$$\theta = \begin{cases} \dfrac{E\left(y_T - y_R\right)^2 - E\left(y_R - y_{R'}\right)^2}{\dfrac{E\left(y_R - y_{R'}\right)^2}{2}} & \text{if } \dfrac{E\left(y_R - y_{R'}\right)^2}{2} \geq \sigma_0^2 \\ \dfrac{E\left(y_T - y_R\right)^2 - E\left(y_R - y_{R'}\right)^2}{\sigma_0^2} & \text{if } \dfrac{E\left(y_R - y_{R'}\right)^2}{2} < \sigma_0^2 \end{cases},$$

where σ_0^2 is a given constant. If y_T, y_R, and $y_{R'}$ are independent observations from different subjects, then the two drug products show population bioequivalence when $\theta < \theta_P$. On the other hand, if y_T, y_R, and $y_{R'}$ are independent observations from the same subject, then the two drug products exhibit individual bioequivalence when $\theta < \theta_I$. Thus, as indicated in Section 8.2.3, for the assessment of individual bioequivalence, the criterion proposed in the FDA guidance (FDA, 2001) can be expressed as

$$\theta_I = \frac{\left(\delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2\right)}{\max\left\{\sigma_{W0}^2, \sigma_{WR}^2\right\}}, \tag{8.1}$$

where $\delta = \mu_T - \mu_R$, σ_{WT}^2, σ_{WR}^2, σ_D^2 are the true difference in means, intra-subject variabilities of the test product and the reference product, and the variance component due to subject-by-formulation interaction between drug products, respectively. σ_{W0}^2 is the scale parameter specified by the user or regulator. Similarly, the criterion for the assessment of population bioequivalence suggested in the FDA guidance (FDA, 2001) is given by

$$\theta_P = \frac{\left(\delta^2 + \sigma_{TT}^2 - \sigma_{TR}^2\right)}{\max\left\{\sigma_{T0}^2, \sigma_{TR}^2\right\}}, \tag{8.2}$$

where σ_{TT}^2 and σ_{TR}^2 are the total variances for the test product and the reference product, respectively, and σ_{T0}^2 is the scale parameter specified by the user or regulator.

A typical approach is to construct a one-sided 95% confidence interval for $\theta_I(\theta_P)$ for the assessment of individual (population) bioequivalence. If the one-sided 95% upper confidence limit is less than the bioequivalence limit of $\theta_I(\theta_P)$, then we conclude that the test product is bioequivalent to that of the reference product in terms of individual (population) bioequivalence.

8.3.2.1 Masking Effect

The goal for evaluation of bioequivalence is to assess the similarity of the distributions of the PK metrics obtained either from the population or from individuals in the population. Under aggregate criteria, however, different combinations of values for the components of the aggregate criterion can yield the same value. In other words, bioequivalence can be reached by two totally different distributions of PK metrics. This is another artifact of the aggregate criteria. At the 1996 advisory