tend to be skewed, and their variances tend to increase with the means. Log transformation generally remedies this situation and makes the variances independent of the means. In addition, skewed frequency distributions are often made more symmetrical by log transformation.

To summarize, since 1992, the FDA expects applicants to perform ANOVA on the geometric mean test/reference AUC and C_{max} ratios.[23] To obtain geometric means, the data are log transformed before conducting an ANOVA and then back-transformed before calculating the test/reference ratios. Each of the two one-sided tests is carried out at the $\alpha = 0.05$ (5%) level. The 90% CIs of the geometric mean test/reference ratios should fall within 0.8 to 1.25 (80%–125%). The determination of bioequivalence using this approach is termed "average bioequivalence."[20]

REFERENCE-SCALED AVERAGE BIOEQUIVALENCE APPROACH

For drugs with an expected within-subject variability of 30% or greater, the FDA recommends using a reference-scaled average bioequivalence approach.[24,25] Either a three- or a four-period study design can be used, provided that the same lot of the reference product is administered twice to determine its within-subject variability (s^2_{WR}). The test product variability is not used in the bioequivalence statistical calculations. The minimum number of subjects that would be acceptable is 24.

Scaled average bioequivalence for both AUC and C_{max} is evaluated by testing the following null hypothesis:

$$H_0 : \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} > \theta, \tag{10.1}$$

(for given $\theta > 0$) versus the alternative hypothesis

$$H_1 : \frac{(\mu_T - \mu_R)^2}{\sigma^2_{WR}} \leq \theta, \tag{10.2}$$

where μ_T and μ_R are the averages of the log-transformed measures C_{max} and AUC for the test and reference products, respectively; σ^2_{WR} is the reference product within-subject variability; and θ is the scaled average bioequivalence limit. Usually, testing is done at level $\alpha = 0.05$. Furthermore,

$$\theta = \frac{(\ln \Delta)^2}{\sigma^2_{W0}}, \tag{10.3}$$

where Δ is 1.25, the usual average bioequivalence upper limit for the untransformed test/reference ratio of geometric means, and σ_{W0} is a regulatory constant set at a value of 0.25 by the FDA. The regulatory constant rejection of the null hypothesis H_0 supports the conclusion of equivalence.