



OCT 11 2019

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President  
UCB, Inc.  
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Smyrna, Georgia 30080

Re: Docket No. FDA-2006-P-0461

Dear Dr. Fabrice:

This letter responds to the citizen petition submitted by UCB, Inc., and received by the Food and Drug Administration (FDA or the Agency) on October 3, 2006 (Petition).<sup>1</sup> The Petition requests that FDA take action to limit switches of antiepileptic drugs (AEDs) in stabilized patients who are well-controlled, unless the switch is deemed medically necessary. Specifically, the Petition asks that FDA: (1) require the full prescribing information of all AEDs to include a warning that physicians and pharmacists should exercise extreme caution when switching patients who are seizure free or whose seizures are well-controlled from one AED to another, (2) include a discussion in the Orange Book<sup>2</sup> of the risks associated with switching AEDs, and (3) narrow FDA's bioequivalence range for AEDs (Petition at 1-2).

We have carefully considered the issues raised in your Petition and the comments submitted to the docket. For the reasons stated below, your Petition is denied.

## I. BACKGROUND

### A. Epilepsy and AEDs

Epilepsy is a brain disorder in which clusters of neurons in the brain send abnormal signals, causing seizures. When the normal patterns of neuron activity become disturbed, convulsions, muscle spasms, loss of consciousness, and other abnormal sensations, emotions, and behaviors may result. Epilepsy may be caused by an abnormality in brain wiring, an imbalance of nerve signaling, or some combination of these factors. In some individuals, anything that disturbs the normal pattern of neuron activity—including illness, brain damage, or abnormal brain

<sup>1</sup> This citizen petition was originally assigned docket number 2006P-0405/CP1. The number was changed to FDA-2006-P-0461 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

<sup>2</sup> FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book. The Orange Book is available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

development—can lead to seizures. When an individual has had two or more seizures, he or she is considered to have epilepsy. Close to 3 million people in the United States have epilepsy.<sup>3</sup>

AEDs are the most common treatment for epilepsy. For most people with epilepsy, seizures can be controlled with just one AED at the optimal dosage. More than 20 AEDs are currently marketed, with a range of different benefits and side effects. A physician will usually prescribe a low dose of an AED initially and monitor blood levels while increasing the dose to determine when the best possible dose has been reached. Occasionally, patients may no longer require drugs to control their seizures, at which time they can be weaned off the medication. Epilepsy also may be treated through surgical techniques and/or stimulation of the vagus nerve.<sup>4</sup>

As you state in your Petition, some early—or first generation—AEDs that are still marketed include carbamazepine and valproic acid. Some first generation AEDs have nonlinear pharmacokinetics requiring additional considerations by physicians when titrating patients to determine the appropriate therapeutic dose. Newer—or second generation—AEDs have been approved starting in the 1990s. In general, fewer serious side effects have been reported with second generation AEDs.

#### **B. Statutory and Regulatory Standards for Bioequivalence**

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)), which established the current abbreviated new drug application (ANDA) approval process. To obtain approval, an ANDA applicant is not required to submit independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA’s previous finding that the reference listed drug (RLD) is safe and effective.<sup>5</sup> The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.<sup>6</sup>

An ANDA applicant must also demonstrate that its proposed generic drug is bioequivalent to the RLD.<sup>7</sup> Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the

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<sup>3</sup> National Institutes of Health, *The Epilepsies and Seizures: Hope Through Research*, <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through>.

<sup>4</sup> Id.

<sup>5</sup> A *reference listed drug*, or *RLD*, is “the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA” (21 CFR 314.3). RLDs are identified in the Orange Book.

<sup>6</sup> Section 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a).

<sup>7</sup> See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring “information to show that the new drug is

listed drug if: “the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .”<sup>8</sup>

In 21 CFR 314.3(b), FDA defines BE (in pertinent part) as:

... the absence of a significant difference in the rate and extent to which the active ingredient or active moiety . . . becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Section 320.24(b) of FDA’s regulations (21 CFR 320.24(b)) describes the Agency’s preferred bioequivalence methods. They include, in general descending order of accuracy, sensitivity, and reproducibility: (1) in vivo pharmacokinetic (PK) studies in whole blood, plasma, serum, or other appropriate biological fluid, or an in vitro test that has been correlated with and is predictive of in vivo bioavailability data; (2) in vivo studies in which urinary excretion of the active moiety, and when appropriate, its active metabolites, are measured; (3) in vivo pharmacodynamic (PD) effect studies; (4) clinical endpoint studies; and (5) other in vitro studies.<sup>9</sup> In addition, consistent with section 505(j)(8)(C) of the FD&C Act, § 320.24(b)(6) states that FDA has the flexibility to accept “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence.”

The choice of which study design to use is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug. The courts have expressly upheld FDA’s regulatory implementation of the FD&C Act’s bioequivalence requirements.<sup>10</sup>

For most systemically acting drugs in solid oral dosage forms, FDA recommends conducting a two-period, two-sequence, two-treatment, single-dose crossover study in healthy subjects. In this design, each study subject receives each treatment (i.e., the test drug and the reference drug) in random order.<sup>11</sup> Single oral doses of the test and reference drugs are administered, and each

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<sup>8</sup> See also 21 CFR 320.23(b).

<sup>9</sup> § 320.24(b). Whereas a PK study measures the rate and the extent to which the drug is delivered to biological fluids (generally the bloodstream), a PD study measures effects associated with the delivery of the active ingredient to the site of action.

<sup>10</sup> See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3<sup>rd</sup> Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

<sup>11</sup> *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (December 2013) (Draft BE Studies guidance) (available at <https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf>), at 3.

drug's concentration in the blood or other biological fluid is measured over time. To evaluate the rate and extent of test drug absorption, the measured plasma concentrations for each subject should be plotted graphically against time of measurement. The graph depicts the plasma sampling time on the horizontal (*x*) axis and corresponding plasma drug concentration on the vertical (*y*) axis. The relevant pharmacokinetic parameters calculated from these data include the area under the plasma concentration versus time curve (AUC), AUC calculated to the last measured concentration time (AUC<sub>0-t</sub>), and AUC extrapolated to infinity (AUC<sub>∞</sub>). These parameters represent the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant pharmacokinetic parameter is the maximum or peak drug concentration (C<sub>max</sub>), which is used to reflect the rate of absorption.<sup>12</sup>

It is important to analyze the pharmacokinetic parameters statistically because of the variability inherent in human subjects. This variability means that if a subject receives the *same* drug product on two different occasions, the resulting plasma concentrations will not be exactly the same on each occasion. This inherent variability means that the interpretation of a study of two different products is complex, because the concentrations could differ to some extent even if the products have identical bioavailability. Thus, if a single individual takes two *different* products on separate occasions, and there are some differences in the pharmacokinetic parameters, it is not immediately clear whether this difference is the result of a true difference between the products, the result of differences within the individual, or the result of the inherent variability of the measurements. Thus, FDA recommends that ANDA applicants use statistical analyses to evaluate the similarity or differences in pharmacokinetics that result from the two product formulations.

When considering the results from bioequivalence studies, it is important to understand what statistical tests are used and how FDA uses the results of these statistical tests to determine whether two products are bioequivalent. To understand the statistical tests for bioequivalence, one must first understand the relevant statistical terms, particularly the definitions of *mean* and *confidence interval*. The statistical term mean is frequently used in describing bioequivalence study results. Generally, the mean in this context refers to the average of all the values observed in the small group of study subjects.

A confidence interval is used to address the factor of variability. Just as there is variation in pharmacokinetic values within an individual after different treatments, there is also variation in these values between treatment groups. The confidence interval describes where the results can be expected to lie based on the mean values and the variability seen. Essentially, the confidence interval provides an estimated range that is likely to contain the true pharmacokinetic values. The confidence interval's width specifies the location within which the true mean value can be expected to lie.

In analyzing in vivo bioequivalence studies, FDA generally uses a 90 percent confidence interval. For example, the ratio of the mean AUC values for a small study (reflecting the average difference between the test and reference products for all of the study subjects) could be 99

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<sup>12</sup> See Draft BE Studies guidance at 5, 20.

percent. Furthermore, a statistical analysis of the data could determine that the 90 percent confidence interval for this small study is a range of 94 to 112 percent for the ratio of pharmacokinetic values. The 90 percent confidence interval means, generally, if a similar study was carried out many times, and the same procedure was used to construct this interval, 90% of the resulting intervals would contain the true ratio of the AUC of the two products.

If the study had used a greater number of subjects to more accurately reflect the general population's results, then the 90 percent confidence interval would likely be smaller (i.e., a smaller range of the possible pharmacokinetic values in the general population, such as 96 to 110 percent).

FDA determines whether a study shows that two products are bioequivalent based on the confidence interval and not on the mean value of the study. The results of a study are expressed as a confidence interval for the ratio of test to reference products. To decide whether two products are bioequivalent, we compare the calculated confidence interval to an acceptance interval. The acceptance interval (also referred to as acceptance limits) is expressed as two numbers that provide upper and lower limits on the confidence interval. If the confidence interval is contained within this acceptance interval, then FDA concludes that the study demonstrates bioequivalence; if not, then the study does not demonstrate bioequivalence. The acceptance interval is a fixed standard, while the confidence interval is determined from the data in a particular study.

FDA generally considers that products are bioequivalent when the 90 percent confidence interval for pharmacokinetic parameters are entirely within an 80 to 125 percent acceptance interval. The choice of the 80 to 125 percent acceptance interval reflects decades of scientific data on the variability of product characteristics (such as potency) within and between batches, as well as biological variability in patients. From these data, FDA concluded that the variability in pharmacokinetic values allowed under this acceptance interval would not adversely affect clinical outcomes, because this variability is within the range of differences that can already arise due to other product-specific and biological factors.<sup>13</sup>

It is important to note that the 80 to 125 percent boundaries are acceptance limits for the confidence interval and not a judgment about the acceptable mean differences between test and reference products. The sample mean pharmacokinetic values for the test and reference products lie at the center of the confidence interval. Because this confidence interval must fall within the 80 to 125 percent boundaries, these statistical criteria limit the acceptable range in which the mean value can stray from the 100 percent ratio.

In practice, the actual mean differences FDA has found for drugs tested and analyzed under this statistical procedure have been much smaller than the 80 to 125 percent boundaries. In the

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<sup>13</sup> See Dighe, S.V., and Adams, W.P., "Bioequivalence: A United States Regulatory Perspective," in *Pharmaceutical Bioequivalence*, Welling, P.G. et al., eds., 347-380. New York: Marcel Dekker, 1991.

1980s, FDA reviewed 224 bioequivalence studies that passed the 80 to 125 percent criterion.<sup>14</sup> In these studies, the observed mean difference in AUC between the brand name and the generic product was approximately 3.5 percent.<sup>15</sup> A similar analysis was conducted for the 127 bioequivalence studies conducted for generic drugs approved in 1997.<sup>16</sup> The average observed difference in  $AUC_{0-t}$  in this analysis was approximately 3.47 percent, and the average observed difference in  $AUC_\infty$  was 3.25 percent.<sup>17</sup>

Some drug products, such as parenterals or oral solutions, are generally completely absorbed into the bloodstream and the demonstration of bioequivalence for those products is considered self-evident if the formulations being compared are qualitatively and quantitatively the same.<sup>18</sup> In such cases, FDA will grant a waiver of in vivo bioequivalence testing. In addition, for certain drug products, an applicant may submit in vitro data in support of measuring in vivo bioavailability or demonstrating in vivo bioequivalence.<sup>19</sup> In the guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*, FDA provided recommendations related to use of in vitro bioequivalence studies in support of an ANDA for drugs that are classified as class 1 or class 3 under the Biopharmaceutics Classification System (BCS).<sup>20</sup> To be considered BCS class 1, the sponsor should demonstrate that the drug substance is highly soluble and highly permeable, the drug product is rapidly dissolving, and the product does not contain any excipients that will affect the rate or extent of absorption of the drug.<sup>21</sup> To be considered BCS class 3, the sponsor should demonstrate that the drug substance is highly soluble, the drug product is very rapidly dissolving, and the test product formulation is qualitatively the same and quantitatively very similar to the reference product.<sup>22</sup> According to the guidance, an immediate-release (IR) drug product is considered rapidly dissolving when a mean of 85 percent or more of

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<sup>14</sup> Nightingale, S.L., and Morrison, J.C., "Generic Drugs and the Prescribing Physician," *JAMA*, 258(9):1200-1204, 1987.

<sup>15</sup> Id. at 1202.

<sup>16</sup> Henney, J.E., "Review of Generic Bioequivalence Studies," *JAMA*, 282(21):1995, 1999.

<sup>17</sup> Id.

<sup>18</sup> See § 320.22(b).

<sup>19</sup> See § 320.24(b)(6). There are certain circumstances in which bioequivalence can be evaluated using in vitro approaches under 21 CFR 320.24(b)(6). In such circumstances, FDA has determined that in vitro data is the most accurate, sensitive, and reproducible for a product, as required under 21 CFR 320.24(a).

<sup>20</sup> See FDA guidance for industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (December 2017) (BCS guidance), at 9 (available on the FDA Drugs guidance web page).

<sup>21</sup> Id.

<sup>22</sup> Id. at 9-10.

the labeled amount of the drug substance dissolves in specified media within 30 minutes.<sup>23</sup> An IR drug product is considered very rapidly dissolving when a mean of 85 percent or more of the labeled amount of the drug substance dissolves in specified media within 15 minutes.<sup>24</sup> Drug products with these properties are expected to behave like oral solutions in vivo; thus, their in vivo bioequivalence is considered self-evident and they do not present the potential for bioavailability differences caused by formulation differences. The BCS Guidance's recommendations are not applicable for narrow therapeutic index (NTI) drugs due to the critical relationship between the bioavailable dose and the drug's clinical performance.<sup>25</sup>

### C. Warnings in Prescription Drug Labeling

Labeling for prescription drug products is generally governed by several provisions of the FD&C Act<sup>26</sup> and FDA's regulations appearing in 21 CFR Part 201. These regulations state that the WARNINGS AND PRECAUTIONS section of applicable drug product labeling must describe clinically significant adverse reactions,<sup>27</sup> other potential safety hazards, limitations in use, and steps to take if these events occur.<sup>28</sup> Labeling must be revised to include a warning as soon as there is reasonable evidence of a causal association between a clinically significant hazard and a drug.<sup>29</sup> A summary of the most clinically significant warnings and precautions information must be included in the Highlights of Prescribing Information section of labeling for the drug product.<sup>30</sup>

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<sup>23</sup> Id. at 3.

<sup>24</sup> Id.

<sup>25</sup> Id. at 12. NTI drugs are sometimes referred to as exhibiting a "narrow therapeutic ratio," which is characterized by having "less than a 2-fold difference in median lethal dose (LD50) and median effective dose (ED50) values, or . . . less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood," as well as requiring "careful dosage titration and patient monitoring" for the safe and effective use of the drug. § 320.33(c).

<sup>26</sup> Provisions relevant to the issues discussed in this Petition include sections 201(n); 502(a), (f), and (j); and 505 of the FD&C Act (21 U.S.C. 321(n); 352(a), (f), and (j); and 355).

<sup>27</sup> Section 201.57(c)(7) defines *adverse reaction* as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) (Warning Label guidance), at 13, defines *serious adverse reaction* in part as "any event or reaction that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect."

<sup>28</sup> § 201.57(c)(6)(i).

<sup>29</sup> Id.

<sup>30</sup> § 201.57(a)(10).

Serious or otherwise clinically significant adverse reactions observed in association with use of a drug should be listed in the WARNINGS AND PRECAUTIONS section if there is “reasonable evidence of a causal association between the drug and the adverse event.”<sup>31</sup> This section of labeling also should list serious or otherwise clinically significant adverse reactions that are expected to occur with a drug, but have yet to be observed, based on information such as certain observations from other members of the drug class or animal studies. FDA may also require a discussion of adverse reactions associated with an unapproved use if a drug is commonly prescribed for that use.<sup>32</sup> The causal relationship need not have been definitively established.<sup>33</sup>

Under section 505(o)(4) the FD&C Act, FDA is authorized to require holders of approved applications for prescription drugs to make labeling changes based on, among other things, new safety information that becomes available after the approval of the drug that FDA believes should be included in the labeling of the drug.<sup>34</sup>

## II. DISCUSSION

Your Petition makes several specific requests for FDA actions to limit switches of AEDs. These requests, and the Agency’s responses, are discussed in this section of the response.

### A. Warning on AED Labels

You request 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.

(Petition at 1, 19).

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<sup>31</sup> See Warning Label guidance at 3-4.

<sup>32</sup> See Id. at 3-5; 21 CFR 201.57(c)(6)(i).

<sup>33</sup> See Warning Label guidance at 3.

<sup>34</sup> Section 505(o)(4) of the FD&C Act. *New safety information* is defined in the FD&C Act as “information derived from a clinical trial, an adverse event report, a postapproval study . . . or peer reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k); or other scientific data deemed appropriate” by the Agency about, among other things, “a serious risk or an unexpected serious risk associated with the use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved” (section 505(o)(2)(C) and 505-1(b)(3) of the FD&C Act (21 U.S.C. 355(o)(2)(C) and 355-1(b)(3)).

You request that this language appear in the WARNINGS AND PRECAUTIONS section of the labeling.<sup>35</sup>

You state that “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,” and contend that AED switches may cause a disruption in seizure control that leads to such a breakthrough seizure (Petition at 7). You further claim that breakthrough seizures have been encountered with switches from a branded AED to a generic AED as well as with switches from one generic AED to another and cite several surveys as evidence that AED switches are problematic. You also state that AED switching at the retail pharmacy level is commonplace and use testimony from Dr. Steven C. Schachter to illustrate why such “constant generic-generic switching can place a patient at almost constant risk for breakthrough seizures and other side-effects” (Petition at 9).

You state that “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” (Petition at 10). To support this claim, you quote a speaker at an international-industry-sponsored symposium, who stated 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.”<sup>36</sup> In addition, you reference a policy from the American Academy of Neurology that was retired shortly before the submission of this Petition, and which has not been replaced,<sup>37</sup> as well as a recommendation against AED switching from the British National Institute for Health and Clinical Excellence. You argue that several of FDA’s peer regulatory agencies in Europe have taken steps to limit or prohibit substitution of generic AEDs (Petition at 11). Breakthrough seizures, you explain, can lead to many health and social consequences for epilepsy patients, and may even “lead to a permanent loss or reduction of overall seizure control” (Petition at 17-18).

We agree that efforts should be made to minimize changes in therapeutic effect during the treatment of epilepsy, as changes in therapeutic effect may lead to breakthrough seizures in stable and seizure-free patients. While we generally agree that breakthrough seizures are serious and can have a wide-ranging impact on a patient, we are not aware of convincing clinical data

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<sup>35</sup> You also request that the warning appear in the “Highlights” section, as applicable, for labeling subject to FDA’s final labeling rule of January 26, 2006 (71 FR 3986, codified at 21 CFR 201.56 and 201.57).

<sup>36</sup> Petition at 10, citing Krämer, G. (2005), *Generic Substitution in Antiepileptic Drug Therapy: Do New Regulations Match Clinical Experience?* 9 Cong. Eur. Fed’n (Abstract Book) at 10.

<sup>37</sup> The American Academy of Neurology’s website notes that this policy was retired on July 28, 2006, and notes that an update is in progress. See <https://www.aan.com/Guidelines/Home/GuidelineDetail/55>.

indicating that one or more breakthrough seizures leads to an increased likelihood of future seizures in an individual with epilepsy.<sup>38</sup>

Currently, there is insufficient evidence to conclude that a switch from a branded AED to a generic AED increases the risk of seizures and other side effects. Breakthrough seizures have many causes, including drug-drug interactions; noncompliance with dosing requirements; emotional stress; environmental factors such as watching television; and additional health factors such as fever, sleep deprivation, or fatigue.<sup>39</sup> If a breakthrough seizure occurs because of one of these factors and coincides with a switch to a generic AED, the breakthrough seizure may be erroneously attributed to the switch to the generic AED. Similarly, insufficient evidence exists to establish a clear link between generic switches and breakthrough seizures. In a December 1988 response to a letter from what was then called the Generic Pharmaceutical Industry Association, then-Commissioner Dr. Frank Young stated that “at present, there is no credible evidence that the use of agency approved generic anticonvulsants results in an increased frequency of seizures.” Dr. Young further noted that “FDA had not seen any scientifically valid evidence that a generic anticonvulsant failed to deliver appropriate amounts of active ingredient.”<sup>40</sup> Your Petition provides no new evidence upon which FDA can base a scientific determination.

Your assertion that most epileptologists recommend limiting switches of AEDs in stabilized patients who are well-controlled is unpersuasive. It is unclear what evidence served as the basis for the remarks from Dr. Kramer, the speaker at the symposium. In any event, Dr. Kramer’s comments reflect the observation of one individual who practices medicine in a country with a different regulatory framework than the United States. You also cite surveys demonstrating significant disagreement among neurologists regarding whether brand-to-generic switching can be safely done.<sup>41</sup> In addition, as noted above, the American Academy of Neurology guidelines on generic substitution cited in your Petition were retired shortly before submission of your Petition and have not been revised. Finally, the recommendation of the United Kingdom’s National Institute for Health and Clinical Excellence against AED switching is not persuasive in this instance. As with the comments from Dr. Kramer, the Institute’s recommendation was made in the context of a regulatory framework that is different from the drug approval authority in the United States. Moreover, the Agency concludes that insufficient evidence has been provided to

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<sup>38</sup> Sills, G.J., “Seizures Beget Seizures: A Lack of Experimental Evidence and Clinical Relevance Fails to Dampen Enthusiasm,” *Epilepsy Curr*, 7(4):103-104, 2007.

<sup>39</sup> Ettinger, A., and Adigha, R., “Breakthrough Seizures—Approach to Prevention and Diagnosis,” *Touch Neurol*, 4(1):40-42, 2008.

<sup>40</sup> FDA policy on generic anticonvulsants. *SCRIP*. Issue 1469:28-29, 1989.

<sup>41</sup> Petition at 10, citing Guberman, A., and Corman, C., “Generic Substitution for Brand Name Antiepileptic Drugs: A Survey,” *Can J Neurol Sci*, 27:37-43, 39, 2000.

FDA demonstrating a causal association between therapeutic failure or increased risk of side effects and generic substitution.<sup>42</sup>

The surveys you cite in support of your Petition do not adequately demonstrate that switching epilepsy treatments can lead to breakthrough seizures. For instance, you describe results from a 1996 survey<sup>43</sup> suggesting that as many as 30 percent of the patients experienced breakthrough seizures or other side effects after switching to a generic AED (Petition at 8). This survey actually reported that 29.5 percent of respondents reported “perceived” problems. With respect to the patients who reported perceived problems, the authors noted that, “[f]actors other than differences in bioavailability could have led to people reporting problems, for example stress, worry, confusion due to changing pill size and color, attribution bias and poor dispensing.”<sup>44</sup> The authors further stated that patients who reported “validated” problems could not be differentiated significantly in terms of frequency of seizures or number of medications taken from those who did not report problems.<sup>45</sup>

In addition, responses to questions may be influenced by the phrasing of the questions, which could lead to a bias in the results of the survey, or low response rates, which could undermine conclusions derived from the survey. For example, in a 2004 survey cited in the Petition,<sup>46</sup> 68 percent of neurologists who responded to the survey reported patients who had breakthrough seizures following a switch from a branded AED to a generic AED.<sup>47</sup> However, the overall response rate for the survey was only 4.7 percent, with only 301 questionnaires completed out of 6,420 questionnaires distributed to neurologists.<sup>48</sup> Surveys may be useful for evaluating trends

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<sup>42</sup> In addition, your Petition misrepresents the nature of FDA’s concerns regarding prescription drugs imported from Canada, as described in a 2005 letter from Dr. Randall Lutter of FDA to then-Governor Rick Perry. In particular you say that, in the letter, “FDA 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” (Petition at 15). FDA’s concerns discussed in the letter you cite were not related to any alleged difficulty in establishing bioequivalence for AEDs specifically. Rather, as the letter made clear, FDA’s concern was, among other things, that foreign prescription drug products that have not been evaluated by FDA may not be bioequivalent to FDA-approved products by FDA standards. (Letter from Randall W. Lutter to Governor Rick Perry, June 17, 2005.) The letter does not suggest that AEDs that have been found therapeutically equivalent by FDA’s standards are not substitutable. For these reasons, we do not find the results of the observational study of AED switching in Canada cited in your Petition to be persuasive.

<sup>43</sup> Crawford, P., Hall, W.W., Chappell, B., et al., “Generic Prescribing for Epilepsy: Is It Safe?” *Seizure*, 5(1):1-5, 1996.

<sup>44</sup> Id. at 4.

<sup>45</sup> Id.

<sup>46</sup> Wilner, A.N., “Therapeutic Equivalency of Generic Antiepileptic Drug: Results of a Survey,” *Epilepsy Behav*, 5(6):995-998, 2004.

<sup>47</sup> Petition at 9, citing Wilner at 996.

<sup>48</sup> Wilner at 996.

or detecting signs that further evaluation is needed, as in the case of adverse events, but well-controlled randomized studies are required to demonstrate whether the cause and effect relationship between AED switches and breakthrough seizures that you claim in your Petition exists.

The information available to FDA via the FDA Adverse Event Reporting System (FAERS) similarly should not be used to determine whether brand-to-generic switching occurred or led to adverse events. As demonstrated in a recent study investigating adverse event reports for AEDs, FAERS reports do not always contain sufficient information for FDA to determine whether the implicated drug is the brand name or generic. In most cases, the report does not specify whether the AED drug used was brand name or generic. This study demonstrated that the vast majority of reports were innovator-submitted reports, even after generic approval.<sup>49</sup> This disproportionately high share of innovator-submitted reports, even after generic approval, likely indicates patient and provider familiarity with brand names, leading to preferential reporting to innovators of the brand name drugs.<sup>50</sup> Furthermore, it is not possible to use FAERS data to calculate incidence rates because of underreporting and because FAERS does not capture the total number of patients receiving AEDs.<sup>51</sup> Lastly, because epilepsy can be a fluctuating condition,<sup>52</sup> it can be hard to distinguish between adverse events that are caused by the disease itself or those that are caused by another factor.

In addition, in 2012 and 2016, FDA conducted a literature review to evaluate whether brand-to-generic substitution of AEDs led to an increased risk of seizures. The Agency reviewed 14 studies between the two reviews, many of them cohort studies. None of the studies were randomized controlled trials. The Agency concluded that the evidence did not suggest that brand-to-generic switching leads to an increased risk of seizure-related adverse events.

The labeling language you request is not warranted because the currently available scientific evidence does not support the inclusion of that information in the WARNINGS AND PRECAUTIONS section of the labeling. FDA regulations include specific requirements regarding the content of labeling for prescription drug and biological products. Specifically, these regulations provide that the WARNINGS AND PRECAUTIONS section of labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. In addition, the labeling “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable

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<sup>49</sup> Bohn, J., Kortepeter, C., Munoz, M., Simms, K., Montenegro, S., Dal Pan, G., “Patterns in Spontaneous Adverse Event Reporting Among Branded and Generic Antiepileptic Drugs,” *Clin Pharmacol Ther*, 97(5):508-517, 2015.

<sup>50</sup> Id. at 512.

<sup>51</sup> See Strom, B.L., *Pharmacoepidemiology 4th ed.* UK: John Wiley & Sons, at 152-53, 2006.

<sup>52</sup> Dragoumi, P., Tzetzi, O., Vargiami, E., et al., “Clinical Course and Seizure Outcome of Idiopathic Childhood Epilepsy: Determinants of Early and Long-Term Prognosis,” *BMC Neurol*, 13:206, 2013.

evidence of a causal relationship with the drug; a causal relationship need not have been definitely established.”<sup>53</sup>

We agree that breakthrough seizures pose serious risks for patients with epilepsy. The Agency will continue to monitor adverse event reports of possible problems with generic substitution of AEDs and will revise its policy as needed. The Agency has recently worked with the epilepsy community to design two scientifically rigorous, randomized controlled trials in patients with epilepsy to examine whether generic AEDs perform appropriately. One study sought to determine whether generic AEDs that were approved in healthy volunteers would meet FDA’s bioequivalence standard when tested in patients who are potentially sensitive to problems with generic switching, and compared generic lamotrigine to its name-brand counterpart, Lamictal.<sup>54</sup> The study concluded that “[t]he 90% confidence intervals of the mean for steady-state AUC, C<sub>max</sub>, and C<sub>min</sub> for generic-versus-brand were 97.2-101.6%, 98.8-104.5%, and 93.4-101.0%, respectively.”<sup>55</sup> The researchers did not identify a clinically significant difference in exposure or seizure frequency. A second study focusing on generic-to-generic switching of lamotrigine concluded that lamotrigine exposure was equivalent between the two generics tested (the 90% confidence interval for AUC was 98%-103% and the 90% confidence interval for C<sub>max</sub> was 99%-105%) and that there were no clinically significant changes in seizure frequency or adverse events.<sup>56</sup> We would provide similar assistance to other interested parties that wish to conduct additional studies of AED switches. However, we are not persuaded by the evidence available to the Agency that breakthrough seizures may be caused by AED switching.

In the absence of evidence, and in light of the relevant studies and other information discussed above, we find your proposed warning language unwarranted and decline to require the requested labeling revisions for AEDs to warn physicians and pharmacists against switching patients either from a branded AED to a generic AED or from one generic AED to another. Therefore, we deny your request to include a warning in the full prescribing information for all AEDs.

#### B. Orange Book Discussion of Risks of Switching AEDs

You also request that FDA add a discussion of AEDs to section 1.8 (Description of Special Situations) of the Orange Book. Specifically, you request that the discussion highlight the particular risks associated with substitution of AEDs and recommend against switching AEDs for stabilized patients unless medically necessary. Because, as discussed above, we are not

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<sup>53</sup> § 201.57(c)(6) (emphasis added). See also § 201.80(e), describing the WARNINGS section for prescription drugs not labeled pursuant to 201.57.

<sup>54</sup> Ting, T.Y., Jiang, W., Lionberger, R., et al., “Generic Lamotrigine Versus Brand-Name Lamictal Bioequivalence in Patients with Epilepsy: A Field Test of the FDA Bioequivalence Standard,” *Epilepsia*, 56(9):1415-1424, 2015.

<sup>55</sup> Id.

<sup>56</sup> Privitera, M.D., Welty, T.E., Gidal, B.E., et al., “Generic-to-Generic Lamotrigine Switches in People with Epilepsy: the Randomised Controlled EQUIGEN Trial,” *Lancet Neurol*, 15(4):365-372, 2016.

persuaded that the evidence presented to the Agency suggests particular risks associated with substitution of AEDs, we decline to include a discussion of such risks and a recommendation against AED switches. Therefore, this request is denied.

### C. Bioequivalence Criteria for AEDs

Finally, you request that FDA narrow its bioequivalence range for AEDs to require a showing, at the 90 percent confidence interval, that the lower limit is at least 90 percent of its RLD. You assert that many researchers and physicians believe “FDA’s current bioequivalence methodology is not an adequate surrogate for therapeutic equivalence between generic AEDs and their [RLDs],” arguing that switching from one generic AED to another generic poses a significant risk of breakthrough seizures (Petition at 12-13). Among other things, you cite the statement that it is “theoretically possible for the average patient to experience an almost 50 percent increase in serum concentration if switched from a low bioavailability generic formulation (e.g., 80 percent of brand) to a high bioavailability (e.g., 120 percent of brand) generic formulation” (Petition at 14).

You also argue that when, in 2005, FDA cited potential lack of therapeutic equivalence as a reason for opposing State legislation relating to importation of prescription drugs from Canada, the Agency was acknowledging that open questions exist with respect to bioequivalence of AEDs (Petition at 15-16). Finally, you claim that these bioequivalence problems are particularly acute for first generation AEDs, but that even second generation AEDs are “susceptible to failures in bioequivalence” because even a small change in the plasma level threshold caused by an AED switch can lead to loss of seizure control (Petition at 16-17).

The Agency is not persuaded by the evidence presented that there are problems with FDA’s bioequivalence criteria for AEDs. The arguments in your Petition suggesting the potential for a wide difference in bioavailability between brand and generic products demonstrate a misunderstanding of FDA’s bioequivalence criteria and the range of bioavailability differences possible in an approved generic drug. The theoretical possibility of an almost 50 percent increase in serum concentration cited in the Petition is not supported by several decades of experience with bioequivalence testing and generic drug approvals. Generic drugs are not approved based on -20 percent and +25 percent difference in bioavailability (AUC) relative to the RLD. As stated in the Background section of this response, two products are generally considered to be bioequivalent when the 90 percent confidence interval for the geometric mean ratio for AUC and  $C_{max}$  are entirely within an 80 to 125 percent acceptance interval. In general, the mean ratios (or point estimates) are usually close to 100 rather than anywhere near 80 or 125. In fact, the use of a 90 percent confidence interval precludes a point estimate at the bottom or top of the range because the entire confidence interval must fall within the range, and the observed mean falls in the center of the confidence interval.<sup>57</sup> Where FDA has conducted a study of the

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<sup>57</sup> See Vossler, D.G., Anderson, G.D., Bainbridge, J., “AES Position Statement on Generic Substitution of Antiepileptic Drugs,” *Epilepsy Curr*, 16(3):209-210, 2016.

differences between approved generics and innovator products, the average difference in bioavailability (AUC), based on hundreds of bioequivalence studies, was less than 4 percent.<sup>58</sup>

Regarding your argument that FDA's letter opposing the proposed importation of prescription drugs from Canada constituted an acknowledgement that open questions exist with respect to bioequivalence of AEDs, FDA disagrees. As stated above, FDA's concerns with importing drugs from foreign countries described in the Agency's 2005 letter to then-Governor Rick Perry included the fact that foreign prescription drug products have not been evaluated under FDA's regulatory framework, so their bioequivalence to an FDA-approved product cannot be established.<sup>59</sup>

Please note that FDA has described several AEDs as NTI drugs.<sup>60</sup> NTI drugs generally share several common characteristics:

- (i) there is little separation between therapeutic and toxic doses (or the associated blood/plasma concentrations); (ii) sub-therapeutic concentrations may lead to serious therapeutic failure; (iii) they are subject to therapeutic monitoring based on PK or pharmaco-dynamic (PD) measures; (iv) they possess low-to-moderate (i.e., no more than 30%) within-subject variability; and (v) in clinical practice, doses are often adjusted in very small increments (less than 20%).<sup>61</sup>

For drugs that have been identified as NTI, FDA generally applies a narrower bioequivalence acceptance interval based on within subject variability. FDA recommendations are described in the drug's product-specific guidance. While some AEDs are considered NTI drugs, the evidence available to FDA does not suggest that the entire class of AEDs should be classified as NTI. FDA will determine whether other AEDs require NTI classification on a case-by-case basis, in light of these characteristics and the definition of "narrow therapeutic ratio" in our regulations.<sup>62</sup>

Lastly, we note that the in vivo bioequivalence testing described in your Petition would not apply in situations where FDA has determined that in vitro bioequivalence studies may be submitted in lieu of in vivo studies in support of an ANDA for a generic AED. As explained in Section I.B,

<sup>58</sup> Henney, J.E., "Review of Generic Bioequivalence Studies," *JAMA*, 282(21):1995, 1999.

<sup>59</sup> See *supra*, note 42.

<sup>60</sup> See *Draft Guidance on Phenytoin* (May 2017), at 1 (available on the FDA Drugs guidance web page) regarding oral suspension and chewable tablets; *Draft Guidance on Carbamazepine* (March 2015), at 2 (available on the FDA Drugs guidance web page) regarding oral suspension, oral extended-release capsules, and oral extended-release tablets; *Draft Guidance on Carbamazepine* (September 2015), at 2 (available on the FDA Drugs guidance web page) regarding oral tablets; *Guidance on Valproic Acid* (August 2017), at 2 (available on the FDA Drugs guidance web page) regarding oral capsule; and *Draft Guidance on Divalproex Sodium* (December 2016), at 2 (available on the FDA Drugs guidance web page) regarding oral delayed-release tablets, oral delayed-release pellets capsules, and oral extended-release tablets.

<sup>61</sup> Yu, L.X., Jiang, W., Zhang, X., et al., "Novel Bioequivalence Approach for Narrow Therapeutic Index Drugs," *Clin Pharm & Therapeutics*, 97(3):287, 2015.

<sup>62</sup> § 320.33(c).

FDA may make such a determination for a proposed generic, IR solid oral dosage AED if the sponsor demonstrates that the drug meets the criteria for BCS class 1 or class 3. A proposed generic AED with these properties is expected to behave like an oral solution *in vivo*. Consequently, its *in vivo* bioequivalence would be considered self-evident and any formulation differences between the proposed generic AED and the RLD would not be expected to result in differences in bioavailability.

Accordingly, to the extent you request that we narrow the bioequivalence acceptance criteria for all AEDs, we deny your request.

### III. CONCLUSION

FDA has reviewed your Petition, the submitted comments, and other relevant information available to us. For the reasons discussed above, we deny your requests to require all AEDs to include a warning to exercise extreme caution when switching those products, to include a discussion in the Orange Book of the risks associated with switching AEDs, and to narrow the bioequivalence range for AEDs.

Sincerely,



Janet Woodcock, M.D.  
Director  
Center for Drug Evaluation and Research