into six different combinations of triplets with two different reference lots in each triplet. The 10 canisters of a test lot can be paired with the 10 canisters of each of the two reference lots in (10 factorial)^2 = (3,628,800)^2 combinations in each of the lot triplets. Hence, a random sample of the *N*-canister pairing of the six Test–Reference 1–Reference 2 lot triplets is needed. *rd* is estimated by the sample mean of the *rd*s calculated for the triplets in 10 selected samples of *N*. Note that the FDA recommends that $N = 500$ be considered.

8.3.4 Similarity Factor for Dissolution Profile Comparison

In vivo bioequivalence studies are surrogate trials for assessing equivalence between test and reference formulations based on the rate and extent of drug absorption in humans to establish similar effectiveness and safety under the fundamental bioequivalence assumption. However, drug absorption depends on the dissolved state of drug product, and dissolution testing provides a rapid *in vitro* assessment of the rate and extent of drug release. Leeson (1995), therefore, suggested that *in vitro* dissolution testing be used as a surrogate for *in vivo* bioequivalence studies to assess equivalence between the test and reference formulations for postapproval changes. For the comparison of dissolution profiles, the FDA guidance suggests considering the assessment of (1) the overall profile similarity and (2) similarity at each sampling time point (FDA, 1997). Since dissolution profiles are curves over time, Chow and Ki (1997) introduced the concepts of local similarity and global similarity. Two dissolution profiles are said to be locally similar at a given time point if their difference or ratio at the given time point is within some equivalence (similarity) limits, denoted by (δ_L, δ_U). Two dissolution profiles are considered globally similar if their differences or ratios are within (δ_L, δ_U) across all time points. Note that global similarity is also known as *uniformly similar*. Chow and Ki (1997) suggested the following similarity limits for comparing dissolution profiles:

$$\delta_L = \frac{Q-\delta}{Q+\delta} \quad \text{and} \quad \delta_U = \frac{Q+\delta}{Q-\delta},$$

where

- Q is the desired mean dissolution rate of a drug product as specified in the *United States Pharmacopeia and National Formulary* (USP/NF) individual monograph.
- δ is a meaningful difference of scientific importance in mean dissolution profiles of two drug products under consideration.

In practice, δ is usually determined by a pharmaceutical scientist.

In order to achieve these two objectives, based on Moore and Flanner (1996), both the FDA SUPAC (Scale-up and Postapproval Change) guidance (SUPAC-IR, 1995) and guidance on dissolution testing (FDA, 1997) suggest the similarity and difference factor for the assessment of similarity. The similarity factor is then defined as the logarithmic reciprocal square root transformation of 1 plus the mean-squared