9.8.13 Different lots for EAC

The FDA suggests using a different set of lots to establish equivalence acceptance criteria (EAC), choosing a suitable number of lots based on the statistical acceptance criteria of the confidence interval for Tier 1 and Tier 2 testing. A valid hypothesis is not based on the sample to be used to test the hypothesis. Using the same lots tested to generate the EAC is a tautological logic that does not generate any productive information. This behavior is called "data fishing," which just hunts the model that best fits the sample, not the population. It is for this reason that the FDA recommends that the acceptance criteria be established using the separate lots of the reference product. However, where a numerical null hypothesis is not possible to establish a priori, this testing of separate lots can be omitted; the same argument will apply to those numerical data where legacy values or a published values (e.g., Briefing Documents [FDA] or EPARs [EMA]) are used as acceptance criteria such as molecular mass (non-PTM), amino acid sequence, disulfide bonds, and Western blot, where these attributes must be identical, not similar. It is highly recommended that the developer present to the FDA a comprehensive plan, in a Type II meeting, to determine and control the reference variability, σ_R. This may be a challenge when there are a limited number of lots available.

9.8.14 Declared attributes

For Tier 1 testing, if an attribute is declared on the label such as protein content, then a more robust approach is to use the mean value of the reference tested side by side and should be 100%, not the actual percentage of the reference lots.

9.8.15 Reference product variability

Whereas some primary structure attributes are well defined, how would the developer treat a sample of the reference product that does not meet the legacy attributes such as amino acid sequence (e.g., 1 out of 10 samples is not compliant) or the total degradants in the reference lots are above the release limits of the biosimilar product?

Since the primary structure attributes must be identical, not similar or highly similar, there is no variance allowed in the comparison exercise; if the reference product does not meet these attributes, then that specific lot would be labeled as out of specification and excluded from similarity demonstration exercise. The same principle applies to attributes for which a release criterion exists (those not requiring to be identical); the reference lots, in this case, will be excluded if they do not meet predetermined release criteria of the biosimilar product. Examples may include an out of specification impurity level or the formulation attributes.