Information Regarding Anti-Epileptic Drugs

U.S. Food and Drug Administration

in Response to Requests in

Senate Report No. 111-39

and

House Agriculture Committee Report No. 111-279

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I. Introduction

Senate Report No. 111-39 contains the following request for information from the U.S. Food and Drug Administration:

> *Epilepsy Drug Safety Research - The Committee is concerned about recent reports of unexpected side effects, including seizures, when epileptic individuals switch among different manufacturers' versions of the same therapeutic agent. The Committee directs the FDA to submit a report not later than September 30, 2010 detailing FDA's advice on planned research on the impact of substituting bioequivalent anti-epileptic drugs on epileptic individuals and detailing FDA proposed guidance or actions to minimize the health impact or side effects as a result of the agency's research on switching bioequivalent anti-epileptic drugs.*

Similarly, House Agriculture Committee Report No. 111-279 included the following request for information:

> *The conferees request that FDA report on adverse events and seizures associated with brand and generic anti-epileptic drugs. Specifically, the agency should examine the pharmacokinetic profiles of "A" rated anti-epileptic drugs from different manufactures of the same therapeutic agent. The Committee directs the FDA to submit a report not later than September 30, 2010, detailing whether the agency believes that any changes to the current bioequivalence testing should be recommended.*

The Food and Drug Administration (FDA), Department of Health and Human Services (HHS), prepared this report in response to these Congressional requests.

II. Background

Epilepsy is a complex disease affecting approximately three million Americans. The various causes of epilepsy are not fully understood; however, epilepsy is associated with an imbalance between activation and inhibition of neurological systems in the brain. Anti-epileptic drugs (AEDs) are designed to correct this imbalance and thereby prevent seizures by modifying specific biological functions.[1] AEDs approved by FDA have proven to be extremely successful – allowing 80 percent of patients to control their seizures with standard therapy. There are currently 11 AEDs for which approved generic versions are available (see Table I).

[1] The main groups of AEDs include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, and hormones.

Table I.

FDA Approved Generic AEDs
(as of January 2010)

Generic Name	Number of Generic Products Marketed
Phenytoin	**5**
Carbamazepine	**7**
Carbamazepine ER	**2**
Divalproex Na – DR	**13**
Divalproex Na – ER	**6**
Lamotrigine	**14**
Gabapentin	**11**
Topiramate	**16**
Levetiracetam	**17**
Oxcarbazepine	**8**
Zonisamide	**13**

ER = Extended-release formulation
DR = Delayed-release formulation

Some patient and clinician groups have expressed concern that switching between brand name AEDs and FDA-approved generic formulations or between two approved generic formulations may cause clinically significant changes in drug concentrations in the blood stream, leading to unexpected seizures or serious adverse events.[2] The information FDA has seen supporting these concerns is limited to anecdotal reports, focused surveys, small case-controlled studies, and retrospective switchback studies. To date, no one has conducted a well-designed study – prospective, blinded, randomized – comparing brand and generic AEDs in a patient population with a history of problems or adverse outcomes, following a switch between brand and generic AEDs.

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[2] The current position on switching of AEDs by the Epilepsy Foundation (approved on May 2009) states, *"Until both the research and the review of standards and guidelines for determining bioequivalence in antiepileptic therapies occurs, the Epilepsy Foundation recommends extreme caution be taken when switching patients among different versions of a therapeutic agent. Current experience suggests that most patients will be able to switch safely and effectively from one version of a product to another; however, because of the significant number of people who will have difficulty with switching, including potentially serious and costly consequences, and because those people cannot be identified in advance, the Foundation advises that when a switch is contemplated, both the treating physician and the individual be informed and agree in advance, and have the option to stay on the product of choice, or to have the switch occur only under the guidance and direction of the treating physician. The results of such switching should be monitored closely for a few weeks after a switch occurs, and any problems or concerns that arise should be reported to the treating physician, to the pharmacist, and to the FDA's MedWatch program."*

The Drug Price Competition and Patent Term Restoration Act of 1984, an amendment to the Federal Food, Drug, and Cosmetic Act (the Act), has had an extremely positive impact on the availability and affordability of safe and effective drugs for Americans. As of June 2010, FDA's Office of Generic Drugs (OGD) has approved more than 9,000 generic prescription drug products, which now account for more than 69 percent of prescription drugs dispensed.[3]

The Act establishes rigorous standards for FDA approval of generic drugs. An applicant seeking approval for a generic drug must demonstrate, among other things, that the proposed product is the same as the reference listed drug in active ingredient, dosage form, and strength. In addition, the sponsor must submit evidence that the proposed generic drug and the reference listed drug are bioequivalent, meaning the therapeutic ingredient in the generic drug will reach the site of activity in the body at the same rate and to the same extent as the reference product does.[4] Generic applicants submitting Abbreviated New Drug Applications (ANDAs) for oral anti-epileptic drugs generally must submit one or more bioequivalence studies in which, for example, human subjects are given the reference product and the proposed generic product, after each of which the drug concentrations in the blood are analyzed. The resulting analytical information is compared statistically to assess whether the generic drug meets the requirements for bioequivalence.[5,6]

Drug products that meet the FDA approval requirements for generic drugs are considered to be "therapeutically equivalent" to the reference listed drug. Drugs that are therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

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[3] While accounting for the vast majority of prescriptions, generics account for only 16 percent of the dollars spent on prescriptions. According to an analysis conducted by Intercontinental Medical Statistics (IMS) Health and commissioned by the Generic Pharmaceutical Association (GPhA), generic medicines saved the American health care system more than $734 billion in the last decade (1999-2008), with approximately $121 billion in savings in 2008 alone.

[4] Bioequivalence for systemically absorbed products such as AEDs means that the generic drug and the reference drug will reach the systemic circulation at an equivalent relative rate and extent, meaning that the two drug products produce equivalent drug concentration-time profiles in the blood.

[5] The ANDA approval process does not require generic drug manufacturers to submit nonclinical or clinical studies to establish the safety and efficacy of the active ingredient because safety and efficacy were previously demonstrated during the approval process for the reference product. It is assumed that, if the active ingredient was shown to be safe and effective after it is absorbed into the bloodstream, any drug product giving rise to blood concentrations of active ingredient to the same rate and extent, and meeting the other requirements for ANDA approval, will produce the same effect.

[6] CDER Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, General Considerations, posted March 2003, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf (accessed October 13, 2010).

III. Information Requested

FDA's study of adverse events and seizures associated with brand and generic anti-epileptic drugs

Several small analyses conducted by FDA using data available in its Adverse Event Reporting System (AERS) do not provide evidence that generic anti-epileptic drug products are less effective than brand name products. However, it is difficult to draw reliable conclusions about therapeutic equivalence from the AERS data because the adverse event reports are not necessarily representative of a random sampling of the patient population, nor can they be corrected for the relative market share of the various brand and generic products to determine if there is actually a difference in the incidence of adverse events for generic products.

As background, CDER's Office of Surveillance and Epidemiology (OSE) analyzed post-marketing surveillance reports to look for evidence of therapeutic inequivalence for the generic AEDs Levetiracetam and Lamotrigine. OSE initially focused on these two drugs because safety and efficacy concerns for these products were raised by external stakeholders. Investigation of the safety and efficacy complaints about Levetiracetam were of particular interest to FDA because CDER had deemed Levetiracetam immediate release solid oral dosage forms to be eligible for waivers of in vivo bioequivalence testing under the Biopharmaceutics Classification System (BCS). The BCS considers whether the drug substance is highly soluble, over 90 percent absorbed, and whether the drug product dissolves rapidly – more than 85 percent by 30 minutes. This information can be used by FDA to determine that in vivo bioequivalence studies are not necessary for approval. [7]

An analysis of data from OSE led to the following observations:

- Forty-one adverse event reports for Levetiracetam Tablet generic formulations were submitted to FDA from November 2008 until May 2009.
- Twenty-seven of those reported adverse events were from the first approved generic formulation (Mylan Pharmaceuticals) which had been on the market two months longer than the other formulations.
- At the time of the OSE survey, drug usage data were unknown, making the rate of occurrence of adverse events difficult to assess.
- The Levetiracetam AERS reports were inconclusive because some of the individual reports may be generated from duplicated sources.
- In the absence of drug manufacture information included in the AERS report, the adverse event could not be attributed to a particular drug product.

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[7] CDER Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, posted August 2000, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf (accessed September 28, 2010).

OSE conducted two analyses of the AERS database for Lamotrigine Tablets, one from November 2008 to May 2009 and the second from January 2009 through March 2010. The first analysis referenced possible stimulated reporting from internet blogs and websites. The OSE analysis concluded that there were no increased incidences of convulsions, mania, or lack of effect in patients receiving generic Lamotrigine Tablets. The January 2009 through March 2010 analysis, which was initiated at the request of a physician who contacted FDA, focused on Medwatch surveillance reports of recently-approved Lamotrigine Tablets marketed by two generic firms. The main OSE findings in this second analysis were that:

- Only 48 reports were submitted to FDA on these two products during this time period.
- The number of reports increased shortly after approval of these two products but declined by about four-fold by one year after approval.

This latter observation is consistent with the premise of the "Weber effect," an epidemiologic phenomenon stating that the number of reported adverse reactions for a drug rises until approximately the middle to end of the second year of marketing, peaks, and then declines despite steadily increasing prescribing rates.[8] It is likely that the Weber effect is a factor contributing to increased patient complaints following switches from brand name to newly-approved generic anti-epileptic drugs.

In addition, it is possible that the wide publicity given to negative literature about generic anti-epileptic drugs, much of which is disseminated by various epilepsy societies, may influence patients that recently switched to generics. Thus, background breakthrough seizure and adverse event rates may be comparable whether the same patient is being treated with a generic drug or the brand drug, but because of the generic switch, the patient may be more likely to complain of adverse events and breakthrough seizures.

Thus, from preliminary OSE reports, FDA is unable to conclude that adverse events and seizures associated with recently-approved generic versions of Levetiracetam and Lamotrigine are related to lack of therapeutic equivalence between these products and their brand name counterparts. FDA does, however, continue to monitor such reports submitted to MedWatch and any other reports of negative reactions to generic products to determine if follow-up investigation may be necessary.

[8] Hartnell NR, Wilson JP. Replication of the Weber effect using postmarketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy* 2004;24:743-749.

Examination of the pharmacokinetic profiles of "A" rated anti-epileptic drugs

There are two primary parameters that are used to assess the pharmacokinetics of a drug. C_{max} is a measure of the maximum concentration of the drug in the blood stream following oral administration. The area under the plasma concentration versus time curve (AUC) is a measure of the **amount** of drug absorbed and is an accurate estimate of the drug's bioavailability (extent of absorption). FDA considers C_{max} and AUC to be the most clinically appropriate bioequivalence measures for assessing the **rate and extent of absorption**. It is well-established that AUC and C_{max} correlate with a drug's efficacy, as well as with its toxicity.[9]

FDA considers drugs bioequivalent if the 90 percent confidence intervals of the geometric mean of the ratios of generic drug to brand name drug C_{max} and AUC fall within the bioequivalence limits of 80–125 percent.

As shown below in Table II, all approved generic AEDs currently on the market are well within the current FDA 80-125 percent bioequivalence limits for AUC and C_{max}.

Table II[10]
Bioequivalence Measures for Approved Generic AEDs
Mean (upper & Lower 90% Confidence Interval limits)

Drug	AUC Ratio	Cmax Ratio
Phenytoin	0.99 (0.95, 1.02)	1.09 (0.99, 1.20)
	0.88 (0.85, 0.92)	0.88 (0.83, 0.94)
Carbamazepine	1.18 (1.14, 1.22)	1.14 (1.10, 1.19)
	0.97 (0.90, 1.00)	0.90 (0.87, 0.94)
Lamotrigine	1.07 (1.02, 1.12)	1.10 (1.05, 1.15)
	1.00 (0.94, 1.04)	0.91 (0.85, 0.98)
Levetiracetam	1.02 (0.97, 1.04)	1.06 (1.02, 1.12)
	0.97 (0.95, 1.0)	0.92 (0.85, 1.00)
Zonisamide	1.08 (0.99, 1.19)	1.08 (1.01, 1.15)
	0.96 (0.89, 1.03)	0.96 (0.88, 1.05)
Topiramate	1.05 (1.00, 1.10)	1.09 (1.03, 1.15)
	0.95 (0.93, 0.98)	0.92 (0.82, 1.03)

[9] CDER Guidance for Industry, Exposure – Response Relationships: Study Design, Data Analysis, and Regulatory Applications, posted April 2003, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf (accessed September 24, 2010).

[10] The two rows of data represent the highest and lowest point estimates and 90 percent confidence intervals for all approved generic formulations of the antiepileptic drug cited. For example, for phenytoin, there are five approved formulations. We compiled the 90 percent confidence intervals and point estimates from the test/reference AUC and C_{max} ratios from all the bioequivalence studies of these 5 phenytoin products and report the highest and lowest values from this group of studies.

Valproic Acid (limited data)	0.99 (0.96, 1.03)	0.97 (0.90, 1.04)
	N/A	N/A
Divalproex	1.04 (0.96, 1.11)	1.13 (1.06, 1.19)
	0.94 (0.86, 1.03)	0.88 (0.83, 0.93)
Oxcarbazepine	1.03 (0.98, 1.08)	1.04 (0.90, 1.19)
	0.94 (0.91, 0.97)	0.88 (0.81, 0.95)

FDA's advice on planned research on the impact of substituting bioequivalent anti-epileptic drugs on epileptic individuals

Generally, FDA's recommendation for studies designed to detect potential differences in adverse clinical effects between brand name drugs and generic drugs is to focus on patients who have reported a problem after switching from one drug to another. In this way, if there is some unique attribute in this group of patients with regard to drug absorption, distribution, metabolism, or excretion, it is more likely to be detected in such a study.

FDA also recommends comparing bioavailability, not only by comparing the brand name product to the generic, but also by comparing the brand to itself, and the generic to itself, in a four-period study, with each product studied twice. This comparison would allow the day-to-day random differences between blood levels that do not reflect product differences – for example, differences in branded product bioavailability on different days – to be measured and compared to day-to-day differences between brand and generic drugs. FDA expects that there will be such day-to-day differences in absorption; the question is whether such differences are larger between brand and generic drugs.

- **NIH/NINDS Study**

FDA advised the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NIH/NINDS) on the design of a study to evaluate the bioequivalence of AEDs in patients who have reported a problem, such as seizure, adverse event, or change in AED plasma concentration, after switching from a brand to a generic. The purpose of the study is to determine if patients reporting problems associated with switching actually show differences in bioequivalence measures. The NIH/NINDS, in consultation with experts in FDA's Office of New Drugs and OGD, have designed a prospective, open-label, order-randomized, four-period crossover pharmacokinetic trial comparing the C_{max} and AUC of various generic and the innovator formulations of Lamotrigine Tablets in patients who have previously reported a problem.

- **FDA Office of Generic Drugs Science Team Bioequivalence Study**

In order to broaden our assessment of potential non-equivalence to other AEDs, FDA's OGD has designed a study to evaluate bioequivalence of an "older" generic AED, such as carbamazepine, and a "newer" generic AED, such as zonisamide, versus their respective

reference products. The study design is similar to the NIH/NINDS study and will enroll patients who have experienced:

- new onset or exacerbation of adverse events
- loss of seizure control
- an unexpected change in AED blood concentrations.

That is, the study population is "enriched" with patients who potentially respond differently to brand and generic drugs. The study is a prospective, open-label, order-randomized, four-period crossover pharmacokinetic trial comparing the Cmax and AUC. This study will be performed under FDA's Critical Path Program. Currently this study is under evaluation by the FDA Contracts Office. On August 6, 2010, FDA posted a solicitation notice for studies of generic epileptic drugs, Solicitation Number: 10-223-SOL-00277, "Pharmacokinetic Studies" on the FedBizOpps.gov website. Proposals and funding summaries were due by August 23, 2010. The agency received 2 proposals, has selected one, and is currently negotiating the terms of the contract.

Does the FDA recommend any changes to the current bioequivalence testing for AEDs?

FDA is currently exploring the pros and cons of narrowing the acceptance criteria for the 90 percent confidence interval for AUC for certain drugs.[11] Although tightening the standard may sound desirable, such a change in regulatory standards must be based on scientifically justified, objective criteria to ensure that we are not regulating this class of products in an arbitrary and capricious manner.

In April, we asked our Advisory Committee for Pharmaceutical Science to comment on a proposal for tightening the bioequivalence standards for drugs whose dosing must be carefully adjusted, including narrow therapeutic index (NTI) drugs, to avoid adverse events. The Committee was supportive of tightening the standards for NTI drugs. However, not all anti-epileptic drugs are considered NTI drugs based on their efficacy and toxicity profiles. Therefore, other selection criteria would need to be established as a basis for changing the current bioequivalence standards for the AEDs.

FDA proposed guidance or actions to minimize the health impact or side effects as a result of the agency's research on switching bioequivalent anti-epileptic drugs

As described above, FDA is working with NIH to determine if there is a subset of epilepsy patients who respond differently to AEDs from different manufacturers. FDA is also developing a study to be performed under FDA's Critical Path Program to further study this question. Based on the outcome of these studies, FDA will determine if additional guidance or actions are needed.

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[11] An analysis of bioequivalence data for most approved generic drugs (including the AEDs) indicates that most could meet a tighter BE standard of 90 – 111 percent as opposed to the current 80 – 125 percent standard.

IV. Conclusion

FDA agrees that the potential financial savings to consumers and insurers from switching to generic AEDs from brand name drug AEDs needs to be balanced against the possibility of breakthrough seizures and adverse events. Furthermore, controlled, prospective, blinded, randomized studies comparing brand and generic AEDs in a patient population that has reported a history of problems or adverse outcomes following a prior switch between brand and generic AEDs may help to better understand these risks and to determine if there is a subset of patients who are particularly vulnerable.

FDA will continue endeavors to ensure that all patients can rely on safe and effective therapy from generic drug products.