a number of biosimilars. In this historical case of immunogenicity with a branded biologic, Eprex underwent a formulation change that precipitated aggregation of the erythropoietin in the prefilled syringe (PFS); this in turn stimulated a neutralizing antibody response that cross-reacted to endogenous erythropoietin, causing PRCA (Casadevall, 2002). Extensive root cause analyses were performed to address this issue and highlight the importance of maintaining control and the consistency of manufacturing controls for all biologics whether branded biologics or biosimilars. This PRCA episode in the early 2000s does not implicate safety risks with biosimilars, but it does highlight that manufacturing of biologics of all types requires a quality mindset with consistent and appropriate manufacturing controls, and that all manufacturing changes must be undertaken with care.

Each biologic has a unique immunogenicity profile, with some agents frequently stimulating development of neutralizing antibodies (such as with Humira) (Bartelds et al., 2011), whereas others rarely cause immunological responses at all (such as with Neupogen or Zarxio) (Holzmann et al., 2015). Knowledge and a sound understanding of immunological experience with the chosen reference product is critical to evaluating the probability for demonstrating differences in immunogenicity between the biosimilar and the reference product. The goal in such a comparison is to demonstrate that there are no worrisome signals of increased immunogenicity for the biosimilar. This would be unexpected based on the high degree of similarity established in the biosimilarity evaluation. In unique situations, lower immunogenicity may be acceptable for a biosimilar such as in using an alternate expression system. This is the case with centuximab (Erbitux) which is manufactured using an SP2/0 murine expression system that incorporates an immunogenic glycosylation involving alpha galactosylation, Gal α1–3Gal (Galili, 2005). Biosimilar sponsors can use a CHO (Chinese hamster ovary) expression system to produce a product with less of this same immunogenic glycosylation pattern (Bosques et al., 2011). In this case, the biosimilar would be produced with less of the Gal α1–3Gal glycosylation providing less of an immunogenic stimulus, and this would be acceptable provided the other quality aspects or physicochemical properties resulted in the same clinical performance.

Therefore, overall, the biosimilar is designed to be highly similar or essentially the same as the reference product and is expected to have the same immunogenic profile. However, as with all biologics, stability of the final product or formulation is critical and may impact aggregation, thus requiring diligent manufacturing quality control.

7.4 BIOSIMILAR CLINICAL TRIAL DESIGNS

The rationale for clinical trials in the development of biosimilars is to provide confirmation of the "sameness" of the biosimilar to the reference product. This has already been established by the analytical and preclinical comparisons that build the foundation for the "totality of evidence" that the biosimilar can be expected to have the same clinical effect in patients. With this consideration in mind, the clinical trial is specifically designed to demonstrate differences between the biosimilar and reference product should any such differences exist. Hence, the question is how to optimize the sensitivity of the clinical trial to show those differences, even while knowing that it is so much less sensitive than analytical methodologies previously