deviations; or using a Bayesian approach with appropriate choices of priors for the mean and standard deviation of the reference product in order to take into consideration the heterogeneity of mean and variability. The Bayesian approach is to obtain a Bayesian creditable interval, which will consider EAC for the assessment of analytical similarity. None of these are required by the FDA and unless the FDA changes its stance, none of these considerations are needed.

9.8.8 Orthogonal testing

At times, the developer will use two different tests to confirm an attribute; a good example is the protein content where it is measured by UVAS and RPHPLC methods. The question arises, what if the test fails in one and meets in the other? The FDA has not provided any clear guidance. However, generally, the protein content issue can be resolved, as the FDA suggested in its review of EP2006, through manufacturing controls, so the developer may want to test if the attribute passes at a lower confidence interval, say 81.4%. If that is true, then the test may be considered as passing since an orthogonal method is supporting similarity.

9.8.9 Replicates

It is recommended that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.

9.8.10 Equal number side by side

There should be an equal number of lots when tested side by side; so if there are more lots available for reference, an unbiased selection should be made to select the equal number, and the rest can be used separately to develop the range acceptance criteria. This recommendation is challengeable once we demonstrate sufficient power of the test. If the number of samples of reference product is higher, this will lead to a smaller standard deviation and thus a larger difference range that may cause the test to fail because of β error. The critical minimum number of lots tested side by side is approximately 8; however, if there is an unbalanced selection between test and reference, a higher number may be required.

9.8.11 Side-by-side testing

The FDA recommends a side-by-side testing of the test and reference product in an equal number of lots and makes the Tier 1 and Tier 2 analysis by using the standard deviation derived from different lots of the reference product. Several questions arise. For those tests where the output is not numerical, and the comparison is made on the