1.3.1.1 Absolute Change versus Relative Change

In clinical research and development, for a given study endpoint, either post-treatment absolute change from a baseline or posttreatment relative change from a baseline is usually considered for making comparisons between treatment groups. A typical example would be the study of weight reduction in an obese patient population. In practice, it is not clear whether a clinically meaningful difference in terms of an absolute change from a baseline can be translated to a clinically meaningful difference in terms of a relative change from the baseline. Sample-size calculations based on power analysis in terms of an absolute change from a baseline or a relative change from a baseline could lead to a very different result.

Current regulations for the assessment of bioequivalence between drug products in terms of average bioavailability are based on relative change. In other words, we conclude (average) bioequivalence between a test product and a reference product if the 90% confidence interval for the ratio of geometric means of the primary pharmacokinetic response, such as area under the blood or plasma-concentration versus time curve (AUC) between the two drug products, is (in %) totally within 80% and 125%. Note that regulatory agencies suggest that a log-transformation be performed before data analysis for the assessment of bioequivalence.

1.3.1.2 Aggregated versus Disaggregated Criteria

As indicated by Chow and Liu (2008), bioequivalence can be assessed by evaluating *separately* differences in averages, intrasubject variabilities, and the variance due to subject-by-formulation interaction between drug products. Individual criteria for the assessment of differences in averages, intrasubject variabilities, and the variance due to subject-by-formulation interaction between drug products are referred to as disaggregated criteria. If the criterion is a single summary measure composed of these individual criteria, it is called an aggregated criterion.

For the assessment of average bioequivalence (ABE), most regulatory agencies, including the FDA, recommend the use of a disaggregate criterion based on average bioavailability. In other words, bioequivalence is concluded if the average bioavailability of the test formulation is between 80% and 125% of the ABE for the reference formulation, with a certain assurance. Note that EMA disaggregated (2010) and WHO (2005) use the same equivalence criterion of 80%–125% for the log-transformed pharmacokinetic responses such as AUC.

For assessment of population bioequivalence (PBE) and individual bioequivalence (IBE), however, the following aggregated criteria have been considered. For the assessment of IBE, a criterion proposed in the FDA guidance (FDA, 2001) can be expressed as:

$$\theta_I = \frac{\left(\delta^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2\right)}{\max\left\{\sigma_{W0}^2, \sigma_{WR}^2\right\}}, \tag{1.1}$$

where

$\delta = \mu_T - \mu_R$, σ_{WT}^2, σ_{WR}^2, σ_D^2 are the true difference between means, the intrasubject variabilities of the test product and the reference product, and the variance component due to subject-by-formulation interaction, respectively.