European Journal of Pharmaceutical Sciences 50 (2013) 476–483

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Quantitative assessment of the switchability of generic products

Vangelis Karalis [a,*], Meir Bialer [b], Panos Macheras [a]

[a] Laboratory of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, 15771 Athens, Greece
[b] Institute of Drug Research, School of Pharmacy and David R. Bloom Center for Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel

ARTICLE INFO

Article history:
Received 28 May 2013
Accepted 13 August 2013
Available online 24 August 2013

Keywords:
Bioequivalence
Switchability
Pharmacokinetic simulations
Generics
Narrow therapeutic index drugs
Conditional probability

ABSTRACT

Generics are usually considered to exhibit comparable *in vivo* properties in terms of efficacy and safety and for this reason are intended to be interchangeable with the reference product. The aim of this study is to provide a quantitative picture of the switchability problem between two generics and to introduce the concept of conditional probability of bioequivalence (BE) acceptance.

Monte Carlo simulations were performed to examine all possible relationships between the tested products. Four types of percent BE acceptances are defined and evaluated: (a) % BA1, when generic T_1 is compared to the R product, (b) % BA2, in cases of comparison of generic T_2 with the R product, (c) % BA21, when generic T_2 is compared to another generic T_1, and finally (d) % BA21C which is the conditional probability of percent bioequivalence acceptance of generic T_2*versus* another generic T_1 given that both T_1 and T_2 are declared bioequivalent to the same R formulation. The simulations were expanded to study concomitantly the performance of T_1 and T_2 when compared to the same R formulation. In each case, the 2×2 cross-over design was used and evaluation of BE was based on the classic BE limits (0.80–1.25) and the stricter BE limits (0.90–1.11) for narrow therapeutic index (NTI) drugs. A number of 24 and 48 subjects were assumed to participate in the simulated trials, while the coefficient of variation for the within-subject variability (CVw) was 20% and 40%. A number 40,000 BE trials were simulated under each condition. The T_1/R and T_2/R ratios ranged from 0.80 to 1.25 using a step of 0.05.

Even though two generics (T_1 and T_2) can be declared bioequivalent to the same R product, this does not ensure that they are always mutually bioequivalent. On the contrary, two generic products which differ substantially from the R product can still have a high probability to be truly interchangeable. The two generics (T_1 and T_2) can be switched from one to another when the T_1/R and T_2/R ratios are close to the same value, the CVw of the drug is low, and each BE study of T_1–R and T_2–R was conducted using a relatively large number of subjects. In the same context, two generic NTI drugs which differ more than 10% from the R product can still be declared bioequivalent to one another depending on the relative T_1/R and T_2/R ratios. Switchability between generics assessed at the 0.90–1.11 interval is safer, but not always ensured.

1. Introduction

Prescription of generic drug products exerts a predominant role among the strategies to lower medication costs (Sisko et al., 2010; Barros, 2010). Generics are medicinal products which have the same qualitative/quantitative composition in the active compound(s), the same pharmaceutical form with the innovator medicinal product, and whose bioequivalence (BE) with the innovator product has been proved by appropriate bioavailability studies (Directive 2001/83/EC of the European Parliament). A test (T) product is considered bioequivalent to the reference (R) formulation, if after administration in the same molar dose, exhibits similar extent and rate of absorption to the leading brand name product (EMA, 2010).

Bioequivalence assessment, which is usually applied to the approval process of the generics, relies on the fundamental

Abbreviations: BA1 (%), percent bioequivalence acceptance of generic T_1 when compared to the reference product; BA2 (%), percent bioequivalence acceptance of generic T_2 when compared to the reference product; BA21 (%), percent bioequivalence acceptance of generic T_2*versus* another generic T_1; BA21C (%), percent bioequivalence acceptance of generic T_2*versus* another generic T_1 given that both T_1 and T_2 are declared bioequivalent to the same reference formulation; BE, bioequivalence; CI, confidence interval; CVw, coefficient of variation of the within-subject variability; GMR, geometric mean ratio of the bioequivalence metric for the two products (T over R); *N*, sample size; NTI, narrow therapeutic index drug; R, reference product; T, test product (generic); T_1, generic first approved; T_2, generic assessed after the approval of the first generic; θ, acceptance limit of bioequivalence imposed by the regulatory authorities.

* Corresponding author. Address: Laboratory of Biopharmaceutics - Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece. Tel.: +30 2107274267; fax: +30 2107274027.

E-mail address: vkaralis@pharm.uoa.gr (V. Karalis).

0928-0987/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejps.2013.08.023

assumption that two drug preparations are regarded as bioequivalent if their concentration–time profiles are similar enough to ensure comparable clinical performance (Carpenter and Tobbell, 2011; Niazi, 2007). Thus, generics are usually intended to be interchangeable with the reference product and they are considered to exhibit comparable *in vivo* properties in terms of efficacy and safety (EMA, 2010; WHO, 2006).

It is worth mentioned that the underlying assumption in BE is 'equivalence' and not 'equality' between two formulations. If the mathematical term of 'equality' was applicable in case of generics, then it would imply that: when a generic product T_1 is equal to the reference product and when generic product T_2 is equal to the same reference product, then product T_1 will be equal to T_2. Presumably, this analogy cannot be deduced for BE (Davit et al., 2009). A high risk for therapeutic failure due to lack of bioequivalence between two generic products of the same drug can be observed when generic products T_1 and T_2 differ in opposite directions, i.e., T_1 is lower than R, while T_2 is higher than R.

The issue of generic products becomes even more crucial for narrow therapeutic index drugs (NTI) such as antiepileptics (Bialer, 2007; Bialer and Midha, 2010; Gange et al., 2010; Kesselheim et al., 2010; Kraus et al., 2011; Moore et al., 2010; Privitera, 2008). For example, the switch between generic products poses a problem to epileptic patients, since in epilepsy there is no surrogate marker, except from seizure counts, to differentiate between therapeutic success and failure after a generic switch. A situation where a seizure-free patient starts to have seizures following a generic switch might be harmful and non-reversible (Berg, 2007; Berg et al., 2008a; Berg et al., 2008b). Thus, there is a need to differentiate between generic products that are not only bioequivalent to the reference product, but also bioequivalent to one another and consequently, are switchable.

The aim of this study is to examine quantitatively how 'similar' to one another are two generic products that are bioequivalent to the same reference product. Monte Carlo simulations were used to examine all possible relationships between the tested products. This work introduces the concepts of: (a) Multiple comparisons at the same time, namely, to make comparisons for three products in pairs of two according to a specific BE framework; and (b) Conditional probability of BE acceptance which reflects the % acceptance of generic T_2*versus* another generic T_1 given that both T_1 and T_2 are declared bioequivalent to the same R formulation. This study displays results for different scenarios that may be encountered in practice both for the typical as well as the NTI drugs. Subsequently, it draws conclusions on generics' switchability and thus provides knowledge on when or not a switch from one generic to another can be feasible.

2. Methods

2.1. Bioequivalence assessment

2.1.1. General

Assessment of BE is classically based on the concept of average bioequivalence. In this case, a T product is considered bioequivalent to the R product if the 90% confidence interval (CI) around the difference (in the *ln*-domain) of a mean bioequivalence metric is within predefined acceptance limits (EMA, 2010; FDA, 2001; FDA, 2003; Karalis and Macheras, 2012). It has been shown that the 90% CI approach is equivalent to the two one-sided *t*-test procedure (Schuirmann, 1987). The definition of average BE can be expressed mathematically by the following equation:

$$-\ln(\theta) \leqslant m_T - m_R \leqslant \ln(\theta) \quad (1)$$

where θ refers to the acceptance limit imposed by the regulatory authorities. The terms m_T and m_R are the mean (in *ln*-scale) of the pharmacokinetic metric for T and R, respectively. Classically, the acceptance range is set equal to 0.80–1.25. In case of NTI drugs (e.g. many antiepileptics) a stricter acceptance interval (0.9000–1.1111) is suggested for AUC and in some cases for Cmax (EMA, 2010). For simplicity reasons, the narrow acceptance limits will be quoted in this study as 0.90–1.11.

2.1.2. Types of BE acceptance

The aim of this paper is to examine how 'similar' to one another are two generic products, T_1 and T_2, which are also assessed *versus* the same R product. In order to deal with this issue, the concept of multiple comparisons at the same time is introduced and all possible relationships between T_1 vs. R, T_2 vs. R, and T_2 vs. T_1 are evaluated.

Thus, four types of BE acceptances are defined and evaluated:

i. % BA1: percent bioequivalence acceptance of generic T_1 when compared to the R product.
ii. % BA2: percent bioequivalence acceptance of generic T_2 when compared to the R product.
iii. % BA21: percent bioequivalence acceptance of generic T_2*versus* another generic T_1.
iv. % BA21C: percent bioequivalence acceptance of generic T_2 *versus* another generic T_1 given that both T_1 and T_2 are declared bioequivalent to the same R formulation.

It should be underlined that the relationship between T_1 and T_2 is assessed in two different ways; either as the typical probability of occurrence of an outcome (type 'iii') or the 'conditional probability' given that another outcome is already satisfied (type 'iv').

2.2. Simulations

2.2.1. 2 × 2 BE study

Monte Carlo simulations were performed to examine all possible relationships between the tested products. For each comparison between the T (T_1 or T_2) and the R product, the typical two-period, two-sequence, cross-over design was used. A number (N) of 24 and 48 subjects were assumed to participate in the simulated trials. In each simulated crossover study, the geometric mean ratio (GMR) of the bioequivalence metric was estimated. 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 (Schuirmann, 1987; Midha et al., 1998).

The simulated pharmacokinetic parameter values were generated assuming *log*-normal distribution (Tothfalusi et al., 2001; Tothfalusi and Endrenyi, 2003; Karalis et al., 2004, 2005, 2011, 2012). Two levels (20% and 40%) for the coefficient of variation of the within-subject variability (CVw) were considered. In addition, a sole set of using *N*=24 and five levels of CVw (5%, 15%, 25%, 35%, and 45%) were also simulated.

2.2.2. The condition of two T products and one R formulation

The main purpose of this study is to make multiple comparisons of T_1–T_2–R at the same time, namely, to make comparisons for three products in pairs of two according to a specific BE framework. In order to accomplish this task, the simulation work was expanded to study concomitantly the performance of T_1 and T_2 when compared to the same R formulation. For this reason, not only the same 2 × 2 design was used for all possible combinations (T_1–R, T_2–R, and T_2–T_1), but also all comparisons were made concomitantly. This implies that the T_1, T_2, and R estimates used for either the T_1–R or T_2–R comparison were also included in the T_2–T_1 comparisons. The values in the ANOVA effects (Sequence, Period, and Subject) remained unaltered for all comparisons. The only necessary exception was the 'Period' effect in case of T_2–T_1 comparison,

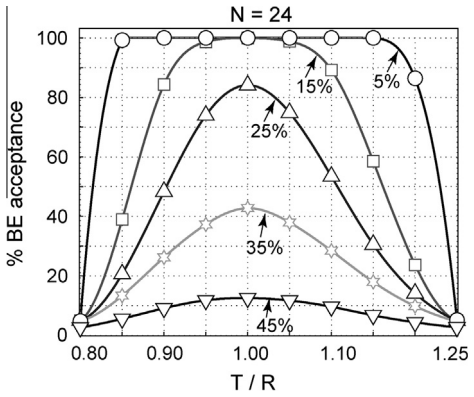

Fig. 1. Percent of bioequivalence (BE) acceptance of a generic (T) medicinal product *versus* the reference (R) formulation. The% numbers placed next to the curves refer to the within-subject variability used in the simulations. *Key*: BE limits are 0.80–1.25; sample sizes (*N*) is 24; geometric mean ratio of T/R ranges from 0.80 to 1.25.

where T_1 administration was unavoidably set to a different period than that used in the T_1–R. However, this arrangement does not lead to any changes in the results.

The theoretically true GMR values for each T_1/R and T_2/R ratio ranged from 0.80 to 1.25 using a step of 0.05. In other words, 10 GMR values for the T_1/R and 10 GMR values for the T_2/R ratio were simulated; thus, a total of $10 \times 10 = 100$ combinations of T_1/R and T_2/R ratios were examined under a specific level of CVw and sample size. For reasons of simplicity in this study the GMR ratio of T_1–R, T_2–R, and T_2–T_1, will be simply termed as T_1/R, T_2/R, and T_2/T_1, respectively.

For each combination of T_1/R and T_2/R ratios a number of 40,000 BE trials were simulated and the percentage of each BE acceptance (% BA1, % BA2, % BA21, % BA21C) was recorded. The entire programming work was implemented in MATLAB® (The MathWorks, Inc.).

The reason for including all these combinations of values was to obtain results for many different scenarios, which may be encountered in practice. This will allow us to draw specific conclusions on generics' switchability. Besides, in certain cases, like when CVw=40%, the possibility of using scaled bioequivalence approaches could be possible (EMA, 2010; Haidar et al., 2008a, 2008b; FDA, 2011). However, it was not the purpose of this study to assess every possible BE approach (e.g. classic, scaled, two-stage designs etc.), but to focus only on drugs' switchability using the classic average BE approach.

3. Results and discussion

The percent of BE acceptance of a generic product *versus* the leading brand name formulation is shown in Fig. 1. The sample size is set equal to 24 and five levels of CVw (5%, 15%, 25%, 35%, and

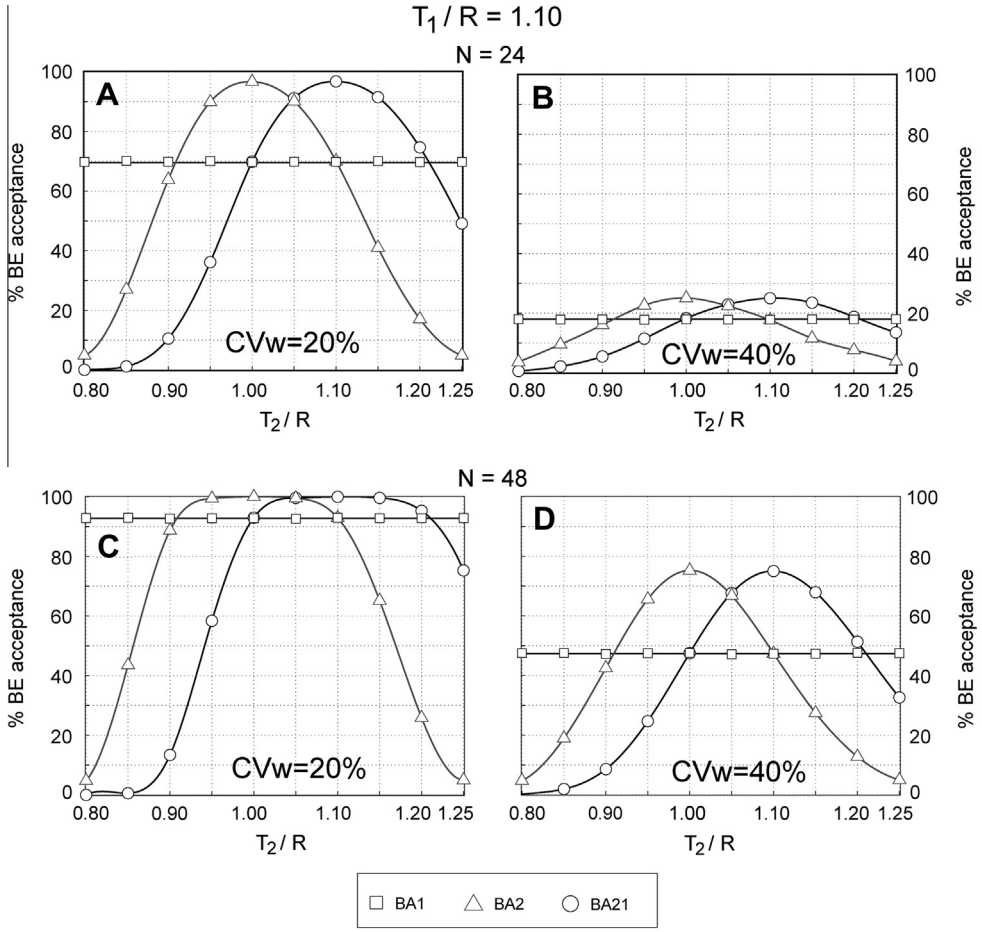

Fig. 2. Percent of bioequivalence (BE) acceptance when two generics (T_1, T_2) are compared to the same reference (R) and to one another as a function of the T_2/R ratio. Three types of BE acceptances are depicted in each plot: (i) % BA1, percent BE acceptance of generic T1 when compared to the R, (ii) % BA2, percent BE acceptance of generic T_2 when compared to the R, and (iii) % BA21, percent BE acceptance of T_2*versus* T_1. *Key*: BE limits are 0.80–1.25; sample sizes (*N*) are 24 and 48; coefficient of variation values of within-subject variability (CVw) are 20% and 40%; the geometric mean ratio of T_1/R is set to 1.10; geometric mean ratio of T_2/R ratio ranges from 0.80 to 1.25.

45%) are examined. Fig. 1 illustrates the general profile of% BE acceptance *versus* the T/R ratio in case of drugs with different within-subject variability values. Visual inspection of Fig. 1 reveals that the highest% BE acceptance is observed when the two formulations, T and R, are identical, namely, the GMR is equal to one. As GMR deviates from unity, the% BE acceptance declines. In addition, as CVw increases, the% BE acceptance decreases, which means that it becomes more difficult to prove bioequivalence. In case of highly variable drugs, namely, when CVw is greater than 30%, the probability for two drug products to be declared bioequivalent becomes rather low even when these two products do not differ at all (i.e. when T/R = 1). This attribute simply implies that more subjects should be recruited in order to increase the statistical power of the study. Alternatively, different BE methods could be applied, e.g. scaled BE approach (see 'Methods' section).

Fig. 2 presents the percent of BE acceptance when two generic products (T_1, T_2) are compared to the same R formulation and to one another as a function of the T_2/R ratio. The number of subjects was equal to 24 and 48, while two levels of CVw (20% and 40%) were considered. In all cases, the T_1/R value was equal to 1.10.

Three types of% BE acceptances are depicted in each plot: % BA1, % BA2, and % BA21. Plausibly, the% BA1 is constant over all T_2/R values, since the T_1/R ratio is always 1.10 and the% BE acceptance of T_1 vs. R is not influenced by the T_2/R ratio. Depending on the relative T_1/R and T_2/R ratios, the % BA21 acceptance can either be higher than or lower to the% BE acceptances of T_1–R and T_2–R. The first situation reveals a positive outcome which implies that the two generic products are more similar to one another than to the brand name drug. However, the second condition, where the % acceptance of T_2/T_1 is lower than that for T_1/R and/or T_2/R, is in essence the reason why concerns are raised about the switchability of generics.

Another interesting finding is the fact that the % BA2 and % BA21 curves exert their peak at different T_2/R values. Plausibly, the % BA2 curve shows its peak value when T_2/R is equal to 1. The % BA21, namely, the % BE acceptance of T_2 vs. T_1, gets its highest value when T_2/R becomes equal to T_1/R. In the case of Fig. 2 this is observed when T_2/R gets equal to 1.10.

Visual inspection of Fig. 2 reveals that the % BA2 and % BA21 curves are similar in terms of the general profile and the peak % acceptance values. The only difference is the exact location of the peak, namely, the T_2/R ratio value at which the highest % acceptance is observed. Depending on the relative values of the T_1/R and T_2/R ratios, the power curve of % BA21 can be located at the left, at the right or being superimposed to the % BA2 curve. As it is expected, when CVw increases, all types of BE acceptance (% BA1, % BA2, and % BA21) decrease. In the same vein, as N rises, these three types of BE acceptance also increase.

Fig. 3 presents the percent of BE acceptance, when two generic products are compared one to another as well as to the same reference product, as a function of their T_2/T_1 ratio. In all cases,

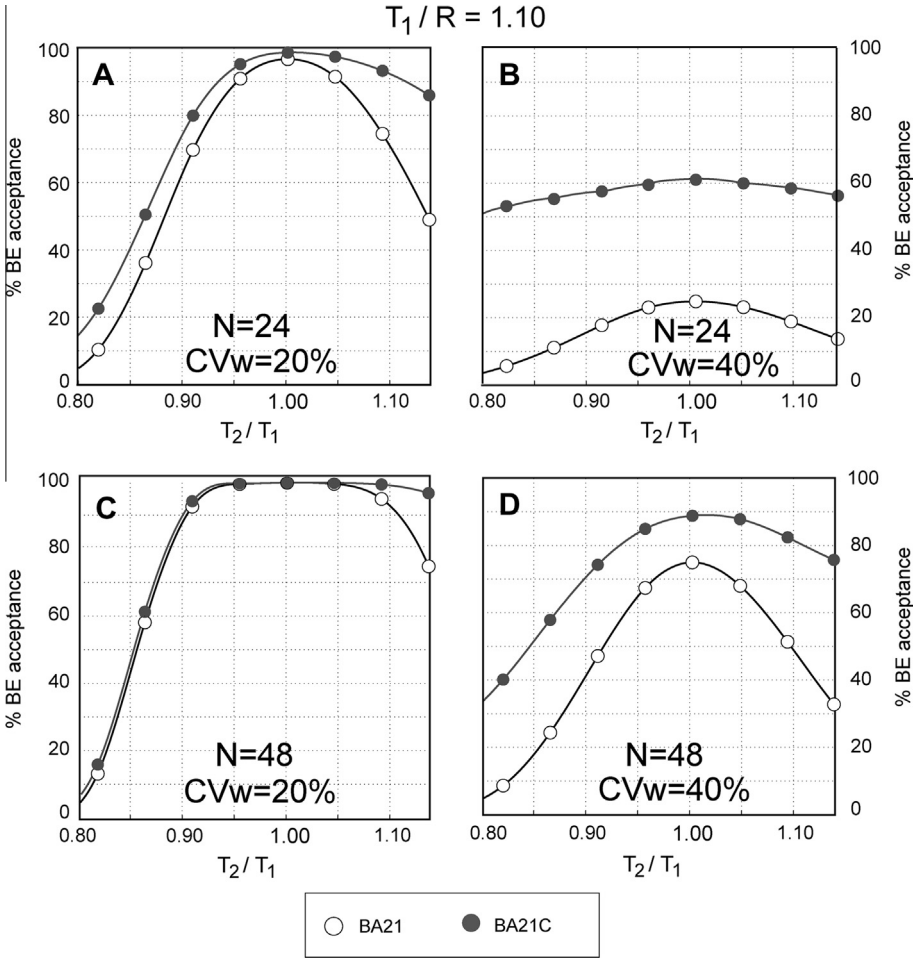

Fig. 3. Percent of bioequivalence (BE) acceptance when two generics (T_1, T_2) are compared to one another as a function of their geometric mean ratio T_2/T_1. Two types of BE acceptances are depicted in each plot: (i) % BA21, percent BE acceptance of T_2*versus* T_1 and (ii) % BA21C, percent BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 were declared bioequivalent to the same R. *Key*: BE limits are 0.80–1.25; sample sizes (*N*) are 24 and 48; coefficient of variation values of within-subject variability (CVw) are 20% and 40%; Geometric mean ratio of T_1/R is set to 1.10; geometric mean ratio of T_2/R ratio ranges from 0.80 to 1.25.

the GMR ratio of T_1/R is set to 1.10. Two types of BE acceptances are depicted in each plot: (i) the percent BE acceptance of T_2*versus* T_1 (i.e.% BA21) and (ii) the percent BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 are declared bioequivalent to the same R (i.e. % BA21C). This figure introduces the concept of 'conditional probability' of BE acceptance. This new term refers to the probability of BE acceptance of a generic T_1*versus* another generic T_2 given that both generics can be declared bioequivalent to the same R. In both cases (% BA21 and % BA21C), the highest acceptance values are observed when the T_2/T_1 ratio is equal to unity, regardless of the individual T_1/R and the T_2/R ratios. Plausibly, the T_2/T_1 ratio arises by dividing T_2/R with T_1/R and the impact of R is excluded.

Generally speaking, as CVw increases, both % BA21 and % BA21C decrease, but % BA21C to a less extent. In the same context, as N rises, both% BA21 and% BA21C increase. It should be highlighted that the % BA21C values are always higher than or at least equal to the% BA21 estimates. This issue actually arises from the nature of the % BA21C term which presupposes that the two generic products are bioequivalent to the brand name product. The major discrepancy between % BA21 and % BA21C is observed in case of highly variable drugs with relatively low sample size (Fig. 3B). On the contrary, the % BA21 and % BA21C become quite similar when the BE study is overpowered (Fig. 3C).

The most important aspect of Fig. 3 is the fact that it quantifies the following well-known issue: Even though, two generic products (T_1 and T_2) can be bioequivalent to the same reference product, this does not ensure that these two generic products will be bioequivalent to one another too. The probability that these two generic products (T_1 and T_2) will be bioequivalent to one another depends on: (a) the relative difference of each one from the R (i.e., T_1/R and T_2/R ratios), (b) the CVw of the study, and (c) the sample size of the BE study used. It is possible that% BA21C can be as high as 100% (e.g., Fig. 3A and C), but there also cases where it can also be rather low. In other words, even though two generic products can be found to be bioequivalent to the same reference product, there is always a risk (low or high) that these two products will not be switchable. Two generic products (T_1 and T_2) can be switched from to one another when as many as possible of the following criteria are fulfilled: (a) the T_1/R and T_2/R ratios are close to the same value, (b) the CVw of the drug is low, and (c) each BE study of T_1–R and T_2–R was conducted using a relatively large number of subjects.

Fig. 4 is similar to Fig. 3, but now several cases of T_1/R ratios are studied. Similarly, Fig. 4 illustrates the percent of BE acceptance when two generic products are compared to one another as a function of their geometric mean ratio T_2/T_1. Two types of BE acceptances are depicted in each plot: percent BE acceptance of T_2*versus* T_1 (i.e. % BA21) and percent BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 are declared bioequivalent to the same R (i.e. % BA21C). Further to the conclusions from Fig. 3, several other findings can be drawn from Fig. 4. The highest BE acceptance is observed when the T_2/T_1 ratio is equal to unity, no matter how large or small is the T_1/R ratio. Depending on the relative T_1/R and T_2/R ratios, two generics products which differ substantially from the R product can have a high probability to be fully interchangeable. The% acceptance profiles of % BA21 and % BA21C remain unaltered regardless of the absolute T_1/R value.

In case of the NTI drugs, the EMA recommends the use of the 0.90–1.11 acceptance criterion (EMA, 2010). Switchability of NTI

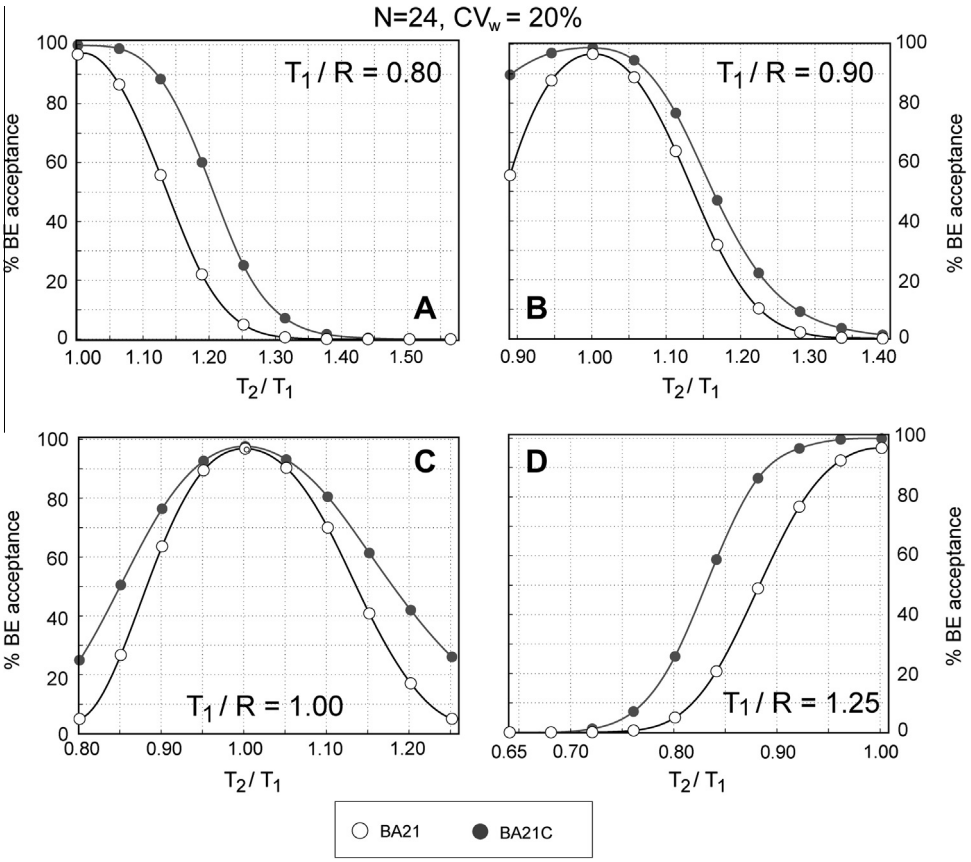

Fig. 4. Percent of bioequivalence (BE) acceptance when two generics (T_1, T_2) are compared to one another as a function of their geometric mean ratio T_2/T_1. Two types of BE acceptances are depicted in each plot: (i) % BA21, percent BE acceptance of T_2*versus* T_1 and (ii) % BA21C, percent BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 were declared bioequivalent to the same R. *Key*: BE limits are 0.80–1.25; sample size (*N*) is equal to 24; coefficient of variation of within-subject variability (CVw) is 20%; geometric mean ratio of T_1/R is set to: 0.80, 0.90, 1.00, and 1.25; geometric mean ratio of T_2/R ratio ranges from 0.80 to 1.25.

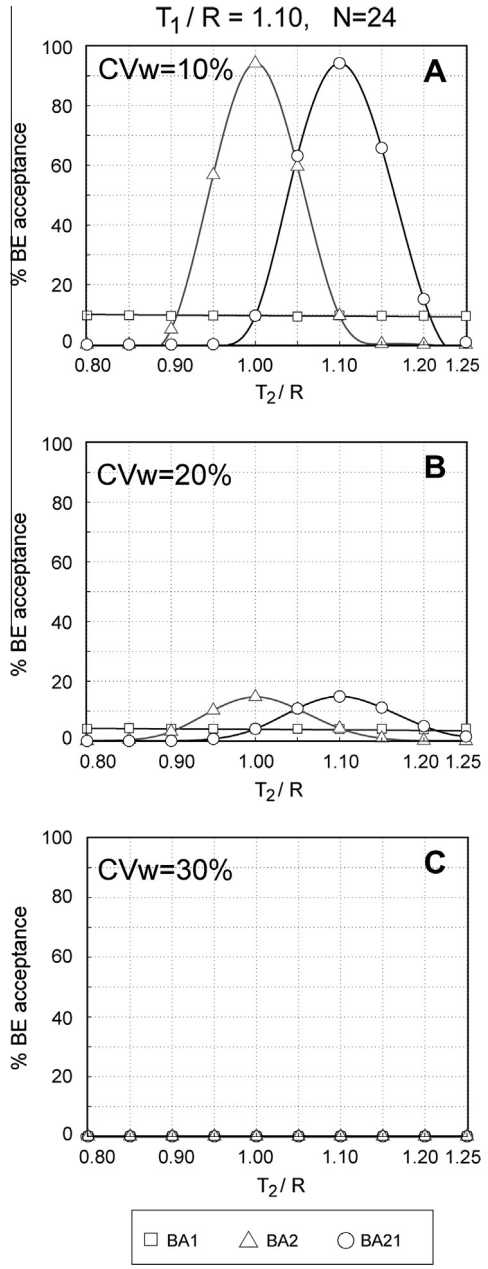

Fig. 5. Percent of bioequivalence (BE) acceptance when two narrow therapeutic index generics (T_1, T_2) are compared to the same reference (R) and to one another as a function of the T_2/R ratio. Three types of BE acceptances are depicted in each plot: (i) % BA1, percent BE acceptance of generic T_1 when compared to the R, (ii) % BA2, percent BE acceptance of generic T_2 when compared to the R, and (iii) % BA21, percent BE acceptance of T_2*versus* T_1. *Key*: BE limits are 0.90–1.11; sample size (*N*) is equal to 24; coefficients of variation of within-subject variability (CVw) are 10%, 20%, and 30%; Geometric mean ratio of T_1/R is set to 1.10; geometric mean ratio of T_2/R ratio ranges from 0.80 to 1.25.

drugs is of paramount importance and for this reason our simulations were expanded to NTI drugs. Fig. 5 depicts the percent of BE acceptance when two NTI generic products (T_1, T_2) are compared to the same R and to one another as a function of the T_2/R ratio. This is similar to Fig. 2, but now the situation is stricter, since the narrow BE acceptance limits (0.90–1.11) are used. Three types of BE acceptances are depicted in each plot: (i) % BE acceptance of generic T_1 when compared to the R (% BA1), (ii) % BE acceptance of generic T_2 when compared to the R (% BA2), and (iii) % BE acceptance of T_2-*versus* T_1 (% BA21).

Visual inspection of Fig. 5 reveals that the % BA1 is constant over all T_2/R values. Plausibly, this is due to the fact that T_1/R is always the same and the % BE acceptance of T_1*vs.* R is not influenced by the T_2/R ratio. The % BA2 and % BA21 curves exert their peak at different T_2/R values. As it is expected the % BA2 curve shows its peak value when T_2/R is equal to 1, since it is not related to the T_1/R ratio. The % BA21, namely, the % BE acceptance of T_2 vs. T_1, gets its highest value when T_2/R becomes equal to T_1/R (e.g. when T_2/R gets equal to 1.10).

In all cases, the % BA2 and % BA21 profiles look similar; both the shape and the peak % acceptance values are identical. The only difference is the T_2/R ratio value at which the peak % acceptance is observed. Depending on the relative values of the T_1/R and T_2/R ratios, the power curve of % BA21 can be located at the left, right or can be superimposed to the % BA2 curve. In the same context, based on the relative T_1/R and T_2/R ratios, the % BA21C and % BA21 acceptances can either exceed the % BE acceptance of T_1 vs. R or be lower than the % BE acceptance of T_1 vs. R. As it is already quoted in case of Fig. 2, the first situation is desired, while the second raises concerns about generics' switchability. Besides, the increase of % CVw leads to a decline of all types of % BE acceptance (% BA1, % BA2, and % BA21), whereas a rise of N results in an increase of % BA1, % BA2, and % BA21 types of BE acceptance.

It should be underlined that comparing the results for NTI drug products (Fig. 5) to the results for non-NTI drugs (Fig. 2) two important conclusions can be drawn: (a) The % acceptances for both % BA21C and % BA21 decline more rapidly as the test/reference ratio deviates from unity. In other words, the bell-shaped curves appear thinner for NTI drugs than typical drugs (shown in Fig. 2). (b) The % BE acceptances of NTI drugs are highly influenced by the level of CVw. In case of CVw = 30%, there appears to be no BE acceptance at all for NTI drugs, whereas % acceptances as much as 70% can be observed for typical drugs.

The % BE acceptance when two NTI generic products (T_1, T_2) are compared to one another as a function of their geometric mean ratio T_2/T_1 is shown in Fig. 6. Two types of BE acceptances are depicted in each plot: the % BE acceptance of T_2*versus* T_1 (% BA21) and the % BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 are declared bioequivalent to the same R (% BA21C). Similar conclusions as in Fig. 4 can be drawn, but now in Fig. 6 the situation is stricter since the narrow BE acceptance limits are used. As expected, the highest % BE acceptances are observed when the T_2/T_1 ratio is equal to unity, regardless of the T_1/R ratio. An important finding is the fact that depending on the relative T_1/R and T_2/R ratios, two NTI generic medicinal products which differ more than 10% from the R product can still be declared bioequivalent to one other, namely, being interchangeable (Fig. 6).

Fig. 6 is constructed using narrower T_1/R deviations than Fig. 4, namely, the T_1/R ratios range from 1.00 to 1.10 in Fig. 6, while the corresponding ratios range from 1.00 to 1.25 (and from 0.80 to 1.00) in Fig. 4. Comparing the results obtained for NTI drug products (Fig. 6) to those obtained for non-NTI drug products (Fig. 4), where the typical (0.80–1.25) BE limits were applied, several important conclusions can be drawn. The% acceptance profile between two NTI generics is narrower and stricter than the profiles shown in Fig. 4. For example, when T_1/R=1 and T_2/T_1=0.90, the % BA21C values are approximately 75% (Fig. 4) and 35% (Fig. 6) for the classic and the narrow BE limits, respectively. This issue arises from the fact that the 0.90–1.11 limits impose stricter assessment for NTI drugs which in turn implies that fewer differences are allowed between two generics.

It is usually anticipated that if two NTI generics, which are bioequivalent to the same R, are further compared to one another using the 0.90–1.11 limits, then the% probability of being bioequivalent to each other will be very high. In other words, it is often hypothesized that switchability between generics assessed at the

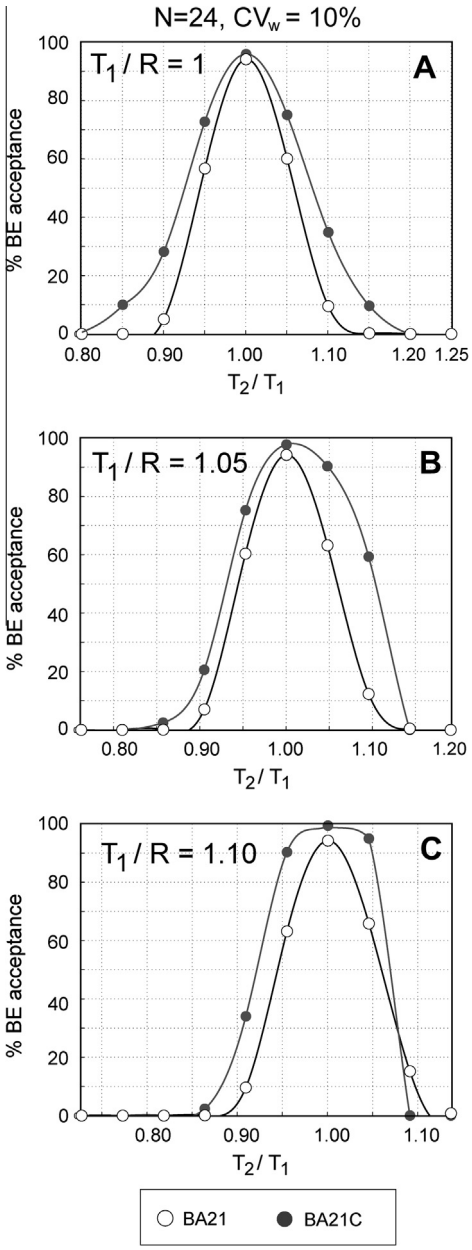

Fig. 6. Percent of bioequivalence (BE) acceptance when two narrow therapeutic index generics (T_1, T_2) are compared to one another as a function of their geometric mean ratio T_2/T_1. Two types of BE acceptances are depicted in each plot: (i) BA21, percent BE acceptance of T_2*versus* T_1 and (ii) BA21C, percent BE acceptance of T_2*versus* T_1 given that both T_1 and T_2 are declared bioequivalent to the same R. *Key*: BE limits are 0.90–1.11; sample size (*N*) is equal to 24; coefficient of variation of within-subject variability (CVw) is 10%; geometric mean ratio of T_1/R is set to: 1.00, 1.05, and 1.10; geometric mean ratio of T_2/R ratio ranges from 0.80 to 1.25.

0.90–1.11 interval is safer. However, the truth is that even though lower differences in the GMR estimates are allowed for NTI drugs, than those drugs assessed with the 0.80–1.25 criterion, the two NTI generics are not always switchable.

4. Conclusions

The aim of this study was to provide a quantitative assessment of the switchability of generic products. In order to unveil the possible relationships, a new simulation framework was developed to allow multiple comparisons of products at the same time as well as to allow the introduction of the concept of conditional probability of BE acceptance. Many combinations of conditions are simulated in order to make inferences for many situations that may be encountered in practice and to draw conclusions on generics' switchability.

Basic conclusions derived from this study are the following:

(a) Depending on the relative T_1/R and T_2/R ratios, the % BE acceptance of T_2–T_1 can either exceed the% acceptance of T_1–R, T_2–R or be lower than the % acceptance of T_1–R, T_2–R.
(b) Two generic products which differ substantially from the R product can still have a high probability to be truly switchable.
(c) The conditional probability of % BE acceptance for T_2/T_1 is always higher than the simple probability of % acceptance for T_2/T_1. In other words, this study quantitatively showed that it is more likely for two drug products to be truly bioequivalent, when they have been proved equivalent to the same reference product.
(d) Two generic products (T_1 and T_2) can be switched from one to another when the T_1/R and T_2/R ratios are close to the same value, the CVw of the drug is low, and each BE study of T_1–R and T_2–R was conducted using a relatively large number of subjects.
(e) In case of NTI drugs, the % BE acceptance of T_2–T_1, either conditional or simple, declines more rapidly and it is more influenced by CVw than the % acceptance of products assessed with the 0.80–1.25 criterion.
(f) NTI drugs which differ more than 10% from the R product can still be declared bioequivalent to one another depending on the relative T_1/R and T_2/R ratios.
(g) Switchability between generics assessed at the 0.90–1.11 interval is safer, but not always ensured.

References

Barros, P., 2010. Pharmaceutical policies in European countries. Adv. Health Econ. Health Serv. Res. 22, 3–27.
Berg, M.J., 2007. What is the problem with generic antiepileptic drugs? Neurology 68, 1245–1246.
Berg, M., Gross, R., Tomaszewski, K., Zingaro, W., Haskins, L., 2008a. Generic substitution in the treatment of epilepsy: case evidence of breakthrough seizures. Neurology 71, 525–530.
Berg, M., Gross, R., Haskins, L., Zingaro, W., Tomaszewski, K.J., 2008b. Generic substitution in the treatment of epilepsy: patient and physician perception. Epilepsy Behav. 13, 693–699.
Bialer, M., 2007. Generic products of antiepileptic drugs (AEDs): is it an issue? Epilepsia 48, 1825–1832.
Bialer, M., Midha, K., 2010. Generic products of antiepileptic drugs (AEDs): a perspective on bioequivalence and interchangeability. Epilepsia 51, 941–950.
Carpenter, D., Tobbell, D., 2011. Bioequivalence: the regulatory career of a pharmaceutical concept. Bull. Hist. Med. 85, 93–131.
Davit, B.M., Nakama, P.E., Buehle, G.J., Conner, D.P., Haidar, S.H., Patel, D.T., Yang, Y., Yu, L.X., Woodcock, J., 2009. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United State Food and Drug Administration. Ann. Pharmacother. 43, 1583–1597.
Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human.
EMA (European Medicines Agency), 2010. Committee for medicinal products for human use, CHMP. Guideline on the Investigation of Bioequivalence. London.
FDA (Food and Drug Administration), 2001. Center for Drug Evaluation and Research (CDER), statistical approaches to establishing bioequivalence. Rockville, MD.
FDA (Food and Drug Administration), 2003. Center for Drug Evaluation and Research (CDER), bioavailability and bioequivalence studies for orally administered drug products. General Considerations. Rockville, MD.
FDA (Food and Drug Administration), 2011. Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry on Bioequivalence. Recommendations for Progesterone Capsules.
Gange, J., Avron, J., Shrank, W., Schneeweiss, S., 2010. Refilling and switching of antiepileptic drugs and seizure-related events. Clin. Pharmacol. Ther. 88, 347–353.
Haidar, S., Davit, B., Chen, M., Conner, D., Lee, L., Li, Q., Lionberger, R., Makhlouf, F., Patel, D., Schuirmann, D., Yu, L., 2008a. Bioequivalence approaches for highly variable drugs and drug products. Pharm. Res. 15, 237–241.

Haidar, S., Makhlouf, F., Schuirmann, D., Hyslop, T., Davit, B., Conner, D., Yu, L., 2008b. Evaluation of a scaling approach for the bioequivalence of highly variable drugs. AAPS J. 10, 450–454.
Karalis, V., Macheras, P., 2012. Current regulatory approaches of bioequivalence testing. Expert Opin. Drug. Metab. Toxicol. 8, 929–942.
Karalis, V., Symillides, M., Macheras, P., 2004. Novel scaled average bioequivalence limits based on GMR and variability considerations. Pharm. Res. 21, 1933–1942.
Karalis, V., Macheras, P., Symillides, M., 2005. Geometric mean ratio-dependent scaled bioequivalence limits with leveling-off properties. Eur. J. Pharm. Sci. 26, 54–61.
Karalis, V., Symillides, M., Macheras, P., 2011. On the leveling-off properties of the new bioequivalence limits for highly variable drugs of the EMA guideline. Eur. J. Pharm. Sci. 44, 497–505.
Karalis, V., Symillides, M., Macheras, P., 2012. Bioequivalence of highly variable drugs: a comparison of the newly proposed regulatory approaches by FDA and EMA Pharm. Res. 29, 1066–1077.
Kesselheim, A., Stedman, M., Bubrick, E., Gange, J., Misono, A., Lee, J., Brookhart, M., Avron, J., Shrank, W., 2010. Seizure outcomes following of generic vs. brand-name antiepileptic drugs: a systmatic reveiw and metanalysis. Drugs 70, 605–621.
Kraus, G., Caffo, B., Chang, Y.T., Hendrix, C., Chuang, K., 2011. Assessing bioequivalence of generic antiepilepsy drugs. Ann. Neurol. 70, 221–228.
Midha, K., Rawson, M., Hubbard, J., 1998. Bioequivalence: switchability and scaling. Eur. J. Pharm. Sci. 6, 87–91.
Moore, N., Barndi, D., Beguad, B., 2010. Are generic drugs really inferior medicines? Clin. Pharmacol. Ther. 88, 302–304.
Niazi, S., 2007. Handbook of Bioequivalence Testing, first ed. Informa Healthcare, New York.
Privitera, M., 2008. Generic antiepileptic drugs: current controversies and future directions. Epilepsy Curr. 8, 113–117.
Schuirmann, D., 1987. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J. Pharmacokinet. Biopharm. 15, 657–680.
Sisko, A., Truffer, C., Keehan, S., Poisal, J., Clemens, M., Madison, A., 2010. National health spending projections: the estimated impact of reform through 2019. Health Aff. (Millwood) 29, 1933–1941.
Tothfalusi, L., Endrenyi, L., 2003. Limits for the scaled average bioequivalence of highly variable drugs and drug products. Pharm. Res. 20, 382–389.
Tothfalusi, L., Endrenyi, L., Midha, K., Rawson, M.J., Hubbard, J.W., 2001. Evaluation of the bioequivalence of highly-variable drugs and drug products. Pharm. Res. 18, 728–733.
WHO Technical report series 937, 2006. WHO Expert Committee on specifications for pharmaceutical preparations. 40th report. Geneva.