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Letter

Reply to "Assessment of Variance in Bioavailability Studies: Comments on the Article by McNamara *et al.*" by Carl M. Metzler.

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The comments of Metzler (1) on the use of the "75/75" rule in the article by McNamara *et al.* (2) are, as a whole, appropriate. As pointed out by Metzler, the 75/75 rule does not *measure* variability, but rather is affected by variability. It is this aspect of the 75/75 rule which was alluded to in the article (2). Metzler notes that the outcome of the 75/75 rule is affected by differences in average bioavailability as well as by variability, and cites the comparison of product C to product F, for which the average AUC for product C was only 71% of the average AUC for product F, as a case where failure to pass the 75/75 rule could well have been due to the average difference. However, in the case of the comparison of product A to product D, for which the ratio of average AUCs was 87%, or the case of the comparison of product D to product F, for which the ratio of average AUCs was 90%, it seems apparent that variability of the test-to-reference AUC ratio from subject to subject was an important factor leading to failure to pass the rule.

Certainly the impact, the statistical basis (or lack thereof), and the interpretation of the 75/75 rule have drawn considerable attention in the area of bioequivalence testing (1,3–4). This concern over the use of this test has prompted the FDA to reconsider its position on the 75/75 rule. The FDA now relies on confidence interval methods or, equivalently, the two one-sided tests procedure (5) for establishing the bioequivalence of drug products and is no longer requesting the use of the 75/75 rule for this specific purpose.

Metzler goes on to suggest ways that intrasubject and intersubject variability could be assessed using the data from the original study. While his ideas have some merit, he omits some important details. The original study was a balanced six-product crossover study. If we assume that the random component of each observation consists of a subject effect, which is assumed to come from a population with variance σ^2_s, and an intrasubject "error" term, which is assumed to come from a population with variance σ^2 (which we will assume for the moment is the same for all six products), then the subjects (within sequences) and the "error" mean squares from the analysis of variance may be used, together, to obtain estimates of σ^2_s and σ^2. However, the subjects (within sequences) mean square, in and of itself, estimates $\sigma^2 + 6\sigma^2_s$. A more meaningful measure of intersubject variability would seem to be $\sigma^2 + \sigma^2_s$, the variance of a randomly chosen observation from a randomly chosen subject.

One may wish to relax the assumption concerning the variance of the "error" component of the observations to allow for the possibility that the intrasubject variance may differ from product to product. Metzler suggests computing the variance of the residuals from the linear model within each product in order to obtain estimates of the intrasubject variances for each product. In fact, the variance of the linear model residuals for a given product estimates a linear combination of the intrasubject variance components for each product in the study. In the case of a six-product study, the variance component for the product whose residuals were used in the computation does dominate the quantity being estimated, so the residuals from the six products could be used to *qualitatively* compare the relative variability of the products, possibly by plotting each set of residuals side by side. However, obtaining *quantitative* estimates of the six variance components would involve a complicated estimation procedure. Naively computing the sample variance of each set of residuals would produce very misleading estimates.

It should be noted that this method would not be applicable at all to a two-product study, for which the sample variances of each product's residuals are always identical, due to the nature of the least-squares estimation procedure.

Finally, we would like to make note of an error that appeared in the original paper (2). It was stated that the effects of dosing sequence, week of administration, and prior treatments were not significant for any parameter. In fact, the effect of week of administration (i.e., period effects) was statistically significant for AUC and C_{max}, as well as for both urinary excretion variables.

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