GENERIC AEDS: CURRENT STANDARDS AND RECOMMENDATIONS

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ABSTRACT

Among strong and conflicting viewpoints on the substitution of brand-name antiepileptic drugs (AEDs) with their generic counterparts, practitioners are sometimes placed in the uncomfortable (or at the very least aggravating) situation of having to challenge who has the final say on a patient's AED prescription. This article reviews the US Food and Drug Administration standards for generic drugs in addition to the position statements from leading professional medical organizations, and discusses how the clinical equipoise created by these forces can be resolved.
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Virtually every state in the United States has adopted laws or regulations that encourage or in some cases mandate the substitution of a brand-name drug with its generic counterpart. In most states, pharmacists can dispense generic substitutes for brand-name drugs unless the prescriber specifies otherwise by writing "dispense as written" or "brand medically necessary" on the prescription (or other appropriate wording as defined by each individual state's law).

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The push for use of generic drugs emerges from the rapidly increasing healthcare costs worldwide. Prescription drugs account for approximately 10% of healthcare expenditures in the United States (total healthcare expenditure in 2007 was $2.245 trillion, or 16% of the gross domestic product). The potential annual cost savings, in the billions of dollars, entices healthcare payers to encourage the use of generic drugs.[1-3] Likewise, an increasing number of individuals have no insurance or governmental coverage, making generics an important option in their care. Switching to generic antiepileptic drugs (AEDs) is an attractive method for reducing costs because it is an easy change to make. Additionally, because generic drugs cost less, their use might improve compliance, and proper use of prescription medication reduces other healthcare expenditures (eg, doctor visits and hospitalizations).

FDA STANDARDS FOR GENERIC DRUGS

To be approved by the US Food and Drug Administration (FDA), a generic drug must be identical to the corresponding brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use; the active ingredients must be chemically identical. Bioequivalence is established using in vitro or in vivo experiments (depending on the drug) according to guidelines set by the FDA. New (or innovator) drugs are almost always developed under patent protection. When the patents expire, manufacturers can apply to the FDA to sell generic versions using an abbreviated new drug application. The abbreviated new drug application process, first created in 1984 via the Drug Price and Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act), removes the requirement (and expense) of repeating preclinical and clinical efficacy studies on active ingredients or dosage forms already approved after 1962.[4]

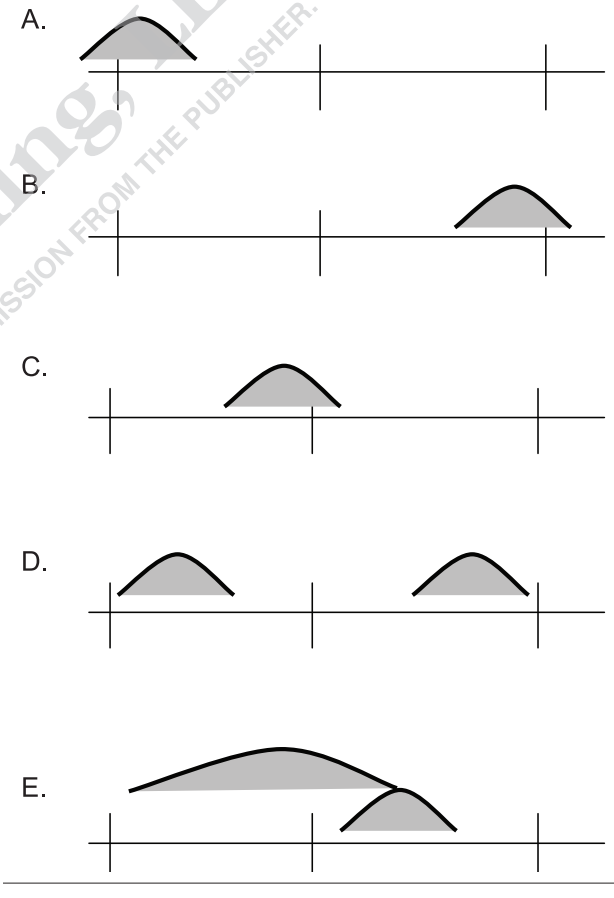
The list of FDA-approved generic drugs is made available by the FDA in its publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book"), with updates as supplements (http://www.fda.gov/cder/ob). In the Orange Book introduction, several key terms are defined. A "pharmaceutical equivalent" is a drug product that has the same active ingredient(s), strength, dosage form, route of administration, and identical strength and concentration as a reference drug (usually the brand-name drug). However, it may differ in shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, and preservatives), expiration time, and "within certain limits" labeling. "Bioequivalent drug products" are pharmaceutical equivalents that display comparable bioavailability when studied under similar experimental conditions. A "therapeutic equivalent" is a drug product that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Drugs that meet the bioequivalence criteria are deemed to be therapeutically equivalent and typically approved. The FDA takes the unequivocal position that "products classified as 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."[5]

The standard bioequivalence (pharmacokinetic) in vivo study for a generic drug is conducted using a 2-treatment crossover design in 24 to 36 healthy adult volunteers (although drugs with a long half-life may be tested in a parallel study design, and drugs for which plasma concentrations are not affected [eg, nasal sprays, aerosols, and topical medications] may be subject to other types of bioequivalence studies). The FDA requires in vivo bioequivalence testing for all of the AEDs. Single doses of the test (generic) and reference (brand) drug are administered and plasma concentrations of the drug are measured over time. The maximum blood concentration (Cmax) and area under the concentration-time curve (AUC) at the last measured time (AUC_t) and extrapolated to infinity (AUC_∞) are determined, to measure the rate and extent of absorption, respectively, and the logarithm of their ratio is calculated.

For a generic drug to be bioequivalent to the brand drug, the 90% confidence interval for these ratios of the C_{max}, AUC_t, and AUC_∞ must be entirely within 80% to 125% of the mean value for the brand drug. This is often misunderstood to mean that the amount of drug can vary from 80% to 125%. In fact, this statistical measure is fairly rigorous, and the mean values for the pharmacokinetic measures of most approved generics are within 5% of the brand drug.[5] The Figure demonstrates this concept and illustrates the tolerances for the standard of bioequivalence for a generic drug.

The Office of Generic Drugs (part of the FDA) conducted 2 internal studies to quantify the differences between generic and brand-name drugs. The first report reviewed 224 bioequivalence studies submitted in

Figure. Testing for Bioequivalence



Hypothetical illustration of the FDA requirement that the 90% CI of the pharmacokinetic parameters fall within the range of 80%–125% of the brand name drug (100%) to be considered bioequivalent. In this figure, the 90% CI is indicated by the shaded curves. **A** and **B** show test drugs that have 90% CIs that fall outside the 80%–125% range and would not be approved by the FDA. **C** shows a test drug that meets the FDA criteria with the 90% CI within the 80%–125% range. **D** shows the potential difference between generic drugs when their CIs are close to but near the extremes of the 80%–125% parameters. **E** shows a comparison when the CIs for the bioavailability ratio for the 2 generic versions overlap each other, which is the more common situation. CI = confidence interval; FDA = US Food and Drug Administration.

approved applications from 1985 to 1986. The observed mean differences between brand and generic drugs for AUC was 3.5%.[6] The second evaluation focused on studies submitted in 1997 and showed variation between brand and generic drugs of approximately 3.5% for AUC and 4.29% for C_{max}.[7] Of potential interest is that in the survey from the 1980s, 13 of the 224 drugs (6%) had mean AUC differences of 10% or more from the brand.[6]

In a 1997 letter to the National Association of Boards of Pharmacy, the FDA stated, "If one therapeutically equivalent drug is substituted for another, the physician, pharmacist, and patient have the FDA's assurance that the physician should see the same clinical results and safety profile. Any differences that could exist should be no greater than one would expect if one lot of the innovator's product was substituted for another."

Concerns with Generic AEDs

Currently, 8 major AEDs have generic formulations available, totaling 187 different formulations and 4 more AEDs will go off patent in the next 2 years (Table 1). The controversy surrounding generic formulations of AEDs began with anecdotal reports of breakthrough seizures in people with previously well-controlled epilepsy when they switched to generic versions of the brand drugs. Questions on bioavailability are of particular concern with drugs classified as having a narrow therapeutic index (NTI). A drug with an NTI is defined as: (1) having less than a 2-fold difference in the median lethal dose and the median effective dose; (2) having less than a 2-fold difference in the minimum toxic blood concentration and minimum effective blood concentration; or (3) a drug in which its safe and effective use requires careful titration and patient monitoring. Because of prior experiences with older AEDs, many clinicians may consider the entire class of AEDs to be NTI drugs. In a somewhat dated list from 1995, the FDA classifies valproic acid, carbamazepine, and phenytoin as NTI drugs, although it does not think any additional testing or regulations are required for NTI drugs. In general, the FDA does not distinguish AEDs from other types of drugs when considering their requirements for bioequivalence.

As reviewed by William R. Garnett, PharmD, later in this monograph, there are numerous supporters and critics of blanket generic substitution, especially for the treatment of people with epilepsy. Chief among the concerns is the dilemma faced by the physician when a breakthrough seizure occurs shortly after a person is switched from a brand to generic AED. If there is no obvious proximate cause for the seizure, the prescriber must decide if the generic switch played a role and, if so, whether to maintain the generic formulation or switch back to the brand formulation and subject the patient to higher drug costs.

There are 2 main issues regarding the therapeutic equivalence of a drug's various formulations. The first is bioequivalence, which depends on the rate and amount of absorption through the gastrointestinal tract. In drugs with non-linear pharmacokinetics (eg, phenytoin), the metabolic rate may amplify a smaller effect of differences in rate of absorption. The testing required by the FDA to assess bioequivalence is limited because of the single-dose design using healthy controls. It is not clear that bioequivalence assessed in this highly controlled setting actually reproduces the situation in real life—that is in people with epilepsy, in varying states of health, and taking a variety of different medications.

The second issue concerns variability in the actual amount of medication available from each pill. As a result of manufacturing limitations, some variation is allowed between lots of medications. The FDA requires that manufacturers (both brand and generic)

Table 1. Currently Available Generic AEDs

AED	Manufacturers, *n*	Pill Doses, *n*
Phenytoin	4	1
Carbamazepine	7	1
Valproic acid	3	1
Gabapentin	11*	8*
Zonisamide	17	3
Oxcarbazepine	6	3
Clonazepam	9 (2†)	3 (5†)
Clorazepate	6	3

*Three additional manufacturers only make 100-, 300-, and 400-mg doses of gabapentin; †Orally-disintegrating form of clonazepam.
Patents expire for 4 AEDs within the next 2 years: Depakote (2008 [divalproex sodium; Abbott Laboratories, Abbott Park, IL]), Topamax (2008–2009 [topiramate; Ortho-McNeil Neurologics, Titusville, NJ]), Lamictal (2009 [lamotrigine; GlaxoSmithKline, Research Triangle Park, NC]), and Keppra (2008 [levetiracetam; UCB, Inc, Smyrna, GA]). (Of note, Depakote ER and Lyrica [pregabalin; Pfizer Inc, New York, NY] patents will not expire until 2018 and 2019, respectively.)
AED = antiepileptic drugs.

meet the US Pharmacopeia (USP) standards. Table 2 lists some of the currently available USP standards for AEDs. It is not known whether one manufacturer consistently adheres to stricter standards than another; for example, the amount of chemical in a pill could potentially vary from lot to lot by more than 20% for some of the AEDs. However, the FDA is clear that, although there is a range for the USP manufacturing guidelines, all companies are expected to target 100%.

The bioequivalence assessment required by the FDA compares each generic to a reference (typically the brand) product. Generics are not compared to each other. In the United States, "branded generics" for AEDs are generally not available, thus once a transition is made to a generic AED, generic-to-generic switching is highly likely and will depend on which particular formulation the pharmacy has in stock at the time of dispensing. With so many AED generic manufacturers (eg, 17 for zonisamide [Table 1]), generic-to-generic switching will probably occur several times per year in most people on chronic AEDs. A difference in bioavailability between one generic formulation and another in some cases is going to be greater than the difference of either of the generics compared to the brand. Whether this larger difference between generics is ever clinically relevant has not been systematically studied.

The bioequivalence data and manufacturing lot-to-lot data are currently considered proprietary and not published but may be critical to making informed decisions.

Reconciling Clinical Recommendations

The American Academy of Neurology and American Epilepsy Society have published position statements on the use of generic AEDs for the treatment of epilepsy. Both organizations oppose substitution of brand AEDs with generic AEDs without physician and patient approval (Table 3).[8,9] Underlying both of these position statements is a lack of data. No prospective, randomized, controlled trials have ever been done to validate the safety and efficacy between different formulations of AEDs. There is little doubt that if such trials are performed and demonstrate bioequivalence in a scientifically valid manner, then generics would be preferred in almost all cases because of the cost savings.

Interestingly, the Italian League Against Epilepsy recommends generic substitution only for patients

Table 2. Current Standards for Assay from the USP

AED	Acceptable Range
Carbamazepine tablets	92%–108% of the labeled amount of $C_{15}H_{12}N_{20}$*
Carbamazepine extended-release tablets	90%–110%†
Valproic acid capsules and oral suspension	90%–110% of $C_8H_{16}O_2$
Phenytoin chewable tablets, oral suspension, and tablets	95%–105% of $C_{15}H_{12}N_2O_2$ 95%–105% of $C_{15}H_{12}N_2NaO_2$ for extended phenytoin sodium capsules

*Assay with 20 tablets; †Assay with 10 tablets.
AED = antiepileptic drugs; USP = US Pharmacopoeia.
The chemical assay is one of the many standards set by the USP for manufacture of medications. USP standards for the newer AEDs are not yet listed by the USP.

Table 3. Summary of Position Statements on the Use of Generic AEDs for the Treatment of Epilepsy

American Academy of Neurology

- Opposes generic substitution of AEDs for the treatment of epilepsy without the attending physician's approval
  - AEDs differ from other drugs in ways that make generic substitution problematic
  - Physicians should be able to prescribe their AED of choice, unimpeded by legislation or formulary policies
  - Informed consent of both physician and patient should be required by law
  - These positions are only applicable to the use of AEDs for the treatment of epilepsy

American Epilepsy Society

- Opposes formulation substitution of AEDs for the treatment of epilepsy without physician and patient approval
- Opposes all state and federal legislation and formularies that limit the ability of physicians to choose an AED formulation
- Supports development and completion of valid clinical trials to study the impact of differences between AED formulations of different manufacturers
- Supports the development of federal regulations, validated in people with epilepsy, that ensure that various AED formulations are therapeutically equivalent and can be used interchangeably without concern for safety or efficacy

Data from Liow et al[8] and American Epilepsy Society.[9]

initiating monotherapy or adjunctive treatment and in those with persistent seizures. Generic substitution is not recommended for patients who have achieved seizure remission.[10] This distinction is defined as prescribability (ie, a patient is treated for the first time so that a brand or a bioequivalent generic AED can be chosen) versus switchability (ie, when a brand AED is switched to a bioequivalent generic product of the same AED). The current bioequivalence approach by the FDA may be sufficient to evaluate the prescribability of generic products, but may not ensure the switchability between prescribable formulations.[11]

The American Medical Association (AMA) has also published a policy statement regarding generic drugs in general. In brief, the AMA believes that physicians should be free to choose either generic or branded formulations of a drug, considering cost in conjunction with medical judgment. Substitution with generic drug products that are not considered by the FDA to be bioequivalent should be prohibited by law, except with a prior authorization from the prescribing physician. The AMA further acknowledges the difficulty physicians face in understanding bioequivalency issues and calls for the AMA and USP to work together to better explain these issues to physicians.[12]

There is equipoise between the professional organizations' positions, which reflect concern among patients and physicians, and the FDA's position on generic AEDs, along with the financial forces that promote generic substitution. Conversely, a recent *Wall Street Journal* article highlighted a concern for the influence that industry may hold over professional societies and patient advocacy groups.[13] The discrepancy between the American Academy of Neurology/American Epilepsy Society and the FDA's position on therapeutic equivalence of AEDs compels attention.[14-16] Either the FDA has not sufficiently convinced healthcare providers of the interchangeability of approved drugs or the equivalency issues have not yet been adequately addressed by the FDA.[17] A series of prospective randomized clinical trials is needed to settle the issue and ultimately lead to fully interchangeable generics.

Making the Switch

There is no consensus about what to do when switching a person to a generic formulation. If patients are to be switched to a generic AED, whether through legislative or formulary mandate or physician or patient choice, the switch should be planned in advance. In patients who are seizure free or have been sensitive to AED concentration fluctuations or required careful titration to achieve a seizure-free or nearly seizure-free state, I recommend that blood concentrations of the drug be obtained both before and after the switch. Although the FDA states that no additional testing is needed when switching to a generic, in my opinion, it is prudent to check blood concentrations in these higher-risk patients. It is in the patient's best interest to keep a diary documenting medication adherence, seizures, and toxic side effects.[18] Should a breakthrough seizure occur, these blood concentrations and patient data may help determine its cause. In cases when the physician or patient attributes an adverse effect to a formulation change, a report should be filed with the FDA using the MedWatch system, which is easily accessible on the Internet (http://www.fda.gov/medwatch). Filing a report takes only a few minutes and could help guide the FDA's understanding about the safety and efficacy of generic AEDs.

Conclusions

Until the issues surrounding generic substitution are resolved, physicians, pharmacists, and patients are in the precarious position of balancing cost containment with the potential risks of adverse events. As concerned practitioners and scientists, we need to continue our efforts to encourage the development and completion of appropriate studies to answer the questions and settle the issue. Eventually we must achieve a state in which all generic drugs are fully bioequivalent in everyone's view.

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