a sufficient number of lots from the proposed biosimilar product used in clinical studies as well as from the proposed commercial process if the process used to produce the material utilized in the clinical studies is different.

3.7.3 Assessment of physicochemical properties

Physicochemical evaluation of the proposed product and the reference product should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structures; PTMs; and functional activities). The objective of this assessment is to maximize the potential for detecting differences in quality attributes between the proposed product and the reference product.

The sponsor should address the concept of the desired product (and its variants) as discussed in ICH Q6B when designing and conducting the characterization studies. Thus, it will be significant to understand the heterogeneity of the proposed product and the reference product (e.g., nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from PTMs.

Particular analytical methodologies can be used to assess specific physicochemical characteristics of proteins. These methodologies are described in published documents, including scientific literature, regulatory guidelines, and pharmacopoeial compendia. Some techniques provide information on multiple characteristics. It is expected that appropriate analytical test methods will be selected based on the nature of the protein being characterized and the knowledge regarding the structure and the heterogeneity of the reference product and the proposed product, as well as those characteristics that are critical to product performance.

To adequately address the full range of physicochemical properties or biological activities, it is often necessary to apply more than one analytical procedure to evaluate the same quality attribute. Methods that use different physicochemical or biological principles to assess the same attribute are especially valuable because they provide independent data to support the quality of that attribute (e.g., orthogonal methods to assess aggregation). In addition, the use of complementary analytical techniques in series, such as peptide mapping or capillary electrophoresis combined with mass spectrometry of the separated molecules, should provide a meaningful and sensitive method for comparing products.

Unlike routine quality control assays, the tests used to characterize the product do not necessarily need to be validated. But the tests used to characterize the product should be scientifically sound, be fit for their intended use, and provide results that are reproducible and reliable. In selecting these tests, it is important to consider the characteristics of the protein product, including known and potential impurities. Information regarding the ability of a method to discern relevant differences between