In addition, the FDA assumes that the difference in mean responses between the reference product and the proposed biosimilar product is proportional to the variability of the reference product. In other words, $\Delta = \mu_T - \mu_R$ (in log scale) $\propto \sigma_R$. The FDA suggests that the power for detecting a clinically meaningful difference be evaluated at $\sigma_R/8$. Thus, under the assumption, the FDA's proposed equivalence testing is straightforward and easy to implement. However, Chow (2014) indicated that the FDA's proposed testing procedure depends on the selection of the regulatory standard $c = 1.5$, the anticipated difference $\Delta = \mu_T - \mu_R$, and the compromise between the test size (type I error) and statistical power (type II error) for detecting Δ (Chow, 2015).

3.5.2 Justification for the Selection of *c*

The FDA indicates that a potential approach is to assume that the equivalence limit (similarity margin) is proportional to the reference product variability (i.e., $\delta = c \times \sigma_R$). The constant c can be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and reference products, when a moderate number of reference product and biosimilar lots is available for testing. The FDA's recommended approach for the assessment of analytical similarity for a critical attribute is to choose $\delta = 1.5\sigma_R$ (i.e., $c = 1.5$) and then to select an appropriate sample size for achieving a desired power in order to establish similarity at the $\alpha = 5\%$ level of significance when the true underlying mean difference between the proposed biosimilar and reference product lots is equal to $\sigma_R/8$. The FDA did not provide scientific/statistical justification for the selection of $c = 1.5$ for the EAC. Since the FDA's proposed equivalence test was motivated by the bioequivalence assessment for generic drug products, the selection of $c = 1.5$ can be justified by the following steps:

Step 1. We start with $0.8 = \delta_L \leq \mu_T - \mu_R \leq \delta_U = 1.25$, where μ_T and μ_R are the reference mean and test mean (in log-scale), respectively.

Step 2. For drug products with large variabilities (i.e., highly variable drug products), the FDA recommends the scaled average bioequivalence (SABE) criterion by adjusting the above bioequivalence limits for variability of the reference product (Haidar et al., 2008; Tothfalusi et al., 2009). This gives

$$0.8\sigma_R = \delta_L \times \sigma_R \leq \mu_T - \mu_R \leq \delta_U \times \sigma_R = 1.25 \times \sigma_R$$

Step 3. The FDA assumes that the difference between means is proportional to σ_R and allows a mean shift of $\sigma_R/8 = 0.125$, which is the half-width of the margin. The worst possible scenario for the shift is that the true mean difference falls on $1.25 \times \sigma_R$. In this case, the FDA expands the margin by $0.25 \times \sigma_R$. Thus, the upper margin of EAC becomes

$$1.25 \times \sigma_R + 0.25 \times \sigma_R = 1.5 \times \sigma_R.$$