7.4.4.2 Case Study

This is the case, for example, with Genentech/Roche's approval of Gazyva, which is a follow-on product or lifecycle management strategy for Rituxan, wherein increased antibody-dependent cellular cytotoxicity (ADCC) was achieved by altering the glycosylation structure of the molecule. Such modifications are easily determined and are known to have an impact on ADCC. Therefore, it is unrealistic to consider that a biosimilar sponsor creating essentially the same active substance as an originator would produce a product with superior clinical efficacy without evidence of analytical differences. This is an issue because the design and conduct of an equivalence trial generally requires more subjects than a noninferiority design, which can complicate the operational and financial aspects of developing biosimilars. This is an example of biosimilars seemingly being held to a higher standard than development of novel drugs.

Equivalence trial designs require biosimilar sponsors to justify the statistical assumptions for the comparability margin (noninferiority or equivalence margin). To do so there has to be sufficient literature using the reference product to describe the clinical effect of the dose and other comedications used to produce a given effect size or difference between the group treated with placebo or standard of care. The determination of the comparability margin is critical as both sample size and interpretation of the study depend on this margin. This margin is essentially the largest difference between the use of the two products that can be judged as clinically acceptable or the "same." This margin must clearly be smaller than differences observed in superiority trials of the reference product. Regulatory guidance suggests that this margin should allow retention of at least 50% of the effect size of the reference product (EMA, 2005; FDA, 2010). In general, the larger the effect-size of the reference product, the smaller the sample size of the biosimilarity equivalence trial. Those products with smaller effect sizes such as with Avastin are challenging as they therefore require quite large clinical trials. Most sponsors are conducting clinical trials in non-small-cell lung cancer (NSCLC) with Avastin biosimilars with patient sample sizes over 700 (Amgen, 2015b). Considering that acquiring the reference product from the US market is very expensive, this can add $100,000 to each patient enrolled in the trial, depending on how long the trial lasts (Jirillo et al., 2008).

Physicians are not as familiar with equivalence trial designs and become concerned when the protocol or discussion mentions retaining only 50% of the effect size of the reference product as demonstrated in comparison to a placebo or standard of care active control. Let us attempt to put this in the context of clinical relevance by using an example.

7.4.4.3 Case Study

To establish the justification for an equivalence trial design for the use of an anti-TNF biologic in psoriasis, in this case etanercept, one uses existing literature to establish a justified overall response rate as the starting point. In this case, Leonardi et al. (2003) have published a pivotal trial used for approval of etanercept in the psoriasis indication. In this study, they demonstrated a 55% effect size, that is, the difference between using etanercept (59%) versus the placebo (4%) based on those subjects achieving at least a 75% improvement in their PASI (Psoriasis Area Severity Index) score (Fredriksson