy*. Epilepsia 44(Suppl. 6):1-88, 19; Guberman, A., & Corman, C. (2000). *Generic substitution for brand name antiepileptic drugs: a survey*. Can. J. Neurol. Sci. 27:37-43, 39.

seizures often result in significant social, legal, and developmental consequences for patients such as loss of drivers license, loss of employment, and loss of self-esteem.[10]

AED treatment of epilepsy is significantly different than most other pharmaceutically treated conditions. When treating hypertension or high cholesterol, for example, physicians seek to bring levels down to certain pre-established "normal" or "healthy" ranges. While titrating dose, physicians can take simple, accurate, and reliable measurements and continue making adjustments until blood pressure or cholesterol is well-within the pre-defined range.[11] Once the patient is stabilized at a normal level, small changes in therapeutic effect brought about, for example, by pharmacy switches are unlikely to have a significant effect on patient outcomes. Because the patient has been accurately titrated to a point well within the normal range, the patient can tolerate small changes in therapeutic effect without causing him or her to leave that normal, healthy range. Even if a switch should cause a patient to leave the normal range, the effect of short-term increased blood pressure or increased cholesterol is unlikely to be immediately catastrophic and can easily be noticed and corrected by further titration upon the patient's next visit to his or her physician.

With AED treatment of epilepsy, however, small differences in plasma levels can have significant consequences for the individual seizure free patient. Unlike hypertension or high cholesterol, there is no universally-defined normal or protective plasma range that will result in seizure freedom. This may reflect significant inter-individual differences in seizure thresholds, as evidenced by preclinical data from amygdala kindled rats, an epilepsy model that closely mimics temporal lobe epilepsy in man.[12] Indeed, these animals display significant inter-individual differences in their seizure thresholds. This appears to correspond to the clinical experience that individual epilepsy patients require individual minimal plasma levels of an AED (plasma level

---

[10] *See, e.g.*, Guberman, *supra* note 9. *See also* Krämer, G., et al. (2005). *Generics in antiepileptic drug therapy: what has to be considered?* Akt. Neurol. 32:275-278, 276 ("Just one single case of recurrence can have far reaching sociomedical consequences, even to the point of the patient losing his or her job); Begley, C.E., et al. (2000). *The cost of epilepsy in the United States: an estimate from population-based clinical and survey data.* Epilepsia 41(3):342-51; Halpern, M., et al. (2000). *Cost of illness of epilepsy in the US: comparison of patient-based and population-based estimates.* Neuroepidemiology 19(2):87-99.

[11] *See, e.g.*, Krämer, *supra* note 10, at 277.

[12] *See, e.g.*, Rundfeldt, C., et al. (1990). *Phenytoin potently increases the threshold for focal seizures in amygdala-kindled rats.* Neuropharmacology 29(9):845-851.

threshold) that, once reached, can prevent the precipitation of a seizure. Individual dose titration permits patients to pass this threshold rendering them seizure free. Unfortunately, physicians usually do not know the true effective plasma level threshold for any given individual patient because the titration to the therapeutically effective dose is done by dose unit steps. As a result, it is usually not possible to know by how much this threshold has been passed in the course of the up-titration to the effective daily dose.[13] In many cases, treatment with the original AED will result in freedom from seizures even though the plasma threshold has been passed by only a small margin.

Because such patients have been titrated so close to their plasma threshold, even a small downward change in plasma concentration could have a significant effect. If a change in therapeutic effect pushes the patient to a level just below his or her plasma threshold, for example, this may result in breakthrough seizures.[14] In stark contrast to hypertension or raised cholesterol, there is no way for the treating physician to know that the individual threshold has been breached until this manifests itself through an immediate and catastrophic relapse of the patient.

B. AED Switches Can Result in Disruption of Seizure Control

As a result of the above, once a patient has become stabilized and achieved seizure freedom or seizure control on a given AED, it is critical that every possible precaution be taken to minimize the potential for changes in therapeutic effect that could lead to breakthrough seizures. Unfortunately, AED switches may cause just such a disruption. Breakthrough seizures and other side effects have been encountered following both branded to generic AED switches as well as switches from one generic to another.

Reports of problems with AED switches began in the 1960s when patients reported several incidents of phenytoin intoxication following a switch.[15] Shortly after the Hatch-Waxman Amendments to the FD&C Act created the ANDA approval pathway for post-1962 drugs, various reports emerged of breakthrough

---

[13] *See, e.g.,* Krämer, *supra* note 10, at 277.

[14] *See id.*

[15] *See, e.g.*, Crawford, P., et al. (1996). *Generic prescribing for epilepsy. Is it safe?* Seizure 5:1-5.

seizures and product intoxication after switches from branded AEDs to generics, including phenytoin and carbamazepine.[16]

Reports continued throughout the early 1990s. For example, several surveys of patients and practicing physicians confirmed that real problems exist when patients are switched from branded AEDs to generics, or from one generic manufacturer to another. After the recall of a generic phenytoin formulation used in the Veterans Administration ("VA") medical system, a VA study of patients found serum phenytoin levels to be 22-31% lower during the period of generic intake as compared with levels receiving the branded version.[17] In a survey conducted by the British Epilepsy Association, 46.5% of patients surveyed reported a worsening of their condition upon being switched to a generic AED.[18]

These reports have persisted through the introduction of so-called "second generation" AEDs and continue to the present day. In a 1996 survey of patients whose AED had been switched, 21% of responders reported breakthrough seizures or other worsening of their conditions. Eleven percent of these were validated. Another nine percent of patients reported problems, but follow-up was incomplete, leading to the possibility that a full 30% of patients experienced breakthrough seizures or other side-effects after a switch.[19] Similarly, a 1998 study conducted by the Epilepsy Foundation showed that 41% of responding patients whose medication was switched noticed a worsening of seizure control.[20] In a 2004 survey conducted by Andrew N.

---

[16] *See, e.g.*, Trimble, M. (1987). Editorial, *Generic prescribing*. Hum. Psychopharmacol 2:1-2; Welty, T., et al. (1992). *Loss of seizure control associated with generic substitution of carbamazepine*. Ann. Pharmacother. 26:775-777.

[17] *See, e.g.*, Rosenbaum, D.H., et al. (1994). *Comparative bioavailability of a generic phenytoin and Dilantin*. Epilepsia 35(3):656-60. This study did not directly examine incidence of breakthrough seizures or other side-effects upon a switch from a branded AED to a generic. *See also* Nuwer, M.R., et al. (1990). *Generic substitutions for antiepileptic drugs*. Neurology; 40:1647-1651; Sachdeo, R.C. & Belenduk, G. (1987). Letter, *Generic versus branded carbamazepine*, Lancet; 1:1432; Soryal, I., & Richens, A. (1992). *Bioavailability and dissolution of proprietary and generic formulations of phenytoin*. J. Neurol. Neurosurg. Psychiatry 55:688-691.

[18] *See* Chappell, *supra* note 2.

[19] *See* Crawford, et al., *supra* note 15, at 3.

[20] *See* Testimony of Steven C. Schachter, M.D., before the FDA Advisory Committee for Pharmaceutical Science, Executive Summary (Sept. 23, 1999) ("Schachter Testimony"), *available at* http://www.fda.gov.ohrms/dockets/ac/99/slides/3547sli.pdf (continued...)

Wilner, M.D., 68% of responding neurologists reported patients with breakthrough seizures following generic substitution from a branded AED.[21] Furthermore, 33% of responding neurologists reported breakthrough seizures attributable to a switch from one generic AED to another, and 27% reported increased side-effects after such switches.[22]

One reason for these reports is that AED switching at the retail pharmacy level is commonplace. Many pharmacies carry several different versions of any given AED, and patients refilling their prescriptions at different pharmacies may be subject to even more frequent switches. As Steven C. Schachter, M.D., (former Chair of the Professional Advisory Board of the Epilepsy Foundation) has explained, this constant generic-generic switching can place a patient at almost constant risk for breakthrough seizures and other side-effects:

> 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

---

(last visited Sept. 20, 2006). *See also* Burkhardt, R. (2004). *Lower Phenytoin serum levels in persons switched from brand to generic Phenytoin.* Neurology 63:1494-1496.

[21] *See* Wilner, A.N. (2004). *Therapeutic equivalency of generic antiepileptic drugs: results of a survey.* Epilepsy Behav. 5:995-998.

[22] *See id.*

approved by the FDA. An additional change in dose is made and the cycle repeats.[23]

Because of this clear risk, and the severe consequences that can attend a breakthrough seizure, most epileptologists agree that once a patient is stable and has achieved seizure freedom or seizure control on an AED, a switch should be undertaken only when medically necessary. For example, at a recent Symposium sponsored by GlaxoSmithKline ("GSK"), Günter Krämer, M.D., Medical Director of the Swiss Epilepsy Centre in Zurich, Switzerland, noted that "the general consensus among experts in this field is that the switching of AEDs presents unnecessary additional risks to patients and should only be undertaken when medically necessary."[24] The American Academy of Neurology's current guidelines on generic substitution state that AEDs should not be substituted unless it is medically necessary.[25] Similarly, in its guideline on the diagnosis and management of epilepsy in adults and children, the National Institute for Health and Clinical Excellence ("NICE") recommends that "[c]hanging the formulation or brand of AED is not recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects."[26] In a recent article coauthored

---

[23] Schachter Testimony, *supra* note 20, at 4.

[24] *See* Krämer, G. (2005). *Generic substitution in antiepileptic drug therapy: do new regulations match clinical experience?* 9 Cong. Eur. Fed'n (Abstract Book) at 10. *See also*, Nuwer, *supra* note 17, at 1647; Wyllie, E., et al. (1987). *Increased seizure frequency with generic primidone*. JAMA 258(9):1216-1217. *But see* Guberman, *supra* note 9, at 42 (results of survey of 46 Canadian neurologists indicated that the group was "almost evenly divided over the question of whether various brand name AEDs could be safely switched to generics and were usually uncomfortable about starting a patient on the generic preparation of one of the newer AEDs.").

[25] *See* Therapeutics & Technology Assessment Subcommittee, American Academy of Neurology (1990). *Assessment: Generic substitution for antiepileptic medication.* Neurology 40:1641-1643 ("AAN Assessment") (This policy is no longer available on AAN's website (http://www.aan.com/professionals/practice/guideline/index.cfm?a=0&fc=1#), where it states that an update to the policy is in progress).

[26] NICE (2004). Guideline CG020, The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care 19, *available at* http://www.nice.org.uk/pdf/word/CG020niceguidline.doc (last visited Sept. 20, 2006). NICE is a governmental expert body that advises the United Kingdom's National Health Service on appropriate use of medicines and medical technology. *See also* All (continued...)

by Mark B. McClellan, M.D., Ph.D., Administrator of the Centers for Medicare and Medicaid Services, Dr. McClellan noted that "working with physicians and other health care providers, we identified six critical categories of drugs -- antidepressants, antipsychotics, *anticonvulsants,* anticancer agents, immunosuppressants, and antiretroviral drugs for patients with HIV infection. For patients who require these drugs, therapeutic substitutions could be harmful, even over the short term."[27]

Recognizing these potential risks, several of FDA's peer bodies in European countries have taken steps to limit or even prohibit substitution of generic AEDs. For example, Sweden's Medical Products Agency ("MPA") (Läkemedelsverket) has determined that the first and second generation AEDs lamotrigine, carbamazepine, phenytoin, valproic acid, and gabapentin cannot be substituted with a generic version. Thus, the MPA recently published a new list of substitutable products covering generic drugs as well as parallel imports (drugs from a single manufacturer imported from one EC country to another). Although some parallel imports and a few authorized generics may be substituted, true generic versions of the above-mentioned AEDs are not included on the list.[28] Finland has also taken steps to limit substitution of AEDs. According to the 2006 Guidelines for Drafting the List of Medicines Substitutable by Generic Medicines of its National Agency for Medicines (Lääkelaitos), epilepsy medicines will not be included on the list.[29]

Wales Medicines Strategy Group ("AWMSG"). Inappropriate Generics Working Group (2005). Patient safety issues involving generic subscribing at 3, *available at* http://www.wales.nhs.uk/sites3/Documents/371/Enc%204%20Inappropriate%20generic%20prescribing.pdf (last visited Sept. 20, 2006) (stating that for patients with a history of seizures, "it would be good practice to maintain a consistent supply of a particular preparation (brand or generic) for an individual epileptic patient").

[27] Bach, P.B., & McClellan, M. (2005). *A Prescription for a modern Medicare program*. N. Engl. J. Med. 353:2733-2735, 2734 (emphasis added). *See also* Krämer, *supra* note 10 (noting that the ad-hoc commission for the German Society for Epileptology has recommended against branded-generic or generic-generic switching of AEDs solely for cost reasons, and/or without the informed consent of the patient).

[28] *See* MPA (Läkemedelsverket) (2006), Substitutable Medical Products (preamble and relevant entries included with this submission, English version provided in the original document). *See also* MPA (Läkemedelsverket) (2004). *Neurontin and Gabapentin Nycomed -- why aren't they interchangeable?* (English translation).

[29] *See* National Agency for Medicines (Lääkelaitos) (2005). The National Agency for Medicines' updated (November 2005) principles for the preparation of interchangeable (continued...)

Finally, the Danish authorities have also taken steps to limit substitution of the second generation AED, lamotrigine. In late 2005, the Danish Medicines Agency ("DMA") decided to authorize substitution of medicinal products containing lamotrigine only if they comply with more stringent requirements for bioequivalence. According to the DMA, "[t]hese stringent requirements mean that studies of test subjects must show that both the amount absorbed from the copy and the rate at which this takes place with at least 90% probability are between 90% and 110% in comparison with the original medicinal product."[30]

C. There May Be Several Causes for Breakthrough Seizures Following an AED Switch

A frequently asserted explanation for problems with AED switches is that FDA's current bioequivalence methodology is not an adequate surrogate for therapeutic equivalence between generic AEDs and their reference listed drugs. As stated by Steven C. Schachter, M.D., then Chair of the Professional Advisory Board of the Epilepsy Foundation, not all patients with epilepsy are the same. For some, small variations in serum concentrations are not critical to seizure control, 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

---

drugs that are authorized for sale (English translation), *available at* http://www.laakelaitos.fi/laaketieto/laakevaihto/uudet_laatimisperiaateet/index.html (last visited Sept. 20, 2006).

[30] *See* DMA (June 10, 2005). Press release. *Increasingly stringent requirements for authorisation of substitution for epilepsy medicine.*

show that bioequivalence does not necessarily equal therapeutic equivalence for certain seizure medications.[31]

Through guidance documents, FDA has established a general standard for demonstrating bioequivalence applicable to most orally administered drug products. In general, FDA requires *in vivo* study data demonstrating dose-form proportionality, assessed through analysis of log-transformed AUC_{0-t} and C_{max}. For most drugs, dose-form proportionality is established if the 90 percent confidence interval falls within the 80% to 125% range.[32]

In addition to Dr. Schachter, many researchers and physicians have argued that FDA's 80-125% range of bioequivalence for AUC and Cmax may be inadequate to ensure therapeutic equivalence between AEDs. For example, a 1990 report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology argues that FDA's bioequivalence range is too large to ensure therapeutic equivalence in AEDs.[33] More recently, in Dr .Wilner's 2004 survey discussed above, 81.6% of responding neurologists indicated that they believe that FDA's current standards for bioequivalence are not sufficiently narrow.[34] As discussed above, the Danish Medicines Agency has recently narrowed the acceptable bioequivalence range for generic lamotrigine.[35]

---

[31] Schachter Testimony, *supra* note 20, at 3.

[32] *See* FDA (2003). Guidance for industry, *Bioavailability and bioequivalence studies for orally administered drug products - general considerations*; FDA (2001). Guidance for industry, *Statistical approaches to establishing bioequivalence*. *See also* FDA (2006). Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), at viii.

[33] AAN Assessment, *supra* note 25.

[34] *See* Wilner, *supra* note 21, at 996-997. *See also*, Guberman, *supra* note 9, at 39.

[35] *See infra*, section III(B). It has been noted that even with Denmark's more narrow bioequivalence requirements for lamotrigine, individual variability can remain substantial and cause potentially serious complications for patients. *See, e.g.*, Dahl, M., & Wolf, P. (2006). Conference poster. *Comparative daily profiles of Lamotrigine preparations*. 7 Eur. Cong. Epileptology (providing six case studies and noting that despite Denmark's new bioequivalence requirement "larger deviations connected with serious morbidity could be observed with continuous medication."). As a result, the agency should consider additional adjustments to its bioequivalence testing requirements for AEDs beyond what has been suggested herein.

Several commentators have argued that generic to generic switches may pose an even greater risk for stabilized patients than do branded to generic switches. As FDA is aware, because of FDA's 80% to 125% range, "[i]t is theoretically possible for the 'average' patient to experience an almost 50% increase in serum concentration if switched from a low bioavailability generic formulation (e.g. 80% of brand) to a high bioavailability (e.g. 120% of brand) generic formulation. Conversely, the average patient could have an almost 33% decrease in serum concentration if switched from a high to a low bioavailability formulation."[36] In addition, as multiple generic versions of a branded product reach the market, a patient may be subjected to multiple generic/generic switches as pharmacies look to contain costs.[37] As discussed above, in an effort to contain costs, pharmacies typically stock several different generic brands at any given time and often change generic versions frequently in order to stock the low-price leader. Furthermore, there can be considerable variation between pharmacies as to which generics are stocked. As a result, patients refilling prescriptions can find their AED switched almost routinely, without their knowledge. Each generic may occupy a different point on the 80/125 range, thus subjecting patients to repeated and potentially large swings in therapeutic effect.[38] This problem is further complicated by the fact that many generic medications are similar in physical appearance. Thus patients may not be aware of the switch or, if a problem arises, may not be able to identify the supplier or manufacturer of the generic medication.

Other physicians and researchers have suggested that the breakthrough seizure problem has other causes such as patient compliance, not bioequivalence.[39] In the mid-1990s, FDA convened several panels and advisory committees to examine a variety of generic drug issues. These included, among others, a task force on the bioequivalence of AEDs. FDA also sponsored clinical studies to compare the

---

[36] Feely, *supra* note 9, at 85 (citing Nuwer, *supra* note 17, at 1648). *But see* Guberman, *supra* note 9, at 39 (suggesting that an almost 50% plasma concentration swing, though theoretically possible, is unlikely given the fact that the 90% confidence interval must fall entirely within the 80-125% range).

[37] Interestingly, there is at least some evidence to suggest that the costs to the health care system involved in treating the breakthrough seizures and side-effects that can result from AED switches may outweigh the cost-savings gained from the original switch. *See, e.g.*, Heaney, D., & Sander, J.W. (2006). *Cost-effectiveness in carbamazepine in epilepsy*. Expert Rev. Pharmacoeconomic Outcomes Res. 6(1):13-18, 14-15.

[38] *See* Guberman, *supra* note 9, at 39.

[39] *See, e.g.*, Feely, *supra* note 9, at 86 (noting other possible causes).

bioavailability of several branded AEDs and their generic counterparts. FDA concluded at that time - more than 10 years ago - that although some AEDs do indeed have narrow therapeutic ranges, generic AEDs are, in general, bioequivalent to their reference listed drugs and thus are therapeutically equivalent.[40]

Despite FDA's conclusions at that time, the agency recently acknowledged that there are at least some open questions regarding bioequivalence of AEDs, when it cited a potential lack of therapeutic equivalence as a primary reason for opposing the importation of prescription pharmaceuticals from Canada. In response to the Texas State legislature passing a bill authorizing Canadian pharmacies to import prescription drugs to Texas, FDA wrote a June 17, 2005 letter to Texas Governor Rick Perry. FDA wrote to "bring to [the Governor's] attention some of FDA's safety and legal concerns with the proposed law."[41] Among these, FDA noted that were such imports permitted ,

---

[40] *See, e.g., FDA policy on generic anticonvulsants*, Scrip 1469:28-29 (1989) (quoting response of then FDA Commissioner Frank Young to correspondence from Bill Haddad, GPIA); Letter from Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science, FDA, to the National Association of Boards of Pharmacy (April 16, 1997) (indicating FDA's belief that its bioequivalence standards are appropriate for narrow therapeutic index drugs and pointing to two FDA-sponsored studies conducted at the University of Tennessee and Wake Forest University that failed to show any "problems with bioequivalence" or comparative safety/effectiveness between branded carbamazepine and generic versions). *But see* Crawford, et al., *supra* note 15, at 1 (citing conflicting evidence from controlled studies on comparative safety and effectiveness); *see also* Oles, K.S. (1992). *Therapeutic bioequivalency study of brand name versus generic carbamazepine*. Neurology 42(6):1147-1153 (describing controlled study in which 4 of 20 patients experienced breakthrough seizures when switched between branded and generic versions of carbamazepine). FDA issued an Interim Guidance to Industry on phenytoin bioequivalence in 1994. *See* FDA (1994). Interim guidance, *Phenytoin/phenytoin sodium capsules, tablets, and suspension* in vivo *bioequivalence and* in vitro *dissolution testing*. *See generally* Letter from Stuart L. Nightingale, M.D., FDA Associate Commissioner for Health Affairs to Health Practitioners (January 28, 1998) (explaining FDA policy regarding bioequivalence and substitution of narrow therapeutic ratio drugs).

[41] Letter from Randall W. Lutter, Ph.D., FDA, to the Honorable Rick Perry, Governor of Texas (June 17, 2005), *available at* http://www.fda.gov.oc/opacom/hottopics/importdrugs/perry061705.html (last visited Sept. 20, 2006).

> physicians, pharmacists and patients would be unable to judge properly whether products are truly substitutable. Some consumers' health may be at risk, since some medications that are safe and effective only in a narrow therapeutic range, such as anti-seizure medications, may be replaced with foreign versions whose therapeutic equivalence to U.S. versions that are not substitutable or whose therapeutic equivalence to U.S. versions is unknown to American health care providers.[42]

The bioequivalence problems discussed above are particularly acute for first generation AEDs such as phenytoin, carbamazepine, and valproate. These older drugs are generally characterized by one or more of three factors - a narrow therapeutic index, low water solubility, and nonlinear pharmacokinetics - all of which complicate bioequivalence for the individual patient.[43] Newer AEDs exhibit fewer, if any, of these classic toxicity risk factors and there is less specific, documented data in the current literature regarding bioequivalence problems with second generation AEDs. However one example, a recent observational study conducted out of the University of Alberta, found that spontaneous reports of adverse events involving the second generation AED lamotrigine, rose from 30 in the 16 months prior to introduction of generic lamotrigine to 56 (87% increase) in the 16-month period following introduction of generics. Breakthrough seizures were reported in 25% of these cases.[44] At least some neurologists have separately suggested that even the newer AEDs are susceptible to failures in bioequivalence.[45]

Even for second generation AEDs, small differences in plasma levels can play an important role for the individual seizure free or seizure controlled patient depending on the individual plasma level threshold preventing the precipitation of a

---

[42] *Id.*

[43] *See, e.g.*, AAN Assessment, *supra* note 25, at 1641 (stating that low water solubility, a narrow therapeutic range, and nonlinear pharmacokinetics are "risk factors" associated with difficulty in creating a new drug formulation).

[44] *See* Makus, M.G. (2005). *Generic substitution of antiepileptic drugs: preliminary observational reports of lamotrigine switching in Canada.* Epilepsia 46 (Suppl. 6):279.

[45] *See, e.g.*, Feely, *supra* note 9, at 87 (suggesting that switches involving newer AEDs may still expose patients to unnecessary risk of breakthrough seizures); Guberman, *supra* note 9, at 39 (suggesting that the susceptibility of second generation AEDs to bioequivalence problems has not yet been determined).

seizure. As discussed above, although individual dose titration permits patients to pass this threshold rendering them seizure free, it is usually not possible to know by how much this threshold has been passed. In many cases, AED treatment will result in freedom from seizures even though the plasma threshold has been passed by only a small margin. Thus, even with newer AEDs, a small change in plasma AED levels caused by a switch (branded to generic or between generics) could result in a breakthrough seizure if the switch subjects the patient to a plasma level just below his or her plasma threshold.

D. FDA Should Take Every Precaution to Reduce Breakthrough Seizures

Whatever the underlying cause or causes, switching patients who have achieved stable seizure freedom or who are generally well controlled on an AED exposes them to an unacceptable and unnecessary risk. In addition to the risks of injury or death (including SUDEP) discussed above, breakthrough seizures can also have serious social and legal consequences for patients who experience interruptions in seizure control. For example, in the State of New York, drivers who have lost consciousness in the preceding 12 months are subject to forfeiture of their drivers-license.[46] Since seizures routinely result in loss of consciousness, a single breakthrough seizure could cause the patient to lose his or her driving privileges for 12 months, resulting in a significant disruption in his or her life. Similarly, the State of California may refuse to renew the license of any person who has epilepsy or has otherwise experienced a loss of consciousness in the past three years.[47] Virtually every other state in the country has a provision that could result in significant loss of driving privileges as

---

[46] N.Y. Veh. & Traf. Law § 502; see N. Y. Comp. Codes R. & Regs. tit. 15, §§ 9.1 & 9.3. The State of New York may opt not to suspend driving privileges under certain circumstances, including if the driver presents a physician's statement certifying that the event was caused by a directed change of medication. Obviously, this is of little solace to patients who (a) may incur more than one breakthrough seizure as a result of a single switch, and (b) may routinely be exposed to multiple switches from the branded to a generic and then between generic AEDs.

[47] *See* California Department of Motor Vehicles. Driver safety information: lapses of consciousness disorders, *available at* http://www.dmv.ca.gov/dl/driversafety/lapes.htm (last visited Sept. 20, 2006) (seizure free periods of 3 and 6 months are considered in making individual determinations).

a result of a single breakthrough seizure.[48] Breakthrough seizures also typically cause disruption of employment, disruption of social networks, and hospitalization.[49]

Breakthrough seizures can also have significant consequences for cognitive development in children. Higher seizure frequency is a demonstrated risk factor for central nervous system dysfunction and academic underachievement.[50] This suggests that breakthrough seizures may contribute to other neurological disorders. In addition, breakthrough seizures in children often result in removal of the child from school for significant periods of time, resulting in immediate academic delays.

Finally, a single breakthrough seizure can lead to a permanent loss or reduction of overall seizure control. Data suggests that a significant proportion of patients who experience a breakthrough seizure never again become seizure free.[51] In addition, preclinical testing has suggested that some epilepsy patients, once titrated down and/or removed from their AED treatment, may become refractory to treatment by that same AED once placed back on drug therapy. For example, researchers at Dr. Post's Laboratory at the National Institute of Mental Health have observed a similar phenomenon in the kindled rat model. Rats kindled in the presence of carbamazepine or lamotrigine in Dr. Post's laboratories subsequently have become resistant to high challenge dose by those drugs once they become fully kindled. By contrast, control animals are sensitive to an acute challenge dose of either carbamazepine or

---

[48] *See* Epilepsy Foundation. Driver information by state, *available at* http://www.epilepsyfoundation.org/answerplace/Social/driving/statedrivinglaws.cfm (last visited July 24, 2006). There has been a trend in recent years towards state law permitting physicians to report patients with medical conditions, like epilepsy, to state departments of motor vehicles. Some states require such reporting. *See, e.g.*, Aschkenasy, M.T., et al. (2005). *Physician Reporting of Medically Impaired Drivers*, J. Emerg. Med. 30(1):29-37, 30-31.

[49] This can lead to significant costs to, among other things, the health care system. *See, e.g.*, Begley, Halpern, *supra* note 10.

[50] *See, e.g.*, Noeker, M., et al. (2005). *Development of mental health dysfunction in childhood epilepsy*. Brain Dev. 27:5-16, 7-9; McNelis, A.M., et al. (2005). *Factors associated with academic achievement in children with recent-onset seizures*. Seizure 14:331-339.

[51] *See, e.g.*, Schmidt, D., & Löscher, W. (2005). *Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience*. Acta Neurol. Scand. 111:292-300.

lamotrigine.[52] This effect could be mimicked by a switch to a generic AED, which could result in a de facto downward titration due to inexact bioequivalence.

As a result, UCB urges the FDA to take action to ensure that stabilized patients who are seizure free or whose seizures are well-controlled on a given AED do not have their medication switched unless it is deemed by the physician to be medically necessary and full disclosure is made to the treating physician and the patient. To this end, UCB makes three requests. First, UCB requests that FDA include the following warning in the full prescribing information for all AEDs:

> "Physicians and pharmacists should exercise extreme caution when switching patients who are seizure free or whose seizures are well controlled on a given antiepileptic drug. In general, switches in patients who are well controlled and have achieved stability on a given antiepileptic drug should be undertaken only when medically necessary and with full disclosure to treating physician and the patient."

This language, appearing in the Warnings (or Warnings and Precautions) section of the label, as applicable, would remind prescribing physicians and practicing pharmacists of the risks associated with switching AED medication in stabilized patients. In some cases, physicians may choose to indicate their preference to "dispense as written" on prescriptions. The warning may also prompt pharmacists to discuss these risks with patients when seeking their consent to a switch under state pharmacy laws. This warning should also appear in the "Highlights" section, as applicable, for labels subject to FDA's final labeling rule of January 26, 2006 (to be codified at 21 C.F.R. §§ 201.56 and 201.57), making it easily accessible to patients, physicians, and pharmacists.

Second, FDA should add a discussion of antiepileptic drugs to Section 1.8 (Description of Special Situations) of the Orange Book. This discussion should highlight the particular risks associated with substitution of AEDs and recommend against switching patients who have achieved stable seizure freedom or seizure control

---

[52] *See, e.g.,* Krupp E., et al. (2000). *Tolerance to the anticonvulsant effects of lamotrigine on amygdala kindled seizures: cross-tolerance to carbamazepine but not valproate or diazepam*, Exp. Neurol. 162:278-289. *See also* Rundfeldt, C., et al., *supra* note 12 (suggesting that one breakthrough seizure may contribute to further seizures by noting large inter-individual variations in the seizure threshold of amygdala-kindled rats).

on a given AED unless it is medically necessary, and only with full disclosure to the treating physician and the patient. Placing this material in the Orange Book would provide another way to alert physicians, pharmacists, and other health care providers of the risks associated with switches in stabilized patients.

Finally, UCB urges FDA to tighten its 80/125 bioequivalence standard with respect to AEDs. As discussed above, for a not insubstantial minority of patients, seizure control and avoidance occurs at a very narrow range of serum concentrations. In light of the literature reports and surveys regarding patients suffering breakthrough seizures after switching from branded to generic AEDs, FDA's current limits are not a sufficiently robust surrogate for therapeutic equivalence. In order to limit the number of stabilized patients unnecessarily exposed to breakthrough seizures, we urge FDA to tighten its bioequivalence limits by requiring generic applicants to show to a 90% confidence interval, that the lower range of the bioequivalence standard is at least 90% of that of the reference listed drug. Employing a more focused range will help reduce the amount of patients exposed to the risk of therapeutic inequivalence and significant negative medical outcomes such as breakthrough seizures.[53]

IV. Conclusion

The goal of AED therapy for epilepsy patients is seizure freedom with minimal side-effects. As a result, every effort must be taken to ensure that patients who have achieved seizure freedom or who are well-controlled on AED therapy are not subject to unnecessary risks of breakthrough seizures. It is implausible to think that there could be any responsible opposition to this position. There may be some situations in which a switch of AED medication for such patients is medically necessary, and UCB supports such switches. In many cases, however, AED switches of stabilized patients are undertaken purely for cost savings. Such a switch places otherwise stabilized patients at unacceptable risk of a catastrophic breakthrough seizure. Many of these patients may not even be aware that their branded AED will be switched to a generic version, nor do they (nor in some cases their treating physicians) realize that they may be routinely switched between generic versions of the same AED. Ironically, switches based solely on immediate cost savings at the pharmacy level may

[53] Because the primary safety concern with AED switches is the occurrence of breakthrough seizures, UCB has focused on the bottom bioequivalence limit and this Petition does not address the upper limit. In light of the Danish Medicines Agency's recent decision to tighten both the upper and lower bioequivalence limits, however, FDA may wish to consider additional steps to address safety concerns associated with AED switches.

ultimately cost the health care system more in the long run due to the cumulative effect of increased doctor and emergency room visits, and the socio-economic consequences of breakthrough seizures.

V. Required Material

A. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31(a).

B. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

C. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Egros Fabrice, Pharm. D., Ph.D.
President
UCB, Inc.