σ_{W0}^2 = a scale parameter specified by the regulatory agency.

Similarly, the criterion for the assessment of population bioequivalence suggested in the FDA guidance (FDA, 2001) is given by:

$$\theta_P = \frac{\left(\delta^2 + \sigma_{TT}^2 - \sigma_{TR}^2\right)}{\max\left\{\sigma_{T0}^2, \sigma_{TR}^2\right\}}, \tag{1.2}$$

where

$\sigma_{TT}^2, \sigma_{TR}^2$ = the total variances for the test product and the reference product, respectively.

σ_{T0}^2 = a scale parameter specified by the regulatory agency.

Population and individual bioequivalence are discussed in greater detail in Chapter 8 of this book.

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. More details regarding individual and population bioequivalence can be found in Chow and Liu (2008).

Note that although individual bioequivalence has been discussed extensively in the past, it has been dropped by the FDA and is no longer used or considered.

1.3.1.3 Moment-Based versus Probability-Based Criteria

Schall and Luus (1993) proposed moment-based and probability-based measures for the expected discrepancy in pharmacokinetic responses between drug products. The moment-based measure suggested by Schall and Luus (1993) is based on the following expected mean-squared differences:

$$d\left(Y_j;Y_{j'}\right) = \begin{cases} E(Y_T - Y_R)^2 & \text{if } j = T \text{ and } j' = R \\ E\left(Y_R - Y_R'\right)^2 & \text{if } j = R \text{ and } j' = R \end{cases}. \tag{1.3}$$

For some prespecified positive number R, one of the probability-based measures for the expected discrepancy is given as (Schall and Luus, 1993):

$$d\left(Y_j;Y_{j'}\right) = \begin{cases} P\left\{\left|Y_T - Y_R\right| < r\right\} & \text{if } j = T \text{ and } j' = R \\ P\left\{\left|Y_R - Y_R'\right| < r\right\} & \text{if } j = R \text{ and } j' = R \end{cases}. \tag{1.4}$$

$d(Y_T;Y_R)$ measures the expected discrepancy for some pharmacokinetic metric between test and reference formulations, and $d\left(Y_R;Y_R'\right)$ provides the expected discrepancy between the repeated administrations of the reference formulation. The role of $d\left(Y_R;Y_R'\right)$ in the formulation of bioequivalence criteria is to serve as a control. The rationale is that the reference formulation should be bioequivalent to itself.