(b) a polyol, (c) a polysorbate at a concentration of 0.1 to 10 mg/mL, and (d) a buffer system comprising histidine and having a pH of 4.5 to 7.0, wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7.

The example provided above should serve as a warning to biosimilar product developers of the challenges they will face in establishing formulation similarity.

The native structure of a protein molecule is the result of balancing effects such as covalent linkages, hydrophobic interactions, electrostatic interactions, hydrogen bonding, and van der Waals forces. Protein stability is controlled by innumerable intrinsic and extrinsic factors, but the major ones are primary sequence, 3D structure, subunit associations, and PTMs. Extrinsic contributing factors include pH, osmolarity, protein concentration, formulation excipients, and exposure of a product to physical stress from temperature, light, and/or agitation. Leachables from container-closure systems and contamination from the environment (e.g., metals and proteases) also exacerbate product degradation. All these features make protein degradation a very complex physiochemical phenomenon, so formulation optimization is a core aspect of biotechnology product development.

8.2 Drug substance and drug product stability

A biosimilar developer has access to the exact formulation used by the originator because of the nature of the product being an injectable. In almost all instances, unless otherwise dictated by IP, safety improvement and constraints related to the availability of inert components of the correct specification, the formulation of a biosimilar should be the same as that of the originator product. However, in developing a QTPP, the biosimilar developer must analyze multiple lots of the originator product since the labeling of inactive components gives no indication of the acceptance ranges; for example, it is not uncommon for a product to contain a surfactant with a range of ±50% to 80%.

The formulation of biopharmaceuticals is a vast field of study with two peculiarities compared to small-molecule drugs. First, most protein drugs are administered by parenteral routes, and, as a result, most of the science of protein drug formulation deals with the art of injectable formulations. Second, there are several common structural features of all proteins, such as functional groups like methionine, cysteine, histidine, tryptophan, and tyrosine, all of which are subject to oxidation, requiring some common approaches to establishing stable products. On the other hand, conformational changes and aggregation are properties peculiar to large molecules that require the inclusion of formulation components that can be highly specific. The quality of inactive components can have a far greater impact on the formulation than those found in pharmaceuticals,