



**FIGURE 7.3** (See color insert.) For all patient responses to be within the equivalence margin, the actual point estimates or average responses for the patients treated with either drug must be fairly close to each other. Clinicians would be reassured about average responses of the patients treated with the biosimilar and the reference product being relatively close. Focus on the maximum margin justified does not represent the clinically relevant representation of the data.

the increased sample size induces clinical trial operational challenges and increases costs commensurately. Finally, a sponsor may have to have two different statistical analysis plans (SAPs), one for a 90% confidence interval outside of Europe and one for a 95% confidence interval for EMA.

The clinical effect size of the reference product (the difference in clinical response between the reference product and placebo) is important not only for sizing the study but also in context of sensitivity to pick up differences. The clinical indication with the largest effect size would be able to pick up smaller differences between the reference product and the proposed biosimilar. Therefore, regulatory authorities are also interested in using the “most sensitive” patient population when conducting the final efficacy study to confirm similarity (McCamish and Woollett, 2012). This can be illustrated in the choice of patient populations for biosimilar studies with anti-TNF biosimilar candidates. Many sponsors have or are using rheumatoid arthritis patients in the confirmatory study for their biosimilar (Yoo et al., 2013; Amgen, 2015c). For this class of drugs, psoriasis is actually a more sensitive population to use since the effect size is generally much larger. In addition, cotreatment with other immunosuppressive drugs is not as common in treating psoriasis as it is in treating rheumatoid arthritis (where methotrexate as a comedication is almost universal). Such immunosuppressants can impact the evaluation of immunogenicity, which is usually a key point of interest in the final confirmatory clinical trial for biosimilars. Therefore, use of a psoriasis population would be a more sensitive “model” for testing biosimilarity and, as with rheumatoid arthritis, published data allows for a robust statistical justification of the equivalence margin.