9.8.16 Assay variability

Other aspects of the FDA understanding is that the high assay variability would not justify a large σ_R. In such a situation, the assay would need to be optimized, and/or the number of replicates increased to reduce variability. Also, in cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range. In those cases where data do not follow a normal distribution, the developer may use nonparametric tolerance interval, but the large sample size is generally required.

The high assay variability would not justify a large σ_R. In such a situation, the assay would need to be optimized, and/or the number of replicates increased to reduce variability. What is considered a high variability that is acceptable is a difficult question to answer, but there are several guiding principles that can be applied. First, it involves instrumentation variability—can we use a better equipment? Second, it requires understanding what limit of the variability of CQA is acceptable—for example, many pharmacodynamic responses are highly variable by nature involving biological testing systems—the same applies to bioassays (Tier 1 testing) or binding assays (which will likely be Tier 2 tested). For example, if literature confirms, especially the reports from the originator data that the variability is ±30%, then that could be taken as the limit to achieve. The developers may also want to adopt tests other than those prescribed in the compendia (if so) or other routine methods of testing, and also adopt higher sensitivity and repeatability testing. There is no particular method that the FDA requires one to use, as long as it can be justified and demonstrated to be appropriate and suitable—later it can be validated if it is used for release purpose. (Note: Even though the guidance suggests that for analytical similarity demonstration, the methods must be suitable, the FDA may require validation, so be prepared and always remember that the FDA is never bound by its own guidance—this disclaimer is provided in every guidance document—read it and understand it.)

9.8.17 Margins and ranges

In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range. This position of the FDA creates a scientific challenge for the developer; this applies to both Tier 1 and Tier 2 testing. The scientific basis first comes from the lot release specification. For example, if the release specification calls for a smaller EAC, this should override a higher limit drawn from the testing of the reference product—this can happen, for example, if a few lots of the reference products have out of range values—whether these reference lots should be excluded is another consideration discussed below. The biosimilar developer should examine the legacy values, the known and accepted standards of variability, in determining the interval or range of a critical quality attribute.