Logarithmic means of the two drug products, denoted by μ_T and μ_R, respectively, are typically compared. The acceptance of bioequivalence is claimed if the difference between the logarithmic means is between prespecified regulatory limits. The limits (θ_A) are generally symmetrical on the logarithmic scale and usually equal ±ln(1.25). Thus, the criterion for ABE can be expressed as follows:

$$-\theta_A \le \mu_T - \mu_R < \theta_A$$

In a bioequivalence study, the individual kinetic responses are evaluated from the measured concentrations. The means of the logarithmic responses of the two formulations are calculated. These sample averages estimate the true population means. A variance is also estimated for each kinetic response. It is a measure of the intrasubject variance but not always identical to it. The FDA suggests that the above ABE could be scaled by a standard deviation as follows:

$$-\theta_s \le \frac{(\mu_T - \mu_R)}{\sigma_W} \le \theta_s,$$

where θ_S is the SABE regulatory cutoff. Here the standard deviation (σ_W) is the within-subject standard deviation. In a replicate design, σ_W is generally the within-subject standard deviation of the reference formulation (denoted by σ_{WR}). Thus, the scaling factor of SABE has similar features to the scaling factor of individual bioequivalence (IBE).

8.3.2 Population/Individual Bioequivalence

In the early 1990s, as more generic drug products became available, it was a concern whether the use of generic drug products was safe and whether the approved generic drug products could be used interchangeably. The FDA indicates that an approved generic drug product can be used to substitute the innovative (brand-name) drug product. However, the FDA does not indicate that generic drug products can be used interchangeably. Since generic drug products are approved based on the criterion of the 80/125 rule, there may be a drastic change in blood concentration if one switches from one generic drug to another. For example, if one switches from a drug that was approved on the lower end of the 80/125 rule (say 80%) to another drug that was approved on the higher end of the 80/125 rule (say 120%), then there would be a sudden 50% increase in blood concentration, which may cause a potential safety concern. To address the issue of drug interchangeability in terms of drug prescribability and switchability, between the early 1990s and early 2000s, the FDA suggested using the concepts of population bioequivalence for addressing drug prescribability and individual bioequivalence for addressing drug switchability.

Let y_T be the PK response from the test product and y_R and $y_{R'}$ be two identically distributed PK responses from the reference product. Now consider a measure of the relative difference between the mean squared errors of $y_T - y_R$ and $y_R - y_{R'}$. Thus