Quantitative Assessment of the Interchangeability of Generic Products
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Purpose
To examine quantitatively how ‘similar’ is a new generic (T1) to an existing generic (T2) when both of them were proved bioequivalent to the same reference (R) product.

Methods
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 T1 is compared to the R product, b) BA2, in cases of comparison of generic T2 with the R product, c) BA21, when generic T2 is compared to another generic T1, and finally d) BA21C which is the conditional probability of percent bioequivalence acceptance of generic T2 versus another generic T1 when both T1 and T2 are declared bioequivalent to the same R formulation.

The typical 2x2 cross-over 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%) 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) took values of 20% and 40%. A number 40,000 BE trials were simulated under each condition.

Results
Even though two generics (T1 and T2) can be declared bioequivalent to the same R product, this does not ensure that they are always mutually bioequivalent. Depending on the relative T1/R and T2/R geometric mean ratios of the bioequivalence metrics, the BA21 and BA21C acceptances can exhibit two diametrically opposed performances. Both BA21 and BA21C may exceed the % acceptance of T1 vs. R which is a desired property for the switchability of generics. However, BA21 and BA21C values can be lower than the % acceptance of T1 vs. R, which may imply to a therapeutic failure of the patients.

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 T1/R and T2/R ratios.

Conclusion
This study provides a quantitative picture of the switchability problem introducing the concept of conditional probability of BE acceptance.