simple terminology such as "phase III" can wrongly communicate to physicians and clinical reviewers that the purpose of the study is to point to the safety and efficacy of the biosimilar when the goal is to confirm similarity and address any residual uncertainty based on the totality of evidence available at the time the clinical program starts.

When designing the confirmatory study evaluating the efficacy and safety of the biosimilar, it is obviously necessary to compare the response of the biosimilar to the reference product in a head-to-head study. Comparisons to historical data are not useful in picking up differences between the biosimilar and the reference product if differences exist. Comparing responses to the reference product is a major challenge for biosimilar sponsors because they must purchase reference products from the market in order to facilitate the best scientific comparison. This is a significant financial undertaking, and it is an operational challenge in many ways. The biosimilar sponsor must acquire and relabel the reference product to enable blinded clinical trials, repackage and ship to all clinical sites, and analyze every batch of reference product acquired and used in clinical trials so as to prove the reference product actually used is analytically "highly similar" to the specific biosimilar lots used in the same trial. Such analytical characterization often requires purchasing 100 additional vials or prefilled syringes of each batch of the reference product used. Lastly, some originator companies create barriers to biosimilar sponsors being able to acquire consistent lots for use in biosimilar trials.

7.4.4 Trial Designs

Most regulatory authorities prefer equivalence trial designs that test to exclude a biosimilar that is inferior or superior to the reference product (two-sided testing) versus noninferiority designs that focus on excluding only an inferior response (EMA, 2007; Health Canada, 2010). The rationale for this approach is that a biosimilar with superior efficacy should not be considered a biosimilar. Thus, the burden on the biosimilar sponsor is to prove that the proposed biosimilar is neither inferior nor superior to the reference product. This is in contrast to originator product development wherein noninferiority studies are often used when developing novel drugs using the same receptor or mechanism of action. Regulatory authorities approve such a drug when it is shown to have at least the same clinical effect as the comparator drug.

7.4.4.1 Case Study

With the development of Neulasta and Aranesp, which were designed to have the same clinical effect as their forerunners with less frequent injections, noninferiority studies were used (Amgen, 2015a,d).

To always require an equivalence trial design for development of biosimilars is inappropriate as it is not possible for a biosimilar with highly similar product attributes to produce statistically superior clinical responses when compared to the reference product. When small differences in product attributes, clearly determinable by analytics, are able to produce a superior clinical response, the originator company will have discovered and patented this minor change as part of the lifecycle development of its drug.