Bioequivalence as a linear structural relationship: Estimation of formulation intersubject and intrasubject variability and a two-step method for assessing bioequivalence
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Bioequivalence data arising from a two-period crossover trial are routinely analyzed in an attempt to establish equivalence of the population means of a characteristic of the blood level curve, e.g., AUC, for each formulation. Current methods proposed only address equivalence of the formulation means, while both between subject (intersubject) and within subject (intrasubject) variations are often neglected and assumed to be equal for each formulation. Moreover, extended period crossover designs are usually recommended for estimating intersubject and intrasubject variability for each formulation. These designs can be lengthy, time-consuming, and costly when compared to the usual two-period crossover design.

Methods for estimating intersubject and intrasubject variability separately for both the reference and test formulations in a two-period crossover bioequivalence trial are presented. Assuming an underlying linear structural relationship of the response on the test formulation to that of the reference formulation, it is shown that separate estimates of intersubject and intrasubject variability may be obtained using the method of maximum likelihood. An approximate large sample $(1-2\alpha)100\%$ confidence interval for the ratio of the intersubject standard deviations is presented. The estimated coverage probability of the approximate interval is studied via simulation. Application of the methods are illustrated with data from an actual bioequivalence trial.

A new two-step decision rule which takes into account intersubject variability is considered. The two steps consist of (1) applying the current 90% parametric confidence interval method for equivalence of population means and (2) applying a 90% approximate confidence interval method for equivalence of population (intersubject) standard deviations. The ratio of the population standard deviations is shown to be the slope of the linear structural relationship. Bioequivalence is concluded if and only if both (1) and (2) result in an equivalence claim. The consumer risk of erroneously accepting bioequivalence and power of the two-step decision rule are computed via simulation. The new decision rule is applied on data from an actual bioequivalence trial.