The above test can be referred to as a test for the two-way translational process. The idea is to reject H_0 in favor of H_a. In other words, we would like to reject the null hypothesis and conclude the alternative hypothesis that there is a two-way translation between x and y (i.e., the established predictive model is validated). Under the null hypothesis of Equation 3.4, a test based on an estimate of δ_0 can be similarly derived. We use the previous example for illustration.

Given the dataset, we set up the regression model by using y as the independent variable and x as the dependent variable. The estimates of the model parameters are $\hat{\gamma}_0 = 0.468$, $\hat{\gamma}_1 = 0.519$, and $\hat{\sigma}^2 = 0.121$. Based on this model, for the same α and p_0, given $(x_0, y_0) = (1.0, 1.2)$ and $(5.2, 9.0)$, the fitted values are given by $\hat{x} = 0.468 + 0.519 y_0$. We obtain $\delta_0 = 0.67$ and 0.71, respectively. If the required difference $\delta > \delta_0$, the null hypothesis will be rejected. We conclude that the probability that the difference between x and $\hat{x}$ is less than δ is larger than 0.8.

3.4 FDA'S APPROACHES FOR TIER ANALYSIS

Analytical similarity assessment is referred to as the comparisons of functional and structural characterizations between a proposed biosimilar product and a reference product in terms of CQAs that are relevant to clinical outcomes. The FDA suggests that the sponsors identify CQAs that are relevant to clinical outcomes and classify them into three tiers depending on the criticality or risk ranking (e.g., most, mild to moderate, and least) relevant to clinical outcomes. At the same time, the FDA also recommends some statistical approaches for the assessment of analytical similarity for CQAs from different tiers. The FDA recommends an equivalence test for CQAs from Tier 1, a quality range approach for CQAs from Tier 2, and a descriptive raw data and graphical presentation for CQAs from Tier 3 (see, e.g., Chow, 2015; Christl, 2015; Tsong, 2015). They are briefly outlined in the subsequent subsections.

3.4.1 Equivalence Test for Tier 1

For Tier 1, the FDA recommends that an equivalency test be performed for the assessment of analytical similarity. As indicated by the FDA, a potential approach could be a similar approach to bioequivalence testing for generic drug products (FDA, 2003; Chow, 2015). In other words, for a given critical attribute, we may test for equivalence by the following interval (null) hypothesis:

$$H_0: \mu_T - \mu_R \le -\delta \text{ or } \mu_T - \mu_R \ge \delta, \tag{3.5}$$

where $\delta > 0$ is the equivalence limit (or similarity margin), and μ_T and μ_R are the mean responses of the test (the proposed biosimilar) product and the reference product lots, respectively. Analytical equivalence (similarity) is concluded if the null hypothesis of nonequivalence (*dis*-similarity) is rejected. Note that Yu (2004) defined inequivalence as occurring when the confidence interval falls entirely outside the equivalence limits. Similarly to the confidence interval approach for bioequivalence testing under the raw data model, analytical similarity will be accepted for a quality attribute if the $(1 - 2\alpha)100\%$ two-sided confidence interval of the mean difference is within $(-\delta, \delta)$.