between the proposed biosimilar product and the reference product (i.e., $\mu_T \neq \mu_R$ and $\sigma_T \neq \sigma_R$). In practice, it is recognized that biosimilarity between a proposed biosimilar product and a reference product could be established even under the assumption that $\mu_T \neq \mu_R$ and $\sigma_T \neq \sigma_R$. Thus, under the assumption that $\mu_T = \mu_R$ and $\sigma_T = \sigma_R$, the quality range approach for analytical similarity assessment for CQAs from Tier 2 is considered more stringent as compared to equivalence testing for CQAs from Tier 1 (most relevant to clinical outcomes), regardless of the fact that they are mild-to-moderately relevant to clinical outcomes. This is because that equivalence testing allows a possible mean shift of $\sigma_R/8$, while the quality range approach does not. In what follows, several examples for the possible scenarios of (1) $\mu_T \approx \mu_{R,}$ or there is a significant mean shift (either a shift to the right or a shift to the left) and (2) $\sigma_T \approx \sigma_R$, $\sigma_T > \sigma_R$, or $\sigma_T < \sigma_R$.

3.4.2.1 Example 1

First consider the case where $\mu_T \approx \mu_R$ and $\sigma_T \approx \sigma_R$. In this example, if we choose $x = 1.645$, we would expect 90% of the test results from the test lots to lie within the quality range obtained based on the test values of the reference lots. This case is illustrated in Figure 3.2.

3.4.2.2 Example 2

When $\mu_T \approx \mu_R$ but $\sigma_T > \sigma_R$, if we choose $x = 1.645$, we would expect <90% of the test results from test lots to lie within the quality range obtained based on the test values of the reference lots. The percentage of test values from test lots decreases as $C = \sigma_T/\sigma_R > 1$ increases. This case is illustrated in Figure 3.3.

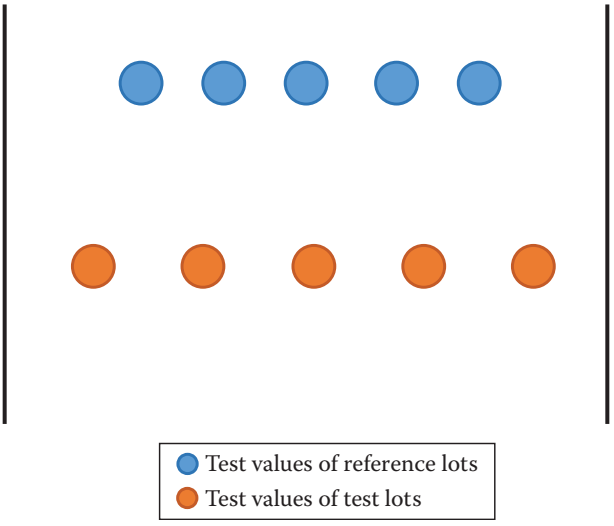

FIGURE 3.2 Quality range approach when $\mu_T \approx \mu_R$ and $\sigma_T \approx \sigma_R$.