TWO ONE-SIDED TESTS PROCEDURE FOR ANALYZING BIOEQUIVALENCE DATA

The two one-sided tests procedure, used by the FDA since 1986 for bioequivalence analysis, resolved the problems of hypothesis testing.[20] The two one-sided tests procedure tests two conditions. Stated simply, the first condition tests if the test product is significantly less bioavailable than the reference product. The second condition tests if the reference product is significantly less bioavailable than the test product. A significant difference is defined as 20% at $\alpha = 0.05$. The criteria above may be restated to illustrate the rationale for the 0.80 to 1.25 (or 80%–125%) confidence interval (CI) criteria. In the first test, the bioequivalence limit for the test/reference ratio is 0.80. In the second test, the bioequivalence limit for the reference/test ratio is 0.80. Because, by convention, bioequivalence ratios are expressed as test/reference, the second bioequivalence limit is 1.25, that is, the reciprocal of 0.80. This may be stated in clinical terms as follows. If a patient is currently receiving a brand-name reference product and is switched to a generic product, the generic product should not deliver significantly less drug to the patient than the brand-name product. Conversely, if a patient is currently receiving the generic product and is switched to the brand-name reference product, the brand-name product should not deliver significantly less drug to the patient than the generic product. Computationally, the two one-sided tests procedure as described above (with each of the two tests conducted at an $\alpha = 0.05$) yields exactly the same results as an analysis of variance (ANOVA) conducted at the 90% level. This ANOVA procedure is much easier to conduct using standard statistical analysis software.

LOGARITHMIC TRANSFORMATION OF BIOEQUIVALENCE DATA

Until 1992, the FDA generally recommended that applicants perform ANOVA on untransformed AUC and $C_{\max}$ data to determine the 90% confidence limits of the differences. After a 1991 meeting of the Generic Drugs Advisory Committee, which focused on statistical analysis of bioequivalence data, the FDA began to recommend that applicants perform ANOVA on log-transformed data.

The Generic Drug Advisory Committee recommended log transformation for bioequivalence analysis for two reasons. First, the ANOVA used to conduct the bioequivalence statistics is based on a linear statistical model.[21,22] However, the form of expression for AUC suggests a multiplicative model, because AUC = $(F * D)/(V * Ke)$, where F is the fraction of drug absorbed, D is the dose, V is the volume of distribution, and Ke is the elimination rate constant. For this reason, FDA statisticians concluded that effects on AUC are not additive if the data are analyzed on the original scale of measurement. Thus, because ln(AUC) is equal to $\ln(F) + \ln(D) - \ln(V) - \ln(Ke)$, logarithmic transformation of AUC allows it to be analyzed using the ANOVA, which assumes a linear statistical model. A similar argument can be made for $C_{\max}$.

The second reason for log transformation is that $C_{\max}$ and AUC, like much biological data, correspond more closely to a log-normal distribution than to a normal distribution.[23] Plasma concentration data and derived pharmacokinetic parameters