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EPILEPSY (CW BAZIL, SECTION EDITOR)

Risk-Based Bioequivalence Recommendations for Antiepileptic Drugs

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Abstract
Purpose of Review This review summarizes the current FDA practice in developing risk- and evidence-based product-specific bioequivalence guidances for antiepileptic drugs (AEDs).
Recent Findings FDA's product-specific guidance (PSG) for AEDs takes into account the therapeutic index of each AED product. Several PSGs for AEDs recommend fully replicated studies and a reference-scaled average bioequivalence (RSABE) approach that permit the simultaneous equivalence comparison of the mean and within-subject variability of the test and reference products.
Summary The PSGs for AEDs published by FDA reflect the agency's current thinking on the bioequivalence studies and approval standards for generics of AEDs. Bioequivalence between brand and generic AED products demonstrated in controlled studies with epilepsy patients provides strong scientific support for the soundness of FDA bioequivalence standards.

Keywords AED · Bioequivalence · NTI · PSG

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Introduction

Epilepsy is a neurological condition characterized as an enduring predisposition to generate epileptic seizures [1]. The number of people having epilepsy is estimated to be about 65 million worldwide [2], making it one of the most common neurological diseases. Epilepsy is more common in children younger than 2 years old and adults' age of 65 years and older [3]. Epilepsy-related conditions such as cognitive problems, depression, and anxiety can be chronic and disabling. Although genetic factors, brain conditions, infectious diseases, and developmental disorders may play a role in the etiology of epilepsy disorders, cause of epilepsy remains unknown in many patients.

Current treatment options for epilepsy include medications, surgery, implantable devices, and dietary therapies. While surgery and medical devices are effective in some epilepsy patients, antiepileptic drug (AED) therapy is the current mainstay of epilepsy treatment. The American Academy of Neurology (AAN), the American Epilepsy Society (AES), and other professional organizations have issued evidence-based guidelines for the management of epilepsy [4]. Current clinical evidence indicates that most patients with newly diagnosed epilepsy respond to the first one or two AEDs and their seizure conditions can be completely controlled with a maintenance dose of AEDs [5]. Surgical procedures and medical devices are alternative options for the remaining patients whose seizures cannot be effectively controlled by AEDs.

Over 20 new FDA-approved new drug substances have entered the AED market over the past few decades [6••]. The availability of these AEDs has translated into good control of epileptic seizures in patients. For many patients, epilepsy is a life-long condition requiring chronic AEDs to achieve and maintain seizure control. AED medication

compliance is a particular concern for breakthrough seizures. With more generics of AEDs becoming available for patients, AED medications are becoming more affordable and patient compliance is likely to be facilitated [7].

Before any generic AED can enter the US market, it must meet FDA's high standards for approval. In general, a generic manufacturer submits an Abbreviated New Drug Application (ANDA) to the FDA for review and approval. ANDAs rely on the previously established safety and efficacy of the brand name product, or reference listed drug (RLD) it copies. To ensure that generics are therapeutically equivalent to the RLD, they must show pharmaceutical equivalence together with bioequivalence to the RLD. Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study [8]. In 2013, FDA issued the revised draft guidance, Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA, that provides FDA's general and current thinking on bioequivalence study designs and bioequivalence standards [9]. FDA also published the guidance Statistical Approaches to Establishing Bioequivalence in 2001 [10].

The issue of AED generic substitution and possible impact on therapeutic effect has been debated for many years. FDA continuously monitors and reviews this issue and has found insufficient evidence to indicate that the use of generic AEDs may lead to therapeutic failure or increased risk of adverse events or that the use of FDA-approved generic anticonvulsants results in an increased frequency of seizures [11, 12•]. Additionally, there has been some general misunderstanding of FDA's criteria for demonstrating bioequivalence. To establish bioequivalence, the calculated 90% confidence interval (CI) for geometric mean ratios for AUC (area under the concentration-time curve) and C_{max} (peak serum/plasma concentration) values between the generic product and the RLD generally should fall entirely within an 80.00 to 125.00% acceptance interval. Because the entire 90% CI has to fall within the 80.00–125.00% range, the actual mean pharmacokinetic values of the generic drug must be very close to the mean pharmacokinetic value of the RLD. In a review of 12 years of bioequivalence data submitted to FDA, the average differences in C_{max} and AUC value between approved generic products and respective RLD were observed to be 4.35 and 3.56%, respectively [13].

As the type of studies and evidence required to establish bioequivalence can be different for each AED product, FDA routinely conducts internal research and develops product-specific guidances (PSGs). PSGs describe the agency's current thinking and recommendations on the bioequivalence studies for individual generic products. FDA has issued PSGs for most AED products through the FDA webpage [14]. Table 1 summarizes the PSGs for AED products that include oral tablets, capsules, disintegrating tablets, suspensions and syrups, and some intravenous solutions.

This review focuses on the FDA-recommended in vivo studies for bioequivalence testing of AED products. Consistent with the widely used classification of AEDs based on their respective approval dates, generic bioequivalence is described the in the context of first, second, and newer generation AEDs.

First-Generation AEDs

First-generation AEDs are those that initially entered the market before the 1990s and include phenytoin, trimethadione, primidone, methsuximide, ethotoin, ethosuximide, acetazolamide, diazepam, carbamazepine, clonazepam, valproic acid, valproate sodium, and divalproex. While phenobarbital is considered a first-generation AED, it is not in this review because it is currently marketed as an unapproved drug product [15].

FDA considers four of these first-generation AEDs, phenytoin, carbamazepine, valproic acid, and divalproex, narrow therapeutic index (NTI) drugs [14]. These four AEDs have little separation between therapeutical and toxic concentrations with an estimated therapeutic index of around 2. For instance, phenytoin has a therapeutic concentration range of 10–20 mcg/mL, with serious dose-related adverse events observed more frequently at plasma concentrations above 20 mcg/mL [16, 17]. The therapeutic serum concentration range for carbamazepine is considered to be 4–12 mcg/mL [18]. The serum carbamazepine concentration at the first occurrence of the typical adverse event could be as low as 10 mcg/mL [19], while concentrations above 20 mcg/mL are considered comatose-fatal [20]. Valproic acid has a therapeutic concentration range of 50–100 mcg/mL and the toxic concentration is about 100 mcg/mL [21]. In addition, due to the steep exposure-response relationship for efficacy (i.e., seizure control), patients with sub-therapeutic concentrations may have a higher risk of therapeutic failure. As a result, phenytoin, carbamazepine, valproic acid, and divalproex are subject to routine therapeutic drug monitoring based on serum/plasma drug concentrations. Doses for these four drugs are often adjusted in very small increments (< 20%). These four products have within-subject variability of less than 30% in drug exposure. NTI drugs generally have low within-subject variability because with a combination of a steep exposure-response relationship and high variation in drug exposure, patients would be at risk of serious lack of efficacy or adverse events due to normal variations in drug exposure.

To ensure therapeutic equivalence of generic NTI AEDs to the RLD they copy, FDA recommends a four-way, fully replicated, crossover study design for in vivo testing and

Table 1 PSGs for AED products

Drug	Reference	Approval	Dosage form	Route	Date recommended/revised	Bioequivalence study
Phenytoin	N008762	1953	Suspension	Oral	Posted 5/2008	Two-way crossover or fully replicated crossover, fasting and fed, healthy subjects
Phenytoin	A084349	1976	Capsule, ER	Oral	Posted 5/2007; revised 12/2014	Fully replicated crossover, fasting and fed, healthy subjects
Phenytoin	A040298	1998	Capsule, ER	Oral	Posted 5/2007; revised 12/2014	Fully replicated crossover, fasting and fed, healthy subjects
Ethosuximide	N012380	1960	Capsule	Oral	Posted 7/2008	Two-way crossover, fasting, healthy subjects
Acetazolamide	N012945	1962	Capsule, ER	Oral	Posted 2/2010	Two-way crossover, fasting and fed, healthy subjects
Acetazolamide	A040195	1997	Tablet	Oral	Posted 7/2008	Two-way crossover, fasting, healthy subjects
Diazepam	N020648	1997	Gel	Rectal	Posted 7/2010	Two-way crossover, fasting, healthy subjects
Carbamazepine	N016608	1968	Tablet	Oral	Posted 8/2011; revised 9/2015	Fully replicated crossover, fasting and fed, healthy subjects
Carbamazepine	N018927	1987	Suspension	Oral	Posted 5/2008; revised 3/2015	Fully replicated crossover, fasting and fed, healthy subjects
Carbamazepine	N020234	1996	Tablet, ER	Oral	Posted 2/2008; revised 3/2015	Fully replicated crossover, fasting and fed, healthy subjects
Carbamazepine	N020712	1997	Capsule, ER	Oral	Posted 3/2004; revised 11/2007, 3/2015	Fully replicated crossover, fasting, fed, and sprinkle (fasting), healthy subjects
Clonazepam	N017533	1975	Tablet	Oral	Posted 4/2010	Two-way crossover, fasting and fed, healthy subjects
Valproic Acid	N018081	1978	Capsule	Oral	Posted 2/2010; under revision	Two-way crossover, fasting and fed, healthy subjects; will be revised to fully replicated design
Divalproex	N018723	1983	Tablet, DR	Oral	Posted 12/2009; revised 12/2016	Fully replicated crossover, fasting and fed, healthy subjects
Divalproex	N019680	1989	Capsule, DR	Oral	Posted 5/2006; revised 12/2016	Fully replicated crossover, fasting, fed, and sprinkle (fasting), healthy subjects
Divalproex	N021168	2000	Tablet, ER	Oral	Posted 2/2008; revised 12/2016	Fully replicated crossover, fasting and fed, healthy subjects
Felbamate	N020189	1993	Tablet	Oral	Posted 12/2006; revised 2/2010	Multiple-dose, steady-state crossover, fasting, patients
Felbamate	N020189	1993	Suspension	Oral	Posted 1/2006; revised 2/2010	Multiple-dose, steady-state crossover, fasting, patients
Gabapentin	N020235	1993	Capsule	Oral	Posted 5/2005; revised 5/2007	Two-way crossover, fasting and fed, healthy subjects
Gabapentin	N020882	1998	Tablet	Oral	Posted 5/2008	Two-way crossover, fasting and fed, healthy subjects
Lamotrigine	N020241	1994	Tablet	Oral	Posted 5/2008	Two-way crossover, fasting and fed, healthy subjects
Lamotrigine	N020764	1998	Tablet, Chewable	Oral	Posted 5/2008	Two-way crossover, fasting and fed, healthy subjects
Lamotrigine	N022115	2009	Tablet, ER	Oral	Posted 4/2010; revised 5, 7, 8/2010, 1/2016	Two-way crossover, fasting and fed, healthy subjects
Topiramate	N020505	1996	Tablet	Oral	Posted 5/2007; revised 12/2008, 06/2013	Two-way crossover, fasting and fed, healthy males
Topiramate	N020844	1998	Sprinkle Capsule	Oral	Posted 5/2005; revised 7/2009, 9/2012, 6/2013	Two-way crossover, fasting and fed, healthy males
Topiramate	N201635	2013	Capsule, ER	Oral	Posted 3/2015	Two-way crossover, fasting and fed, healthy males
Topiramate	N205122	2014	Capsule, ER	Oral	Posted 3/2015	Two-way crossover, fasting, fed, and sprinkle (fasting), healthy males
Tiagabine	N020646	1997	Tablet	Oral	Posted 7/2008; revised 8/2010, 6/2015	BCS waiver or in vivo two-way crossover testing, fasting and fed, healthy subjects
Levetiracetam	N021035	1999	Tablet	Oral	Posted 10/2011	

Table 1 (continued)

Drug	Reference	Approval	Dosage form	Route	Date recommended/revised	Bioequivalence study
						BCS waiver or in vivo two-way crossover testing, fasting and fed, healthy subjects
Levetiracetam	N022285	2008	Tablet, ER	Oral	Posted 2/2010	Two-way crossover, fasting and fed, healthy subjects
Oxcarbazepine	N021014	2000	Tablet	Oral	Posted 5/2008	Two-way crossover, fasting and fed, healthy subjects
Oxcarbazepine	N021285	2001	Suspension	Oral	Posted 5/2008	Two-way crossover, fasting and fed, healthy subjects
Oxcarbazepine	N202810	2012	Tablet, ER	Oral	Posted 7/2014	Two-way crossover, fasting and fed, healthy subjects
Zonisamide	N020789	2000	Capsule	Oral	Posted 1/2008	Two-way crossover or parallel, fasting and fed, healthy subjects
Pregabalin	N021446	2004	Capsule	Oral	Posted 10/2011	BCS waiver or in vivo two-way crossover testing, fasting and fed, healthy subjects
Rufinamide	N021911	2008	Tablet	Oral	Posted 8/2011	Two-way crossover, fasting and fed, healthy subjects
Rufinamide	N201367	2011	Suspension	Oral	Posted 6/2012	Two-way crossover, fasting and fed, healthy subjects
Lacosamide	N022253	2008	Tablet	Oral	posted 6/2012	BCS waiver or in vivo two-way crossover testing, fasting and fed, healthy subjects
Vigabatrin	N020427	2009	Tablet	Oral	posted 3/2015	Multiple-dose, steady-state crossover, patients
Clobazam	N202067	2011	Tablet	Oral	posted 11/2013	Two-way crossover, fasting and fed, healthy subjects
Clobazam	N203993	2012	Suspension	Oral	Posted 4/2014	Two-way crossover, fasting and fed, healthy subjects
Ezogabine	N022345	2011	Tablet	Oral	Posted 4/2013	Two-way crossover, fasting and fed, healthy subjects
Perampanel	N202834	2012	Tablet	Oral	Posted 4/2014	Two-way crossover, fasting and fed, healthy subjects
Perampanel	N208277	2016	Suspension	Oral	Posted 12/2016	Two-way crossover or parallel, fasting and fed, healthy subjects
Eslicarbazepine	N022416	2013	Tablet	Oral	Posted 9/2015	Two-way crossover, fasting and fed, healthy subjects

reference-scaled average bioequivalence (RS-ABE) approach for data analysis [12•, 22•]. Since 2014, FDA has revised the PSGs for the first-generation AED products that demonstrate characteristics of NTI drugs to incorporate these recommendations (Table 1). In the RS-ABE approach, the bioequivalence limits are scaled based on the within-subject standard deviation of reference product from a fully replicated, crossover study (Table 2). In addition, comparison of the within-subject standard deviation of test and reference products ensures equivalent therapeutic performance. As an example, details of the statistical analysis using the RS-ABE approach can be found in the PSG for warfarin sodium oral tablet, an anticoagulant NTI drug product [23].

For the other first-generation AED products that are not considered NTI drugs, the average bioequivalence approach is used for bioequivalence assessment of pharmacokinetic data obtained from two-way crossover studies in healthy adult subjects. The 90% CI for the test-to-reference ratio of geometric means should fall within the bioequivalence limits of 80.00–125.00% for C_{max} and AUC [10].

Second-Generation AEDs

The pharmaceutical industry successfully developed and introduced 13 new drug substances to the US market between 1990 and 2010. These drugs are felbamate, gabapentin, lamotrigine, fosphenytoin, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide, lacosamide, and vigabatrin. Based on literature reports [24], many of these drugs greatly improve the treatment of epilepsy because of a more favorable pharmacokinetic property and/or a better safety and efficacy profile due to less adverse effects and fewer drug interactions. Many second-generation brand name AEDs have recently or will soon lose patent and exclusivity protection, creating a significant opportunity for the

development and approval of generic versions of these AEDs. To date, FDA has developed 23 PSGs (Table 1) for these second-generation AED products.

For the most part, FDA does not consider second-generation AED products to be NTI drugs. For instance, the therapeutic index of lamotrigine is estimated to vary largely among patients, up to 20 in a recent systematic review of available literature data [25]. Since the available evidence does not indicate that lamotrigine is an NTI drug, therapeutic drug monitoring is not routinely implemented [26].

Immediate-release products containing tiagabine, levetiracetam, pregabalin, and lacosamide are highly permeable and soluble and are considered to be Biopharmaceutics Classification System (BCS) class I drugs [27]. As a result, generic manufactures of these immediate-release solid oral products may request a waiver of in vivo testing, provided that the drug product is rapidly dissolving and excipients in the product do not affect the rate or extent of absorption of the drug. Although a waiver of in vivo bioequivalence testing is an option, many of the FDA-approved IR solid oral dosage forms of tiagabine, levetiracetam, and lacosamide have been tested for bioequivalence using in vivo studies under fed and fasting conditions. A few pregabalin oral capsule generics have a "tentative approval" status, meaning that they have met FDA's scientific standards for approval, but cannot be approved until unexpired patents or exclusivity issues are resolved.

While most in vivo bioequivalence studies for AED products use healthy subjects, FDA recommends epilepsy patients when evaluating bioequivalence of felbamate and vigabatrin products due to risks associated with these products. Felbamate products have a boxed warning based on the risk of aplastic anemia and acute hepatic failure [28]. Therefore, the safety concerns from life-threatening adverse events of aplastic anemia and acute hepatic failure may preclude enrolling health subjects for the bioequivalence evaluation. Bioequivalence testing for this product should only be conducted in epilepsy patients already established on felbamate monotherapy or adjunctive therapy. Similarly, vigabatrin products have a boxed warning regarding the serious risk of permanent bilateral concentric visual field constriction and vision loss [29]. Therefore, FDA recommends bioequivalence studies in adult patients with refractory complex partial seizures who are already on established vigabatrin adjunctive therapy. When conducting bioequivalence study in patients, attainment of steady state should be confirmed with at least three consecutive measurements of plasma drug concentrations prior to dosing. Peak drug concentrations during a dosing interval at a steady state (C_{maxSS}) and AUC over a dosing interval at a steady state ($AUC_{0\text{-}tau}$) should be assessed [9]. In addition, other pharmacokinetic metrics such as concentration at the end of a dosing interval (C_{minSS}), average concentration during a dosing interval (C_{avSS}), degree of fluctuation [$(C_{max} - C_{min})/C_{avSS}$], swing [$(C_{maxSS} - C_{minSS})/C_{avSS}$], and time to peak concentration (T_{max}) should be reported as supportive information [9].

Newer AEDs

Over the past few years, FDA has approved five new drugs for the management of epilepsy. Clobazam is a member of the benzodiazepine class that includes first-generation AEDs such as diazepam and clonazepam. While it has been clinically used worldwide for about 40 years, clobazam oral formulations were approved by FDA as an adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in 2011 [30•]. Eslicarbazepine, a third-generation dibenzazepine AED, is indicated for the treatment of partial-onset seizures as monotherapy or adjunctive therapy [31]. Brivaracetam, a levetiracetam analog, was approved by FDA as adjunctive therapy in the treatment of partial-onset seizures in 2016 [32]. Ezogabine and perampanel are two novel AEDs unique in the chemical structure and mechanism of action. There are no approved generics for newer generation AEDs due to patents and exclusivity [6••]. Nevertheless, FDA has reviewed product information, clinical pharmacokinetic, and safety data from their original new drug applications and issued PSGs for all except brivaracetam which was approved in 2016. FDA does not considered any of these products to be NTI drugs. Therefore, the PSGs for these products recommend a single-dose, two-way crossover study design for bioequivalence studies in healthy subjects under fasting and fed conditions. For perampanel, adequate washout period between treatments should be considered given that it has a long terminal half-life (about 105 h) [33]. Alternatively, a single-dose, parallel study design can be considered where a separate group of healthy subjects with similar demographics is enrolled [9]. C_{max} and an AUC truncated at 72 h ($AUC_{0–72\ h}$) can be used to characterize peak and drug exposure for the purpose of bioequivalence assessment [14].

Lamotrigine Bioequivalence Studies Funded by FDA: a Case Example

Lamotrigine is one of the most commonly prescribed AEDs due to its broad-spectrum efficacy, good tolerability, and availability in generic forms [34]. To date, FDA has approved lamotrigine generics in all four oral dosage forms: immediate-release (IR) tablet, extended-release (ER) tablet, chewable tablet, and orally disintegrating tablet (ODT). For each oral dosage form, there are multiple generics available on the US market (Fig. 1). Over the last decade, neurologists have raised concerns about the risk of switching to a generic from a brand lamotrigine product or another generic in epilepsy patients [35, 36]. To address neurologists' concerns, FDA has

funded a series of postmarket studies on lamotrigine products since 2010. Specifically, a Bioequivalence in Epilepsy Patients (BEEP) study (ClinicalTrials.gov identifier NCT01995825) was to evaluate the pharmacokinetic performance of the brand name lamotrigine IR product, LAMICTAL® (manufactured by GlaxoSmithKline), against a generic lamotrigine IR product in epilepsy patients which was reported to have a potential problem with generic switching [37••]. The BEEP study was conducted using a randomized, single-center, double-blinded, multiple-dose, steady-state, fully replicated, crossover study design. The study results demonstrated that the generic and brand lamotrigine IR products are bioequivalent in epilepsy patients, validating FDA's recommendation of in vivo testing in healthy subject and approval standards for generic lamotrigine IR products (i.e., the conventional 80.00–125.00% acceptance limit). This study also demonstrated similar seizure control and tolerability in the vast majority of epilepsy patients. Another study, Equivalence among Generic AEDs (EQUIGEN, ClinicalTrials.gov identifier NCT01713777), evaluated whether generic lamotrigine IR products from different manufacturers are bioequivalent in epilepsy patients receiving concomitant AEDs [38••]. This multiple-dose study was conducted using a randomized, double-blinded, fully replicated, crossover design. Similar to the results from the BEEP study, the EQUIGEN study demonstrated that two generic lamotrigine IR products are bioequivalent in epilepsy patients and loss of seizure control or unanticipated adverse events are not evident. Of note, the two generics were the most disparate to each other (but in the allowable range of difference from the brand) in terms of their bioequivalence measures and inactive ingredients in the formulation in their FDA application. Because a multiple-dose study may be less sensitive than a single-dose study in detecting formulation differences between the drug products, a bioequivalence study of LAMICTAL® and these two disparate generic lamotrigine IR products was conducted using a single-dose, three-sequence, six-period replicate study design. The study results demonstrated brand to generic as well as generic to generic equivalence in patients with epilepsy (NCT01733394) [39]. Additionally, the within-subject variability of LAMICTAL® and two generics is similar and relatively low (i.e., < 15%) in epilepsy patients. This EQUIGEN study specifically addressed neurologists' concerns regarding switches among multiple generic AEDs which may have variable differences from the RLD.

Overall, the BEEP and EQUIGEN studies conducted in patients with epilepsy confirm that the current FDA bioequivalence standards are appropriate for lamotrigine IR formulations. Based on these study results, the AES issued a statement acknowledging that drug formulation substitution with FDA-approved generic AEDs does not compromise efficacy in January 2016 [40••]. Of note, a recent case-crossover study using the Medicaid Analytic eXtract and a US commercial health insurance database concluded that switching between different manufacturers of the same generic AED appears to be safe [41•].

Table 2 Tightened bioequivalence limits in RS-ABE approach

Within-subject CV (%)	Bioequivalence limits (lower–upper) (%)
5	94.87–105.41
10	90.02–111.08
15	85.35–117.02
20	81.17–123.20
> 21.42	80.00–125.00

Generic modified-release (MR) product may have different control release mechanism and formulation design from those of the brand AED [42•]. A neurologist has some remaining concerns regarding substitutability of generic MR AEDs [43•]. To ensure therapeutic equivalence for lamotrigine MR products, FDA has established a risk-analysis platform which integrates knowledge in formulation design, clinical studies, modeling and simulation, and postmarket surveillance [44]. Besides statistic assessment on C_{max} and AUC, we routinely evaluate T_{max} differences in the clinical context for generic MR products. FDA also sponsored additional studies on generic MR AED products, e.g., a recent study (NCT02821338) of a generic lamotrigine ER and LAMICTAL® XR tablet products in healthy subjects under fed conditions will help confirm product bioequivalence and provide insights on brand-to-generic AED MR product switching.

Multiple-Dose Versus Single-Dose Bioequivalence Studies

Some AEDs have nonlinear pharmacokinetic properties. For instance, phenytoin can saturate its own metabolism after repeated dose administration. Carbamazepine is an inducer of certain CYP enzymes, so it can auto-induce its own clearance. Therefore, its clearance following repeated oral administration

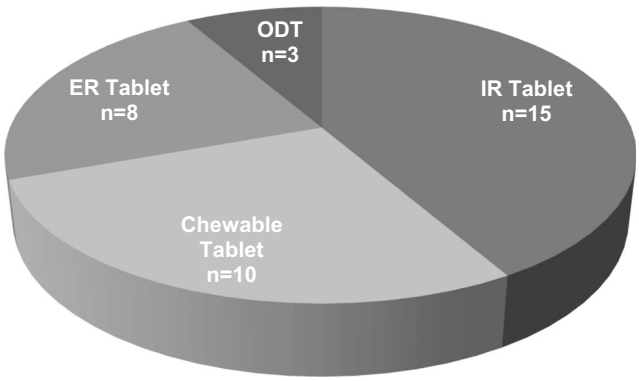

Fig. 1 Lamotrigine generics on the US market

is greater than that following a single-dose administration. Based on these drug metabolism findings, Tothfalusi et al. raised a concern that AED products with established bioequivalence in single-dose bioequivalence studies in healthy subjects may not be bioequivalent in epilepsy patients [45]. To address this concern, a population physiological-based pharmacokinetic (PBPK) model and clinical trial simulations of bioequivalence studies were conducted [46]. The study demonstrated that the FDA's recommended fully replicated single-dose bioequivalence studies with the RS-ABE approach in healthy subjects can ensure bioequivalence in patients following chronic treatment. Therefore, the FDA-recommended single-dose bioequivalence study for carbamazepine is sensitive in detecting both changes in the extent of bioavailability and changes in in vitro drug release profiles associated with formulation changes. Similarly, results from phenytoin modeling work showed that the RS-ABE approach based on the currently recommended single-dose fully replicated bioequivalence studies is appropriate and ensures BE following chronic dosing.

Concluding Remarks

Bioequivalence for generic AEDs is critical for epilepsy management. FDA routinely conducts research to develop risk- and evidence-based bioequivalence recommendations for AEDs. In the case of AEDs that demonstrated characteristics of NTI drugs, FDA recommends a specific bioequivalence approach which permits the simultaneous equivalence comparison of the mean and within-subject variability of the test and reference products. For felbamate and vigabatrin products, safety concerns preclude the use of healthy subjects and FDA recommends bioequivalence testing in epilepsy patients stable on these AEDs. For IR solid oral dosage forms of high solubility and high permeability drug substance, a waiver of in vivo bioequivalence testing can be considered. Moreover, several FDA-funded clinical studies not only demonstrate therapeutic equivalence of lamotrigine products in epilepsy patients but also support current FDA approval standards and bioequivalence criteria. These clinical findings further provide assurance on the safety and efficacy of generic substitution.

Compliance with Ethical Standards

Conflict of Interest Zhichuan Li, Lanyan Fang, Wenlei Jiang, Myong-Jin Kim, and Liang Zhao declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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