Comparative human PD studies are unlikely to substitute all clinical studies. When PD data from healthy volunteers are used as primary evidence, biosimilar sponsors also need to provide sufficient reassurance of clinical safety, including immunogenicity, in a separate repeat-dose clinical trial. Furthermore, for many biologics, especially for mAbs, there are no relevant PD surrogates available and therefore clinical trials are required.

9.3.3 Primary Clinical Studies

If dose comparative and sensitive PD studies cannot be performed to convincingly demonstrate comparability in a clinically relevant manner, adequately powered, preferably double-blind and randomized clinical trial(s) between the biosimilar and the RBD should be conducted. The main purpose of comparative clinical study/ies is to demonstrate that there are "no clinically meaningful differences" between the products.

The type and number of comparative clinical trials required for biosimilars could be affected by many factors: the nature and complexity of the RBD (such as anticancer mAbs); the limitations of studies comparing structural and functional characteristics; the findings of nonclinical testing; the extent to which differences in structure, function, and nonclinical data can predict clinical outcomes; the degree of understanding of mechanism(s) of action of the RBD and disease pathology; the extent to which human PK/PD can predict clinical outcomes; and the extent of clinical experience with the RBD, including the knowledge base with respect to safety, efficacy, and immunogenicity.

Equivalence trials are generally preferred to noninferiority trials because the suggested superiority in a noninferiority setting would raise questions about the comparability of the two products. This is usually demonstrated by showing that the true treatment difference is likely to lie between prespecified lower and upper equivalence margins that are considered clinically acceptable (ICH E9, 1998). This equivalence margin is the largest difference that can be judged as clinically acceptable for the biosimilar and should be smaller than the effect sizes observed in superiority trials conducted for the RBD. In order to detect differences between the biosimilar and the RBD, equivalence trials should be conducted in at least one sensitive population that is representative of authorized therapeutic indications. In general, a homogeneous population of patients would provide a better chance to detect differences between the biosimilar and the RBD. Ideally, the observed clinical effects should be caused by the direct action of the biosimilar or the RBD without interference of other medications, as concomitant medications may affect or mask differences in PK/PD, efficacy, safety, and/or immunogenicity of the tested products. To validate the effect of the RBD and the sensitivity of the study in the chosen study population, a large body of historical data should be available to justify the selection of the study population and equivalence margin. This is generally done through meta-analysis or systematic review. The mechanism of action in the chosen study population should be well-understood and be representative of the mechanism of action of the RBD in other populations in order to support and justify the extrapolation of indications. In some jurisdictions, clinical studies in an unauthorized indication (e.g., line of therapy, combined therapy, disease severity) may be acceptable to demonstrate "no