in the trials that established the efficacy of the RBD is used, then a justification for this endpoint should be provided. The justification provided should include historical evidence to support the sensitivity of the selected endpoint as well as the determination of the equivalence margins.

### 9.4.2 Determining the Equivalence Margins

An equivalence trial is designed with the primary objective of showing that the response to two or more treatments differs by an amount that is clinically unimportant (ICH E9, 1998). The clinically unimportant difference is referred to as the equivalence margin and has to be determined during the planning and design phase of the study. The appropriate determination of the margins is critical as both the determination of the required sample size and the interpretation of study results depend on it. Historical evidence of the effect size of the RBD compared to placebo for the selected endpoint and population should be provided to support the proposed margins and should take into account the magnitude and variability of the effect size. The final choice of the margins is based on a combination of statistical evidence from historical trials and clinical judgment. Typically, symmetric margins to rule out inferiority and superiority are used, and the use of asymmetric margins with a larger margin to rule out superiority compared with the margin to rule out inferiority can be justified in certain cases (FDA, 2015). To date, the biosimilars approved by Health Canada have utilized symmetric margins.

Several equivalence margins can be used to test the hypothesis of equivalence of the biosimilar to the RBD (Chow and Liu, 2004). The first margin is simply the smallest effect size that the reference can be expected to have relative to a placebo control, preferably based on a meta-analysis of historical trials. The second margin is a fraction of the first and is selected because it is considered clinically important to ensure that the biosimilar retains a substantial fraction of the reference. A third limit, which transforms the equivalence hypothesis into a superiority hypothesis, is only used in cases when the active control has not consistently been shown to be superior to placebo and is not considered relevant for biosimilars. In the biosimilar setting, the efficacy of the RBD compared to placebo has already been demonstrated, and the second margin that preserves a proportion of the effect size of the reference is the most relevant and commonly used margin.

The fraction of the effect size of the RBD that must be retained by the biosimilar should be clearly justified in each case and should take into account the smallest clinically important difference in a given setting. A commonly used value is the 50% rule in which 50% of the effect size of the RBD is preserved, and its wide use appears to be historical. For example, the equivalence trial for the biosimilar infliximab that was filed to Health Canada as a biosimilar to the RBD used the 50% rule to determine the equivalence margin based on historical data with the RBD. However, the 50% rule is not expected to be justifiable in all cases, as it could result in a margin that is larger than what is considered the smallest clinically important difference. Once the margin has been selected, the determination of the required sample size should be based on methods specifically designed for equivalence trials (Hwang, 2005).