committee meeting, it was reported that a 14% increase in the average (ABE only allows 80%–125%) is offset by a 48% difference in the variability and the test passes IBE but fails ABE. More details regarding individual and population bioequivalence can be found in Chow and Liu (2008) and Chow (1999).

8.3.3 Profile Analysis for *In Vitro* Bioequivalence Testing

As indicated in the FDA draft guidance for *in vitro* bioequivalence testing, profile analysis using a confidence interval approach should be applied to cascade impactor or multistage liquid impinger (MSLI) for particle size distribution. Equivalence may be assessed based on chi-square differences. The idea is to compare the profile difference between test product and reference product samples to the profile variation between reference product samples. More specifically, let y_{ijk} denote the observation from the jth subject's ith stage of the kth treatment. Given a sample (j_0) from test product and two samples (j_0, j_1) from reference products and assuming that there are a total of S stages, the profile distance between test and reference is given by

$$d_{\mathrm{TR}} = \sum_{i=1}^{S} \frac{\left(y_{ij_0\mathrm{T}} - 0.5\left(y_{ij_1\mathrm{R}} + y_{ij_2\mathrm{R}}\right)\right)^2}{\left(y_{ij_0\mathrm{T}} + 0.5\left(y_{ij_1\mathrm{R}} + y_{ij_2\mathrm{R}}\right)\right)}.$$

Similarly, the profile variability within reference is defined as

$$d_{\mathrm{RR}} = \sum_{i=1}^{S} \frac{\left(y_{ij_1\mathrm{R}} - y_{ij_2\mathrm{R}}\right)^2}{0.5\left(y_{ij_1\mathrm{R}} + y_{ij_2\mathrm{R}}\right)}.$$

For a given triplet sample of (Test, Reference 1, Reference 2), the ratio of d_{TR} and d_{RR}, that is,

$$rd = \frac{d_{\mathrm{TR}}}{d_{\mathrm{RR}}} \tag{8.3}$$

can then be used as a bioequivalence measure for the triplet samples between the two drug products. For a selected sample, the 95% upper confidence bound of $E(rd) = E\left(d_{\mathrm{TR}}/d_{\mathrm{RR}}\right)$ is then used as a bioequivalence measure for the determination of bioequivalence. In other words, if the 95% upper confidence bound is less than the bioequivalence limit, then we claim that the two products are bioequivalent. The FDA draft guidance recommends a bootstrap procedure to construct the 95% upper bound for $E(rd)$. The procedure is as follows.

Assume that the samples are obtained in a two-stage sampling manner. In other words, for each treatment (test or reference), three lots are randomly sampled. Within each lot, ten samples (e.g., bottles or canisters) are sampled. The following is quoted from the 1999 FDA draft guidance regarding the bootstrap procedure to establish profile bioequivalence. For an experiment consisting of three lots each of test and reference products, and with 10 canisters per lot, the lots can be matched