on two considerations: protein content and functional response of the protein. Affecting both of these attributes are the formulation elements, such as inactive ingredients and other attributes like osmolality, pH, appearance, color, clarity, and surfactant or stabilizer concentration. It should be noted that the regulatory agencies allow the use of alternate inactive ingredients as long as they introduce any "clinically meaningful difference." In some cases, this may be difficult to prove and, therefore, the biosimilar product developer is left with fewer choices of excipients. However, the grade of excipients used can be significant. Lately, many higher-quality common components used in these products have become available, higher quality meaning fewer impurities and higher consistency of the specification. The biosimilar product developer is encouraged to acquire the best-quality excipients, even if the originator is not using these grades; the reason why the originator may not be using these grades is to avoid conducting comparability exercise. However, changing the specification of excipients with just cause is also not recommended. When developing a 505(j) product, the goal of the sponsor is to create a quarter-over-quarter (Q/Q) formula; this is not only required, but it also creates needs for more studies since many of the quality attributes that may have little effect on 505(j) products can be significant for 351(k) products. Attributes like pH is necessary for stability, and the osmolality for the comfort of administration and aggregation (immunogenic potential); and the use of surfactants can introduce stability issues because of the traces of peroxides in them.

Potency testing includes three major components: the bioactivity in a bioassay, a receptor-binding study, and also the content of protein, which will then determine the overall potency that may be content dependent; finally, to be potent, the product must demonstrate equivalent PK (what the body does to the molecule) as well as PD (what drug does to the body).

4.11.1 Protein content

One of the most important attributes to meet is the protein concentration, a simple as it might sound. This may appear rather redundant but using methods like A280 can often be misleading, and the biosimilar product developer is strongly urged to adopt orthogonal methods like RP-HPLC for protein concentration. While many other attributes may be described with acceptable or justified ranges, the concentration or the strength must be met. The biosimilar product developer may face a dilemma when a sufficiently large number of reference lots are not available as this might affect the statistical robustness of testing.

4.11.2 Bioactivity

Relevant functional assays are the best possible predictors of clinical bioactivity; these tests help demonstrate the structure–function relationships