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Quantitative assessment of the switchability of generic products

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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.

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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,