

March 9, 2011

TO: Members of the Committee on Public Health

FROM: Kevin W. Chamberlin, PharmD
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RE: Committee Bill No.5610: AN ACT CONCERNING THE DUTIES OF A PHARMACIST
WHEN FILLING A PRESCRIPTION USED FOR THE TREATMENT OF EPILEPSY OR
PREVENTION OF SEIZURES

Dear Members of the Committee:

Generic substitution of antiepileptic drugs (AEDs) is a controversy beyond the purview of the general public. Many newer AEDs (e.g., zonisamide, lamotrigine, topiramate, gabapentin, oxcarbazepine) have had or soon will have patents expire. Nearly all of the AEDs, except one form of divalproex sodium, are available in generic products.

At the 61st Annual Meeting of the American Epilepsy Society (AES) in Philadelphia, PA on December 1, 2007, Michael Privitera, MD (University of Cincinnati, OH) announced that the AES is in discussions with the US Food and Drug Administration (FDA) to get agreement on a protocol for the development and completion of a valid, controlled, prospective clinical trial to determine "...once and for all whether substitution of brand-name antiepileptic drugs with generic agents may put some patients with epilepsy at undue risk of breakthrough seizures and/or toxicity."¹

Such a study has been completed and is out for peer review pending publication, funded by the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services. This analysis was completed by the University of Connecticut/Hartford Hospital Evidenced-based Practice Center based out of Hartford, Connecticut. Early reports on it are that the authors found no substantive differences in terms of benefits or harms associated with the use of a brand versus a generic AED.

Current FDA bioequivalency regulations require the area-under-the-curve and absorption rate of a generic product to be within 80 – 125% of mean values for the brand product and for the 90% confidence interval around the geometric mean for the generic product to be within the 80 – 125% range for the brand product. The FDA currently makes no distinction in these standards for drugs or disease states that are complex or critical.

Generic drug manufacturing rests on "bioequivalence." A generic drug must be determined to be "bioequivalent" to its name brand predecessor drug before the FDA will call it a generic. In order for a drug to be bioequivalent the drug must have the same active ingredients, dosage form, strength, and route of administration as the original. The two pharmacokinetic measurements, area under the drug concentration-time curve (AUC) and maximum concentration (C_{max}), are used to determine bioequivalence. If a drug is determined to be bioequivalent, it is also thought to be therapeutically equivalent. While generics should also have no greater potential for adverse effects, generics are allowed to have differences in color, flavor, shape, appearance, and shelf-life.

They are also allowed to have different salts or esters of the active drug. Some studies have shown that different salts of the same active drug can have distinct chemical properties.^{2 3 4 5}

Many of these resolutions and petitions to change the standards for AEDs include provisions (such as Committee Bill No.5610) that prohibit a pharmacist from making generic substitutions for AEDs.⁶ These proposals come from pharmaceutical manufacturers, legislative groups, patient advocacy groups, and professional organizations.

A number of pieces of “less than idea” pieces of literature on this topic are available for review. One example, a publication by Andrew Wilner, MD, is often quoted in the literature in favor of legislation similar to Committee Bill No.5610, and yet a number of flaws can be identified that even the author suggests are limitations to his findings: (a) the study is retrospective [a weakness]; (b) there was a 4.7% response rate to his survey [a weakness that is not substantiated by a power calculation to determine the number needed to respond to have a valid study]; (c) the survey was not stated as being anonymous, possibly deterring responders from participating [a weakness]; (d) the survey results were not substantiated by documentation from chart reviews – they were simply from ‘memory’ [a weakness].⁷

From: Perucca E, et al.⁸

Quality of the evidence and interpretation of available data

No randomized controlled trials (RCTs) were identified that compared the effects of generic AEDs and corresponding brand products in a sizeable number of patients with epilepsy. The only identified RCT that enrolled at least 50 subjects was a comparative crossover study of 64 patients assigned to receive in random sequence a generic and a brand product of valproic acid, each for four-week periods. This study, of limited quality for its modest sample size and its short duration, did not detect any difference in seizure control and plasma drug levels between the two treatment periods (Vadney and Kraushaar, 1997).

In contrast to the lack of controlled studies, there are several published reports of loss or worsening of seizure control (Koch and Allen, 1978; Pedersen and Dam, 1985; McDonald, 1987; Wyllie et al., 1987; Sachdeo and Belendiuk, 1987; Hartley et al., 1990; Welty et al., 1992; Jain, 1993; Meyer and Straughn, 1993; Guberman and Corman, 2000; Burkhardt et al., 2004; Wilner, 2004; Haskins et al., 2005) or appearance of adverse events (Finestone and Williams, 1985; Gilman et al., 1993; Brown et al., 1998; Guberman and Corman, 2000; Wilner, 2004; Haskins et al., 2005) following substitution of a brand AED with a generic. Many of these reports date back several years, when regulatory requirements for the approval of generics were not as stringent as those currently in force in major industrialized countries (Richens, 1997; American Medical Association, 2006) and therefore some products of inadequate quality found their way into the market (Bochner et al., 1972; Sansom et al., 1975; Manson et al., 1975; Stewart et al., 1975; Tammisto et al., 1976; Hodges et al., 1986; Mikati et al., 1992; Soryal and Richens, 1992; Meyer et al., 1992; Rosenbaum et al., 1994). In 1988, the U.S. Food and Drug Administration (FDA) set up a special committee to investigate these issues. Between 1988 and 2000, the FDA investigated more than 60 reports of potential inequivalence of generic products, and has been unable to document a single example of therapeutic failure when an FDA-designated therapeutically equivalent generic product, which was manufactured to meet its approved specifications, was substituted for the corresponding brand-name drug listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Henney, 2000).

The frequency with which, disregarding any attribution of cause-effect relationship, the switch from a brand product to a generic (or vice versa) is associated with a change in clinical status cannot be established from anecdotal reports: surveys using questionnaires compiled by patients with epilepsy variably reported frequencies in the order of 11% (Crawford et al., 1996), 14% (Guberman and Coman, 2000), 23% (Haskins et al., 2005), or even 46% (Chappell, 1993), but these estimates are probably influenced by selection bias (the patients who believe to have been affected adversely by the switch are also those who are most likely to return the questionnaire) and by the subjective, retrospective and uncontrolled methodology applied in these surveys. Moreover, reported "problems" do not always refer to a worsening in seizure control: for example, in the survey conducted by Crawford et al. (1996), 11% of patients reported a "validated problem," but only one patient (0.4%) complained of reemergence of seizures after 12 months of complete control and only eight patients (3%) reported "increased seizure frequency." A report on an initiative by the International Bureau for Epilepsy, a patients' organization which expressed concerns about the "risks" associated with generic substitution, estimated that the switch from one product to another may involve a risk of breakthrough seizures in 1 to 2% of cases (Van Emmerink, 2005).

While there is no doubt that in some cases a switch between products can be associated with an alteration in clinical status, a critical assessment of available evidence does not allow us to establish a cause-effect relation, at least for the majority of reported cases. In a disorder such as epilepsy, which is known to be associated with spontaneous fluctuation in the manifestations of the disease, a transient deterioration in seizure control after changing a pharmaceutical product may be due simply to chance or to factors which are unrelated to the product prescribed (for example, a change in compliance). This is well illustrated by the controlled study performed by Vadney and Kraushaar (1997): of 64 patients randomized to generic substitution in this study, 17 had been free from seizures during the 12 months preceding randomization. Two of these patients suffered a seizure recurrence during the study, but in both cases the reemergence of seizures occurred during the period in which the product taken was the same utilized by the same subjects during the 12 months prior to the study!

Some pharmacoeconomic evaluations have been published which suggest that the possible costs of managing the potential disease deterioration or adverse effects resulting from generic substitution may outweigh the savings from the lower price of generics (Jumao-as et al., 1989; Crawford et al., 1996; Argumosa and Herranz, 2005). The working group considered these estimates unreliable, because no unbiased quantitative evidence is available on the possible adverse consequences of generic substitution. By contrast, it is a fact that the difference in price between a brand product and a generic can be substantial, sometimes as much as 10-fold (Vadney and Kraushaar, 1997), even though at times the introduction of a generic may also lead to a reduction in the price of the brand product.

Overall, generic AEDs meeting current regulatory criteria for bioequivalence represent a valuable choice in the management of epilepsy by allowing a substantial reduction in treatment costs, particularly in patients initiating monotherapy or adjunctive treatment, and in those with persistent seizures.⁸ Careful review of the literature reveals no adequately powered randomized controlled trials that assessed the risk / benefit ratio of generic substitution.

I encourage members of the committee to review these referenced studies from Welty and the subsequent editorial comment on it by Dr. Randy Hatton, as well as the pending study forthcoming from the Hartford-based AHRQ group.

Question to the Committee: *In a time of economic crisis within the state, is it fiscally responsible to mandate branded medications that are more expensive and no more effective in outcomes than generic alternatives?*

Respectfully submitted,

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¹ Cassels C. AES Calls for Definitive Study to Examine Antiepileptic Drug Substitution. Medscape Medical News 2007. ©2007 Medscape. Published online Dec 3, 2007. Accessed: Mar 10, 2008.

(<http://www.medscape.com/viewarticle/566840>)

² Voegelé L, Puri V. "Concerns over generic substitution of antiepileptic drugs: A review of the literature." Kentucky Pharmacists homepage. Accessed: Mar 10, 2008.

(<http://www.kentuckypharmacists.com/user/Generic%20Epilepsy%20Drug%20Paper.pdf>)

³ Nightingale S, Morrison J. "Generic Drugs and the Prescribing Physician." *JAMA* 1987;258:1200-1204.

⁴ Berg M. "What's the Problem with Generic Antiepileptic Drugs? A call to action." *Neurology* 2007;68:1245-1246.

⁵ Crawford P, et al. "Are there potential problems with generic substitution of antiepileptic drugs? A review of issues." *Seizures* 2006;15:165-176.

⁶ Welty TE. "Pharmacy and Generic Substitution of Antiepileptic Drugs: Missing in Action?" *Ann Pharmacother* 2007;41:1065-1068.

⁷ Wilner A. "Therapeutic equivalency of generic antiepileptic drugs: results of a survey." *Epilepsy and Behavior* 2004;5:995-998.

⁸ Perucca E, et al. "Recommendations of the Italian League Against Epilepsy Working Group on Generic Products of Antiepileptic Drugs." *Epilepsia* 2006;47(Suppl 5):16-20.