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ORIGINAL RESEARCH ARTICLE

Generic Products of Antiepileptic Drugs: A Perspective on Bioequivalence, Bioavailability, and Formulation Switches Using Monte Carlo Simulations

Vangelis Karalis · Panos Macheras · Meir Bialer

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Abstract
Introduction Generic products of antiepileptic drugs (AEDs) are currently a controversial topic as neurologists and patients are reluctant to switch from brand products to generics and to switch between generics.
Objective The aim of this study was to provide enlightenment on issues of bioequivalence (BE) and interchangeability of AED products.
Methods Monte Carlo simulations of the classic 2 × 2 BE studies were performed to study the effect of sample size, within-subject variability, and the true difference in pharmacokinetic values of the products under comparison on BE acceptance of generic AED products. Simulations were extended to study the comparative performance of two generic AED products against the same innovative product. The simulated results are compared with literature data on AEDs.
Results The question with regard to bioavailability (BA) is whether two formulations are different, while for BE the question is whether two formulations are sufficiently similar in terms of extent and rate of absorption. Therefore, the criteria for BA and BE and the statistical analysis involved in their analysis are different. Two generic formulations that meet regulatory approval requirements for generics by being bioequivalent to the same innovative AED may not be bioequivalent to one another and therefore should not be regarded as equal or as therapeutically equivalent products. A switch from a standard or an immediate-release formulation to a modified-release product, which comprises extended-release or delayed-release formulations, should not be regarded as a switch between generics, but rather as a switch between different formulation types.
Discussion Switches between bioequivalent generic AED products could potentially lead to larger changes in plasma levels and exposure than the brand-to-generic switch. The simulation work verified the clinical findings that not all generic AED products bioequivalent to the same innovative product are bioequivalent to one another.
Conclusions Two generic formulations that meet regulatory approval requirements for generics, by being bioequivalent to the innovative AED, may not be bioequivalent to one another. Additional BE criteria are needed for a formulation switch, particularly in epilepsy, where a breakthrough seizure may change a patient's status from seizure-free to refractory.

1 Introduction

Generic products play a vital role in global health care. In the USA, since the passage of the *Drug Price Competition and Patent term Restoration Act* in 1984 (Hatch-Waxman Amendments), which set the rules under which generic drugs could compete with brand (innovator) products, the Food and Drug Administration (FDA) has approved (until 2009) 11,843 generics [1]. In Europe, the European Medicines Agency (EMA) issued, in August 1, 2010, a revised guidance regarding bioequivalence (BE)

V. Karalis · P. Macheras
Laboratory of Biopharmaceutics & Pharmacokinetics, Faculty of Pharmacy, National & Kapodistrian University of Athens, 15771 Athens, Greece

M. Bialer (✉)
Institute of Drug Research, School of Pharmacy and David R. Bloom Center for Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Ein Kerem, P.O.B. 12065, 91120 Jerusalem, Israel
e-mail: bialer@md.huji.ac.il

assessment for the approval of innovator (e.g., bridging studies, variations, line extensions) and generic products [2, 3].

The issue of generic products of antiepileptic drugs (AEDs) continues to be a hot topic [4–8]. Over the last few years, articles have appeared (mostly based on epidemiological studies and retrospective data mining) that have indicated that switching patients from brand to generic or from generic to generic has led to therapeutic issues, reported in the literature as, e.g., breakthrough seizures, relapse, etc. [9–11]. Consequently, AEDs constitute a special group where therapeutic mishaps should be avoided. On the other side, neurologists have noted that some patients with epilepsy go out of therapeutic control and experience breakthrough seizures while being maintained on the same brand AED. Studies have shown that refilling prescriptions for AEDs was associated with an elevated risk of seizure-related events whether or not the refill involved switching from a brand name to a generic product [6]. At the 2011 annual meeting of the American Epilepsy Society (AES), the FDA told the epilepsy community that regulators are taking a closer look at the divisive issue of generic AEDs and considering tightening controls on certain AEDs.

Drug products that meet the FDA or the EMA approval requirements for generic formulations are considered to be "therapeutically equivalent" to the brand (reference) listed drug. Drug products 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 (reference) product [12].

Reduced cost is the driving force in the widespread use of generics as branded product substitutions. Like in all therapeutic areas, generic formulations of AEDs are valuable and widely used after the expiration of the patent on the original or brand AED product. However, in the prescribing of AEDs, this economic driving force has raised the question of whether patients with epilepsy should be switched to generic AEDs only on the basis of cost and not keeping in mind the uniqueness of epilepsy as a disease [13].

The aim of this analysis is to provide enlightenment on the following issues of AED generic products: (i) the differences between the criteria for bioavailability (BA) and BE of AEDs, (ii) the interchangeability and similarity of approved AEDs generics, and (iii) the discrimination between a formulation switch [e.g., from a modified-release (MR) to an immediate-release (IR) formulation] and a generic switch (e.g., from one IR to another) as well as to discuss possible additional BE criteria for formulation switches.

1.1 Bioavailability (BA) Versus Bioequivalence (BE)

In Europe, two products, either pharmaceutically equivalent or alternative (e.g., capsules and tablets), can be considered bioequivalent if pharmacokinetic (PK) similarity can be proven [3]. Thus, two drug products are considered bioequivalent if they contain the same active moiety, are at the same molar dose, and show no significant differences in their rate and extent of absorption when administered under the same conditions [3, 14, 15]. BE testing relies on the comparison of the rate and extent of absorption of the generic and reference products. Extent of absorption is usually expressed by the area under the drug plasma concentration–time curve (AUC), while the maximum observed plasma concentration (C_{max}) is used for the assessment of the rate of absorption [16–18].

In BE analysis, the question imposed is whether the generic (i.e., T) product and reference (i.e., R) product are sufficiently similar in their extent (e.g., AUC) and rate (e.g., C_{max}) of absorption. In other words, BE focuses on the statistical comparison of AUC and C_{max}, of the T and R products, and examines whether the calculated 90 % confidence interval (CI) (two-sided) for the difference of the *ln*-transformed values of AUC and C_{max} lie between the acceptable 80.00 and 125.00 % limits [19].

Also, the within-subject variability (WSV) or intrasubject variability is of paramount importance in BE studies. In the case of BE analysis, ANOVA is applied to the *ln*-transformed values of the PK parameters (e.g., AUC and C_{max}) of the T and R products. For this reason, the coefficient of variation of the WSV (CVw) is estimated from the mean square error (MSE) of ANOVA according to Eq. 1:

$$\text{CVw } (\%) = 100 \times \sqrt{\exp(\text{MSE}) - 1} \quad (1)$$

The number of subjects required to achieve statistical power at least 80 % is strongly depended on, among other things, the WSV of the drug (or drug product) and the geometric mean ratio (GMR) of the PK parameters under study (i.e., AUC or C_{max}).

Classically, BE assessment relies on the concept of average BE, where the T and R products are considered bioequivalent if the calculated 90 % CI for the difference of their *ln*-transformed mean BE measure (e.g., AUC, C_{max}) is within specific limits set by the regulatory authorities [3, 14, 15, 19]. More recently, scaled approaches have also been proposed for the assessment of BE in the case of highly variable drugs [3, 20–22]. In the same vein, reference-scaled BE approaches have been proposed for narrow therapeutic index drugs [23]. According to this approach, for reference variability values lower than 10 %, the BE limits should get narrower as a function of the WSV of the reference product. However, when the

reference WSV exceeds 10 %, the BE limits should expand, but this expansion should be capped at the current level of 80–125 % [23]. Additional BE requirements are also under investigation.

It is worth mentioning that quite recently the US FDA issued two specific product guidelines for two narrow therapeutic index drugs: warfarin sodium and tacrolimus [24, 25]. In these two cases, it is explicitly described by the FDA that a fully replicate crossover design should be used which will allow the estimation of the WSV of both the reference and the test formulation. Then these variabilities should be compared, and eventually reference-scaled BE limits should be applied [24, 25].

1.2 Switchability Terminology

It is generally considered that two drug products that are bioequivalent can be used interchangeably or, in other words, the patients can be switched from one product to another. However, it should be clarified that BE and generic substitutions are interconnected but essentially different regulatory steps. For the purposes of this manuscript, the following types of 'switching' are discussed:

(a) A 'brand-to-generic' switch, which refers to a change from the innovative (reference) product to a generic formulation of the same drug [4, 5].
(b) A 'generic-to-generic' switch, which characterizes a change between two generics approved against the same reference product. This generic–generic switch is accompanied by several special issues, such as the transitivity of BE testing, the appropriateness of the BE metrics, and the appropriateness of using healthy volunteers in BE studies [26–29].
(c) The special case of patients switching AEDs, since these patients constitute a group in which therapeutic failure should be avoided [4–11, 30].
(d) A 'formulation switch,' which is a switch from an IR to an MR product (or vice versa) of the same active substance.

2 Methods

In this work, Monte Carlo simulations were performed in order to highlight the effect of sample size, WSV, and the true difference in PK values of the products under comparison on BE acceptance of generic AED products. In the case of the comparison of the terms BA and BE [31], as well as of the issues referring to formulation and/or typical generic switches, no simulations can be performed.

2.1 Simulations

The typical 2 × 2 crossover design was used, and evaluation of BE was based on the classic BE limits (80.00–125.00 %) and the tighter BE limits (90.00–111.11 %) applied to narrow therapeutic index drugs [3, 5, 32]. In this context, two-treatment, two-period, two-sequence, crossover BE studies with an equal number of subjects in each sequence were simulated. In each simulated crossover study, BE was declared if the 90 % CI around the ratio of the estimated GMR for the two drug products (T over R) was within the BE limits. In the case of the classic 2 × 2 design, the estimated upper and lower limits of the 90 % CI are provided by Eq. 2 [33, 34]:

$$\text{Upper, Lower limits of the 90 \% CI} = \exp\left((m_T - m_R) \pm t_{0.05,N-2}\sqrt{\text{MSE}\cdot\frac{2}{N}}\right) \quad (2)$$

where m_T and m_R refer to the *ln*-transformed mean BE measures for T and R products, respectively. N is the total number of subjects participating in the BE study, and t is the t-student statistic with $N - 2$ degrees of freedom.

Our simulations studied the comparative performance of two test products (T1 and T2) when compared with the same R product. The typical 2 × 2 clinical design was considered for all combinations of products, namely, T1 versus R, T2 versus R, and T2 versus T1. All comparisons were made simultaneously, which means that the T1 and R values generated for the T1 versus R comparison were further used for the T2 versus R and the T2 versus T1 comparisons. Also, the subject, period, and sequence order were kept unaltered for the three comparisons mentioned above. Only in the case of the T2 versus T1 comparison, administration of T2 formulation was unavoidably set to a different period than that used in T1 versus R comparison. This was necessary in order to have BE comparisons for three products in pairs of two according to the specific BE framework. Finally, this analysis can lead to a direct and concomitant evaluation of BE between the three pairs of products T1–R, T2–R, and T2–T1. Several theoretical GMR levels for T1/R and T2/R were examined. Three different T1/R ratios were simulated, which were equal to 95, 100, and 105. For each of the T1/R ratios, a number of T2/R values were simulated, ranging from 80.00 to 125.00 %, using a step of 5.

A number of $N = 24$ subjects were assumed to participate in the simulated trials. The simulated PK parameters were randomly generated from log-normal distribution [35–39]. The true WSV value, expressed as coefficient of variation (CVw), considered for the simulations was 20 %.

The theoretical residual error values were calculated by rearranging appropriately Eq. 1 and solving in terms of MSE. Several values of the theoretically true GMR of the parameters AUC and C_{max} were examined, ranging from 80.00 to 125.00 %, using a step of 5. In both ways of comparison, namely, either the sole T–R or all paired comparisons of the three products described above, 40,000 BE trials were simulated under each GMR and the percentage of accepted studies was recorded. The entire programming work was implemented by developing the appropriate functions in MATLAB® (The MathWorks, Inc.).

To this point, it should be mentioned that perhaps some combinations of factors may be unrealistic. However, this route was followed not only for reasons of completeness, but also to unveil the trends in the performances in BE studies. In the same vein, one could question that for drugs exhibiting high WSV, scaled average BE approaches can be claimed [3, 20–22]. Even though, this rationale is valid, it deviates from the aim of this study. Our goal was not to present and examine all possible BE approaches, but to apply the most typical criteria in order to provide enlightenment on important issues of BE, such as the role of CVw, sample size, and their impact on generics' interchangeability.

3 Results

3.1 Relationship Between Variability, Geometric Mean Ratio, and Acceptance Range

Figure 1 shows the impact of CVw and GMR on the outcome of BE testing in the case of the 80.00–125.00 % and the narrow 90.00–111.11 % BE limits when drugs with low (CVw = 10 %) and high (CVw = 35 %) variability are evaluated. For reasons of comparison, sample size was kept constant and equal to the typical value of 24. Plausibly, the required sample size for a BE study depends on, among other things, the expected GMR, the CVw, and the BE limits used. However, in our case, the use of the same *N* facilitates the visual comparison of the results and allows the extraction of general findings in line with the purpose of this study.

Drug products with GMR values close to 100 % have a greater probability of being accepted since the center of the 90 % CI is located in the middle of the acceptance range. On the contrary, as GMR deviates from 100 % (either above or below), the 90 % CI moves towards the edges (either 125 or 80 %) of the acceptance region and the two drugs can be considered as not bioequivalent. Also, as depicted in Fig. 1, drug products with low CVw values will have a narrower 90 % CI than highly variable drugs, and

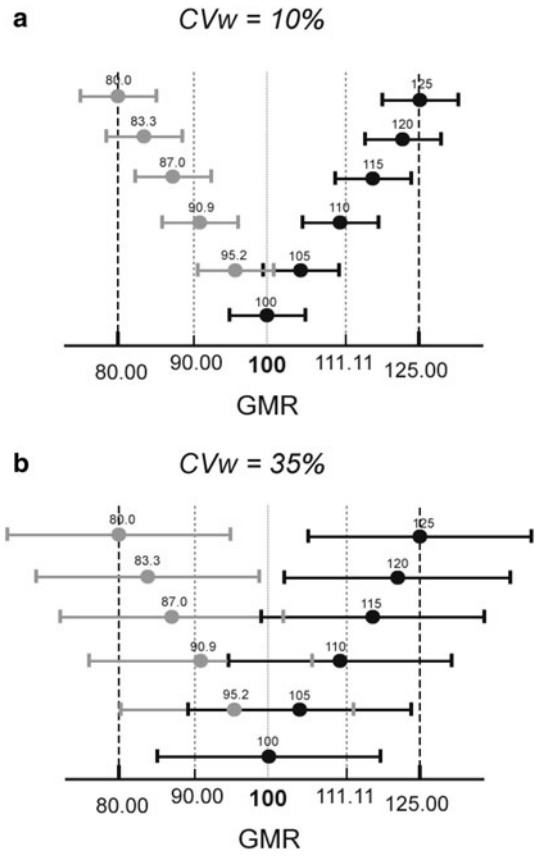

Fig. 1 The relationship between within-subject variability [coefficient of variation of within-subject variability (CVw)], geometric mean ratio (GMR) of test/reference, and the length of the 90 % confidence interval (CI). Sample size is assumed to be 24 and CVw equal to 10 % (**a**) and 35 % (**b**). *Horizontal lines* refer to the 90 % CI, and the numbers above them are the GMRs. Both the classic (80.00–125.00 %) and the narrower (90.00–111.11 %) bioequivalence limits are depicted

therefore low variable drugs can be bioequivalent even if their GMR deviates from the 100 %. In contrast, for drugs with high CVw values, their GMR must be closer to 100 % in order to fit within the acceptable BE criteria.

The same general trend is also present when two drug products are evaluated assuming the narrow BE limits of 90.00–111.11 % (Fig. 1). However, in this case, the effect of GMR and CVw on BE acceptance is more pronounced and lower differences in GMR values are allowed in order to be declared bioequivalent. The 90.00–111.11 % acceptance region imposes a stricter criterion for the two drug products under comparison.

3.2 Drug Interchangeability

The interchangeability regarding a change from an innovative (reference) product to a generic formulation of the same drug is expressed as drug prescribability or drug switchability [4, 5]. FDA and regulatory agencies

supported by eminent pharmaceutical scientists regard BE as an efficient method of assuring therapeutic equivalence and interchangeability [15, 40–43]. In contrast, leading epileptologists disagree with the FDA position, claiming that BE does not assure therapeutic equivalence [4–7, 44].

Figure 2 illustrates the % BE acceptance of a generic drug product T2 when it is compared with another generic T1. Both T1 and T2 have previously been tested against the same reference product. A medium level of CVw is assumed (CVw = 20 %), BE limits were set equal to 80.00–125.00 %, and a typical number of subjects ($N = 24$) was used. Three different cases of the relationship between T1 and R are shown, namely, T1/R equal to 95, 100, and 105 %. For the T2/R ratio, several values are shown, which range from 80 to 125 %, with a step of 5. Visual inspection of Fig. 2 reveals that the % probability of declaring BE between T1 and T2 might be higher than that observed for T1/R, but there are conditions where the % probability of T1 and T2 being bioequivalent can be become rather low. The high % BE acceptance of T2 versus T1 is in essence observed when these products differ less compared with their individual difference from R. Plausibly, the highest % BE acceptance, of T2 versus T1, is observed when the mean BE measures of T1 and T2 coincide, namely, when $GMR_{T2/R} = 95$ % (Fig. 2a). On the contrary, a high risk for therapeutic failure can be observed when T1 and T2 differ in opposite directions, i.e., T1 is lower than R, while T2 is higher than R. Plausibly, many other combinations of T1, T2, and R performances could be tested and different quantitative results will be obtained. However, for the purposes of the current analysis, the message can be clearly derived from the results depicted in Fig. 2, where it is shown quantitatively why two generic products bioequivalent to the same R product may not be bioequivalent to each other. Several other similar results could be obtained; nevertheless the meaning will always be the same.

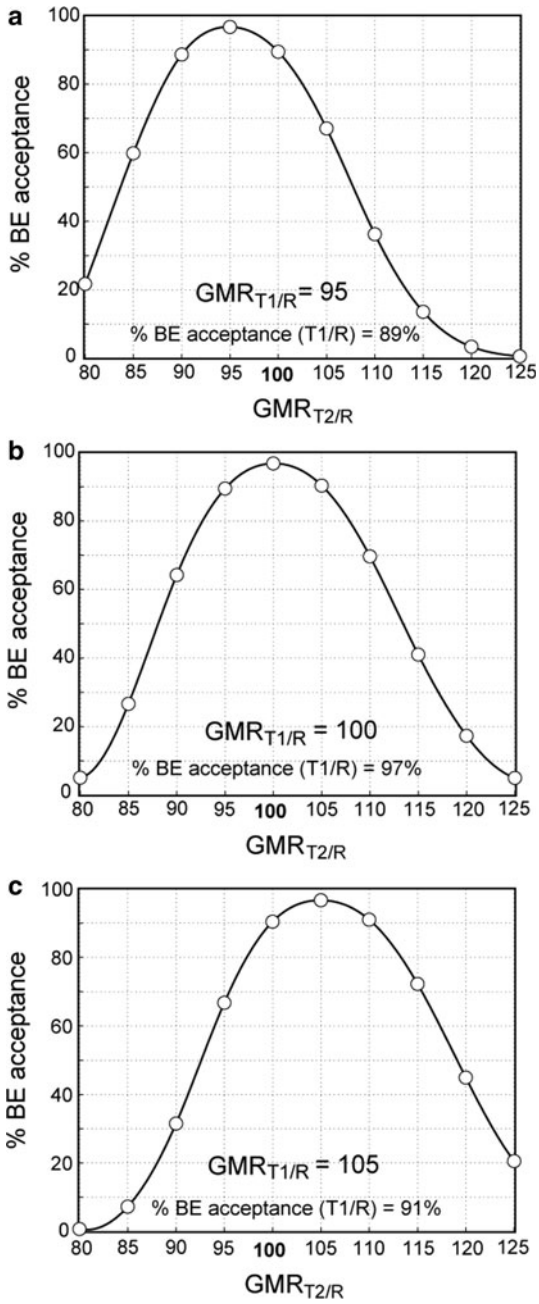

Fig. 2 Percentage of bioequivalence (BE) acceptance of a generic drug product T2 when compared with another generic product T1. The BE of each T1 and T2 was also evaluated against the same reference (R) product. The coefficient of variation of the within-subject variability is assumed to be 20 % for all three (T1, T2, R) products, and the classic 80.00–125.00 % BE limits are used. In all cases, sample size is set equal to 24. *Horizontal axis* refers to the geometric mean ratio (GMR) of T2 over R ($GMR_{T2/R}$). Three different cases of 95, 100, and 105 for the GMR between T1 and R ($GMR_{T1/R}$) are shown in **a**, **b**, and **c**, respectively. The % BE acceptance for T1 vs. R is a constant value in each panel, since a single $GMR_{T1/R}$ value is considered. Under each GMR estimate, 40,000 BE trials were simulated

3.3 Pharmaceutical Principles of Drug Formulations

BE and Therapeutic Equivalence

Recently the FDA reviewed 2,070 (single dose) BE studies of oral FDA-approved generic products between 1996 and 2007 [1]. The results showed that the mean ± SD GMRs were 1.00 ± 0.06 for C_{max} and 1.00 ± 0.04 for AUC. The average difference in C_{max} and AUC was 4.35 and 3.56 %, respectively. In addition, in about 98 % of the reviewed BE studies, the generic product AUC differed from that of the innovator (reference) product by <10 %. These data

support FDA criteria for the approval of generic products and show that bioequivalent generic products are therapeutically equivalent to their respective reference (brand) products [1]. According to this position, it is not necessary for the health care provider to approach any therapeutic class of drug products any differently to any other class when there has been a determination of therapeutic equivalence by the FDA [43].

A recent (2010) FDA report depicted in Tables 1 and 2 shows that the acceptable generic products of various AEDs (including phenytoin) and their 90 % CI are well within the FDA 80–125 % BE limits for both AUC and C_{max}. Table 2 also shows that the generic product with lowest GMR point estimate may not be bioequivalent to the generic products with the highest point estimated and 90 % CI [12]. Thus, the actual (empirical) data presented in Table 2 can be considered in view of our simulation results depicted in Fig. 2.

3.4 Controlled-Release Products Versus Immediate-Release Products of Antiepileptic Drugs: BE Criteria

MR solid oral dosage forms comprise delayed-release (DR) and extended-release (ER) or controlled-release (CR) drug products. Several commercial MR products have been developed using technologies such as osmotic system (e.g., Tegretol XR) and others [45]. An MR product is designed to have a slower absorption rate than an IR formulation and therefore cannot be bioequivalent to the existing IR reference. MR products are designed to release the drug in a controlled manner to achieve the desired efficacy and safety profile. Inappropriate control of drug release from MR products may result in reduced efficacy or increased toxicity [45]. In order to be given at the same daily dose, CR products must show similar AUC as the IR product, demonstrating that their slower absorption rate did not harm the extent of absorption [46].

It should be pointed out that a switch from an IR to an MR formulation of the same drug (AED) is not regarded as a generic switch but rather as a formulation switch. Three types of regulatory applications [new drug applications (NDA) or MAA] for MR products can be expected: (a) an IR-to-MR switch; (b) an MR-to-MR switch with different dosing intervals; and (c) an MR-to-MR with equal dosing intervals.

Table 1 FDA approved generic antiepileptic drugs (as of January 2010)

Generic name*	Number of generic products marketed
Phenytoin	5
Carbamazepine	7
Carbamazepine ER	2
Divalproex sodium DR	13
Divalproex sodium ER	6
Lamotrigine	14
Gabapentin	11
Topiramate	16
Levetiracetam	17
Oxcarbazepine	8
Zonisamide	13

Adapted from FDA Report, 2011 [12]

* The terms *ER* and *DR* refer to extended-release and delayed-release formulations

Table 2 Bioequivalence measures for approved generic antiepileptic drugs, given as mean values with upper and lower 90 % confidence interval limits

Drug	AUC ratio	C_{max} 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)
Valproic Acid (limited data)	0.99 (0.96–1.03)	0.97 (0.90–1.04)
	N/A	N/A
Divalproex (valproic acid)	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)

Adapted from FDA Report, 2011 [12]

The term AUC is the area under the concentration–time curve and the axis of time, while C_{max} is the maximum observed blood concentration of the drug. The AUC and C_{max} ratios refer to the geometric mean ratios of the generic-to-reference product ratios of these parameters

N/A not available

4 Discussion

WSV and sample size play crucial roles in the acceptance of BE (Fig. 1). It has been shown that as WSV increases, the % BE acceptance decreases (Fig. 1). In other words, it becomes difficult to declare BE even when the two drug products under comparison are quite similar [47, 48]. This implies that the larger the CVw value of the drug, the greater the number of subjects required.

Figure 2 actually reflects the fact that BE is not 'equality' between two drug products, but rather 'similarity' within an acceptable range of 80–125 %. In mathematical terms, equality implies that if A is equal to C and B is equal to C, then B should be equal C. However, since BE does not assess equality, but rather similarity, this analogy cannot be deduced or extrapolated from equality to BE. Patients prescribed with generics may face switches from one generic product to another since all generic products of a given AED are considered the same. Although switches between generic products are not currently limited in many countries (e.g., the USA), Fig. 2 shows that switches between bioequivalent generic products could potentially lead to larger changes in AED plasma levels and exposure than the brand-to-generic switch. Thus, generic products with low WSV may not be bioequivalent to one another despite the fact that they are all bioequivalent to the same reference product.

Even though the FDA data (Table 2) indicate that bioequivalent generic products are therapeutically equivalent to their respective reference (brand) products, the Danish National Drug Agency agreed to narrow the 90 % CI BE limits for automatic substitution of generic AED products, primarily lamotrigine, from the traditional 80–125 % to 90–111 % [49, 50]. This raises the question of whether narrowing the BE limits for automatic substitution of all generic AEDs to 90–111 % would resolve AED generic product substitution issues and also the question of whether generic AEDs will have to meet additional BE criteria. The FDA is currently exploring the pros and cons of narrowing the BE acceptance criteria for the 90 % CI for AUC of certain drugs [12]. The FDA's current position is that although tightening the criteria (e.g., 90–111 %) may sound desirable, such a change in regulatory standards must be based on scientifically justified, objective criteria to ensure that AEDs are not regulated in an arbitrary and capricious manner. An FDA internal analysis of the BE data of approved generic drug products (including AEDs) indicates that most could meet a tighter BE standard (90 % CI) of 90–111 % as opposed to the current 80–125 % acceptable criteria [12].

As pointed out previously, AEDs are not highly variable drugs [5] and, except for phenytoin, AEDs do not have a narrow therapeutic plasma concentration range [51, 52]. A recent ILAE position paper states that all AEDs except phenytoin and including carbamazepine [53] and oxcarbazepine have a wide therapeutic plasma range [52].

The package insert of Advagraf, a once-daily oral formulation of the immunosuppressant tacrolimus, clearly states that switching of IR or ER formulations of tacrolimus is unsafe and can lead to graft rejection or increased incidence of adverse reactions [54]. Therefore, patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimens [54]. Similar restrictions of formulations switch might be considered to difficult-to-treat epileptic patients that it took a long time to bring them to a seizure-free situation. This will minimize these patients' morbidity and their greater use of health care resources [55, 56].

As far as formulation switches go, FDA approval of NDAs for MR products is based on a documented, adequate relationship between drug plasma exposure (e.g., AUC, C_{max}) and clinical response [45]. In the case of switching from an IR to an MR product, the key question is whether an adequate exposure–response relationship has been established for the approved (innovative) IR product. If an adequate PK–pharmacodynamic (PD) relationship has been established, then no clinical efficacy trials may be required, only three PK studies: two single-dose studies under fasted and fed conditions and one multiple-dose study at steady-state. However, in the case of AEDs, it is likely that an adequate exposure–response relation has not been established, and, therefore, a single efficacy trial may be requested in the addition to the above three PK studies. In the case of AED MR products, the NDA sponsor would opt to conduct placebo-controlled trials, as there are no requirements to conduct head-to-head comparisons between the MR and IR products [45].

A recent Consensus Statement of scientists from academia and the FDA concluded that in the case of monophasic MR products, the current regulatory approaches and criteria for BE evaluation were considered adequate for therapeutic equivalence assessment [45]. However, additional measures (metrics) such as partial AUC may occasionally be needed for BE assessment of multiphasic MR products [45]. Partial AUC provides information about the shape of the drug concentration–time profile. The cutoff for partial AUCs may be based on the PK–PD correlation of the MR drug products. The acceptable BE range may be based on the known WSV of the reference product's partial AUC. Recently, partial AUC analysis was used for PK evaluation of a novel once-daily topiramate (TPM)-ER formulation (USL255) in comparison to TPM-IR [57]. The 90 % CIs of the USL255/TPM-IR GMR (determined for various partial AUC time intervals) were wholly contained between the 80–125 % BE limits [57]. This substantiates the study's conclusion that USL255 is pharmacokinetically equivalent to TPM-IR in systemic exposure.

Currently, the first AED ER product found to be bioequivalent in its AUC to the existing brand IR formulation is required by FDA and EMA to perform a clinical trial. This poses the question of why when the slower absorption rate of the first AED ER product did not affect its extent of absorption there is also a need for this ER product to demonstrate superior efficacy compared with placebo.

It should be reminded that possible failure to show bioequivalence between generics in an indirect comparison is not evidence that they are not bioequivalent [58]. In the past, efforts have been made to investigate the relative bioavailability between generics (such as artemether/lumefantrine tablets and tacrolimus capsules) by adjusted indirect comparison [59, 60]. These studies showed that the generic products can be bioequivalent with the reference product, but also with each other [59, 60]. Nevertheless, the current study applies simultaneous simulations of the relationship between T1 vs. R, T2 vs. R, and consequently T1 vs. T2 in order to quantify the switchability of generic products.

5 Conclusions

This study provided critical enlightenment on several important issues regarding generic products of AEDs. First, it was highlighted that the criteria for BA and BE and the statistical analysis involved in their analysis are different. Second, two generic formulations that meet regulatory approval requirements for generics, by being bioequivalent to the innovative AED, may or may not be bioequivalent to each other. Simulated data were used to quantify the effect of interchangeability. Our results verified the fact that all generic AED products should not be regarded as equal or as therapeutically equivalent products. Generic product switchability is a critical issue in epilepsy since, unlike for antihypertensive or hypoglycemic drugs, in AEDs there are no biological markers for efficacy (or lack of efficacy) except seizure counts or being seizure-free or not. Third, a switch from an IR formulation to an MR product, which comprises ER or DR formulations, is not regarded as a generic switch, but rather a formulation switch. Consequently, additional BE criteria for switching to MR products might be needed.

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