On the Bioequivalence and Interchangeability of Generic Products of Antiepileptic Drugs
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Purpose
To enlighten issues of bioequivalence and interchangeability of antiepileptic drug (AED) products.

Methods
Simulations 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 bioequivalence (BE) acceptance of generic AED products. The simulations were extended to investigate the comparative performance of two test formulations (T1 and T2) when compared to the same R product. The typical 2x2 cross-over design was used and evaluation of BE was based on the classic (80-125%) BE limits and the tighter (90-111.11%) BE limits applied to narrow therapeutic index drugs. The typical 2x2 design was simulated assuming a number of N=12, 24, 36, 48, and 60 subjects to participate in each simulated trial. The coefficient of variation values of within-subject variability were 10%, 20%, 30%, and 40%. Bibliographical BE data from FDA were compared with the simulation work.

Results
Simulated data were used to quantitate the problem of switchability of AEDs. The % probability of declaring BE between T1 and T2 can be higher than that observed for T1/R or T2/R, but there are conditions where the % probability of T1 and T2 being bioequivalent may be become rather low. The high % BE acceptance of T2 vs. T1 is in essence observed when these products differ less compared to their individual difference from R. The switches between bioequivalent generic AED products could potentially lead to larger changes in plasma levels and exposure than the brand-to-generic switch. The simulated results were compared with literature data on AEDs. The simulation work verified the clinical findings that not all generic AED products, bioequivalent to the same reference (brand) product, are bioequivalent to one another.

Conclusion
The results of this study showed in a quantitative manner that two generic formulations which meet regulatory approval requirements for generics, by being bioequivalent to the innovative AED, may not be bioequivalent to one another.