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Letter

Assessment of Variance in Bioavailability Studies: Comments on the Article by McNamara *et al.*

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For the past two decades analysis of bioequivalence studies emphasized the average (mean) bioavailability, and relative bioavailability usually referred to the difference or ratio of the means of some measure of bioavailability, usually the area under the curve (AUC) and peak concentration. In recent years more attention has been given to the variability of these measures of bioavailability. Thus I read with interest the recent report by McNamara *et al.* (1) which stated some conclusions about the inter- and intrasubject variability of six formulations of furosemide. Because two of the authors are from the Food and Drug Administration, I think it is important that attention be drawn to two concepts discussed in that report.

The first has to do with the use of the "75/75" rule to measure variability. In Ref. 1 (p. 151) it is stated that "the 75/75 rule [is] used as a measure of inter- and intrasubject variability. . . ." Later (p. 152) the authors conclude, "A large intersubject variability was demonstrated in that all tablet dosage forms failed the prescribed FDA 75/75 rule when comparing the AUC and C_{max}. . . ." A little thought and a simple example will show that failing the 75/75 rule cannot be taken as an indication of a large variability. In Ref. 1 the mean AUC of product C was 71% of the mean AUC of product F (the reference solution). If there was no variability in the study, then 100% of the subjects would have failed the 75/75 rule. That is, all of them would have shown a relative bioavailability of 71% when comparing product C to product F. Even with a little variability, all of the subjects would have failed; as the variability increased, and particularly if the intersubject variability got larger than the intrasubject variability, some of the subjects might pass the test.

As far as I know, the 75/75 rule was never proposed as a test of variance. It was proposed as an alternate test for average relative bioavailability. In the two papers by Haynes (2,3), which are included in the References in Ref. 1 but never cited in the text, Haynes points out that the performance of the 75/75 rule is affected by variance; this does not make it a tool for evaluating variances.

The second concept that could be pointed out is that it is possible to evaluate both intra- and intersubject variability from the data of this study. The additional study referred to in the last paragraph of Ref. 1 (p. 153) will provide additional information, but it is not needed. The analysis of variance of the reported data provides, in the subject-effect sum of squares, an estimate of the intersubject variability. The error sum of squares provides an estimate of the intrasubject variability. If an estimate of the intrasubject variability for each product is of interest, this can be obtained by computing the variance of the residuals from the linear model within each product.

Furthermore, the data provided in Table I of Ref. 1 (p. 152) provide an upper limit on the intra- and intersubject variability. From the means and standard deviations in that table, the overall coefficients of variation (CV) can be computed. Looking only at the AUC, the least available formulation, product C, has a CV of 45.6%. The other products range from 29% (B) to 38% (D). These are not particularly large for bioavailability studies (4,5). Since the intra- and intersubject variabilities are components of this overall variability, they would have to be even smaller.

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