9.8.22 Degree of similarity

How similar is similar? Does being highly similar mean that all Tier 1 tests must meet? Does it mean that the α value can be lowered and the manufacturing process controlled to reduce the risk to patients (this is called the FDA risk)? Is there a degree of similarity in Tier 3 evaluations? How close is close? These are some of the key aspects that the developer would need to address in presenting the data. Know that the guidance by the FDA is merely a guidance, not an obligation by the FDA to follow this.

9.8.23 Legacy values

The CQAs that are the subject of analytical similarity can be classified into two categories: inherent and legacy attributes. Inherent attributes are those variable properties that are inherent in the manufacturing of the product that result in the lot-to-lot variability. This classification of attributes includes both process- and product-related factors. A good example will be all types of posttranslational modifications for both cytokines as well as antibodies. Legacy attributes are those characteristics that are not subject to a lot-to-lot variation and must be met essentially in their entirety. A good example of a legacy attribute is the total mass of a protein, its amino acid sequence, and other declared properties such as disulfide bonds, etc., that we widely and completely reported in several protein databanks, patents, and publications, as well as the pharmacopeia. Another category of legacy attributes is the labeled specification of inactive ingredients, the product characteristics such as pH, etc. Historically, we have established rational variance of these attributes, such as a range of content, a range of physical attributes, as well as the expected stability profiles.

Legacy attributes can be tested without reference to the originator product; the inherent attributes require a detailed evaluation of the originator product. Whereas the primary structural attributes must conform to established legacy values, a side-by-side testing of the test and reference product is required to assure that the test methods used are suitable for detecting any differences in these attributes. However, for these attributes the developer need not to develop acceptance criteria using a separate set of lots of the reference product.

9.8.24 Compendia specifications

Drug substance monographs of several biological products are provided in official compendia like EP, BP, and USP; compendia also provide acceptance criteria for attributes such as glycan distribution, isomers, and other structural variants. How much can the biosimilar product developer rely on compendia limits to develop release criteria and also use these values as legacy limits to demonstrate analytical and functional similarity?

The FDA has two concerns regarding the variability: first, the inherent variability in protein structures, and second, the variability introduced