Bioequivalence and Interchangeability

The primary purpose of a bioequivalence study is to determine if two products containing the same active ingredient(s) in the same amount(s) can be used interchangeably. Contrary to prevailing opinion, we believe such studies are of doubtful value with regard to product substitution.

According to the current regulations, two drug products are deemed bioequivalent when their average bioavailabilities are similar. Appreciable individual differences in bioavailability are often tolerated as long as the overall means are similar. For example, in the proposed Bioequivalence Requirement for certain anticonvulsants[1] and tricyclic antidepressants[2], two products can be declared bioequivalent even though the relative bioavailability in half of the test subjects may differ by 25% or more. While intrasubject variation may contribute to the observed range in a given study, the possibility of a real difference among individuals cannot be denied.

In view of this fact, bioequivalence studies should be designed so that the mean subject response as a function of product performance can be assessed. In statistical terminology, this is called a subject-by-product interaction. The quantitative assessment of the significance of this effect requires a study design in which each product is replicated at least once in each subject. With this experimental design, differences in subject response due to product differences can be separated from those due simply to intrasubject variability. Unfortunately, this kind of design is rarely, if ever, used in bioequivalence studies[3]. Therefore, the frequency with which a subject-by-product interaction occurs among so-called bioequivalent products is not known.

Consider the implications of a situation where two products are deemed bioequivalent on average but a significant subject-by-product interaction exists. The substitution of one by the other would result in a loss of therapy or an increase in side effects in a significant fraction of the patient population. Thus, even though average bioequivalence may be an adequate guide to product selection on initiation of therapy, it is far from reassuring as the basis for product substitution.

Although the proposed change in experimental approach would represent an improvement in the state of the art, it is not without practical limitations. In particular, this approach only reduces the risk of inappropriate substitution for the population but fails to warrant the appropriateness of a particular substitution in a given patient. The only way to maintain adequate therapy with substitution is to retitrate the patient. This approach causes unnecessary burdens on both the patient and the physician. In our view, substitution, with proper assurances, is more costly than the difference in the price of a prescription.

In summary, if the intent of bioequivalent studies is to assure product interchangeability, the current criterion is necessary but insufficient. Additional studies with improved experimental designs would strengthen the scientific basis for substitution, but the continuation of proper therapy cannot be assured for all patients. The need for dose titration is understood on initiation of therapy and is similarly indicated upon product substitution. Common sense suggests that once titrated and maintained on a product, patients should remain on that product.

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[1] *Fed. Regist.*, 39677 (Aug. 6, 1977).
[2] *Fed. Regist.*, 6967 (Feb. 17, 1978).
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