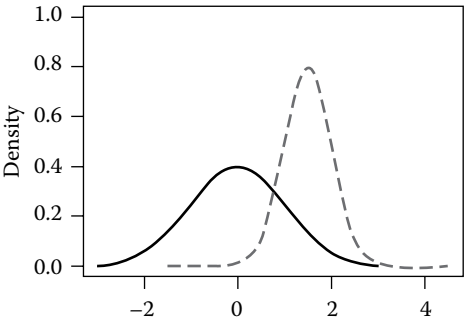

FIGURE 3.8 Graphical comparison for the case where $\mu_T \neq \mu_R$ and $\sigma_T \neq \sigma_R$.

and it is not clear whether a significant difference in distribution of certain CQAs has raised a flag of safety or efficacy concern to demonstrate biosimilarity between the proposed biosimilar product and the reference product (either a US-licensed product or an EU-approved reference product).

3.5 CHALLENGING ISSUES TO FDA'S APPROACHES

The idea of the FDA's proposed equivalence test for Tier 1 CQAs comes from the bioequivalence assessment for generic drugs, which contain the same active ingredient(s) as the reference drug product. It may not be appropriate to apply the idea directly to the assessment of biosimilarity of biosimilar products. The FDA's proposed equivalence test is sensitive to (1) the primary assumptions made, (2) the selection of c, and (3) the estimation of σ_R. Chow (2015) commented on these issues as follows.

3.5.1 Primary Assumptions

Basically, the FDA's proposed equivalence test ignores (1) the lot-to-lot variability of both the reference product and the proposed biosimilar product, (2) the difference between means, and (3) the inflation/deflation in variability between the reference product and the proposed biosimilar product. Suppose that K reference lots will be used to establish EAC for the equivalence test. The FDA suggests that one sample be randomly selected from each lot. The standard deviation of the reference product σ_R can be estimated based on the K test results. Let x_i, $i = 1, 2,\ldots, K$ be the test result of the ith lot. x_i, $i = 1, 2,\ldots, K$ are assumed to be independently and identically distributed with mean μ_R and variance σ_R^2. In other words, we assume that $\mu_{Ri} = \mu_{Rj} = \mu_R$ and $\sigma_{Ri}^2 = \sigma_{Rj}^2 = \sigma_R^2$ for $i \neq j$, $i, j = 1, 2,\ldots, K$. Thus, the expected value of $E(\bar{x}) = \mu_R$ and $\text{var}(\bar{x}) = \sigma_R^2/K$. In practice, it is well recognized that $\mu_{Ri} \neq \mu_{Rj}$ and $\sigma_{Ri}^2 \neq \sigma_{Rj}^2$ for $i \neq j$, where μ_{Ri} and σ_{Ri}^2 are the mean and variance of the ith lot of the reference product. A similar argument applies to the proposed biosimilar (test) product. As a result, the selection of reference lots for the estimation of σ_R is critical for the proposed approach.