evaluate response rate or tumor size prior to surgery when treated with trastuzumab or a proposed trastuzumab biosimilar. The primary endpoint in this setting can be pathological complete response (PCR) during surgery as this more sensitively measures the actual biologic function of the agent being used.

Validated biomarkers have also been used in the approval of novel drugs. Such biomarkers have been validated to predict the ultimate clinical outcome.

7.4.5.3 Case Study

Validated biomarkers include hemoglobin A1c (HbA1c) in approval of antidiabetic drugs, duration of severe neutropenia (DSN) for hematologic growth factors that prevent infection in chemotherapy patients, as well as LDL cholesterol in patients at risk for myocardial infarctions.

Unfortunately, there are very few validated biomarkers. Hence, only rarely is it possible to use one of these biomarkers in the development of biosimilars. However, it is possible to provide information to regulatory agencies about potential biomarkers in biosimilar clinical trials. This is particularly the case when a sponsor provides extended characterization data that provide assurance that there is "fingerprint-like" (FDA, 2015b) similarity of the proposed biosimilar to the reference product.

The medications used for cotreatments are also an important factor not only in considerations of immunogenicity, but also as part of the statistical justification of the equivalence margin. As mentioned above for statistical justification, published studies are required to define the clinical effect size, and this may depend on the comedication utilized. Since the reference biologic was often originally approved well over a decade ago, if not two, the comedications may have evolved. Often there are far less clinical data produced with newer comedications making it more difficult to justify the statistical margins and sample size needed to establish equivalence.

7.4.5.4 Case Study

The largest published database for efficacy of rituximab in treatment of follicular lymphoma includes cotreatment with CVP (Cyclophosphamide, Vincristine, and Prednisone) (Sandoz, 2015a); however, other chemotherapy treatments may be preferred in current clinical practice such as bortezomib (Coiffier et al., 2011). Therefore, although the sponsor can provide statistical justification for effect size, equivalence margin, and number of patients required; enrollment of the clinical trial may be challenging if the cotreatment is no longer the standard of care in major countries. Physicians prefer to use a more modern comedication either because of improved efficacy or better tolerance or safety and, therefore, they prefer to not be involved in a study that uses an older treatment.

This is the same situation as with filgrastim and pegfilgrastim where the most robust published information utilized breast cancer patients treated with TAC (docetaxel, doxorubicin, and cyclophosphamide) (Blackwell et al., 2015) chemotherapy, and current regimens utilize various dose-dense regimens with less risk of neutropenia, thus limiting interest in such a biosimilar clinical trial using TAC chemotherapy. Therefore, a sponsor can design a statistically justified biosimilar clinical trial that is accepted by multiple regulatory agencies but has challenges with recruitment and conduct of the trial.