be examined as well as factors having an influence on immunogenicity such as the disease state wherein the immune systems may be compromised such as in the use in patients undergoing chemotherapy.

Immunogenicity is a problem only when it is clinically relevant—when it has an effect on the safety or the efficacy of the therapeutic protein. Clinically relevant immunogenicity includes when antibodies change how the drug reacts in the body, when antibodies make the protein less therapeutically effective, when antibodies change natural proteins in the body, or when antibodies trigger a severe allergic reaction, which is very rare. Clinically relevant immunogenicity is not common but must be monitored for all therapies.

## 7.2 Immunogenicity

It is well established that repeated injection of even native human proteins can result in a break in immune tolerance to selfantigens in some patients leading to a humoral response against the protein that is enhanced when the protein is aggregated or partially denatured. Although in most cases an immune response to a biopharmaceutical has little or no clinical impact, ADAs do, however, pose a number of potential risks for the patient, particularly in the case of a neutralizing antibody response. Firstly, an ADA response can adversely affect the PK and the bioavailability of a drug thereby reducing the efficacy of treatment and necessitating either escalating the dose or switching to alternative therapy if such therapy is available. An ADA response can also adversely affect the safety of treatment and cause immune complex disease, allergic reactions and, in some cases, severe autoimmune reactions. Serious and lifethreatening adverse events can occur when ADAs cross-react with an essential, nonredundant endogenous protein such as EPO or TPO. Thus, several cases of PRCA were associated with the development of antibodies to recombinant EPO following a change in formulation. Similarly, the development of antibodies to PEGylated MGDF cross-reacted with endogenous MGDF, resulting in several cases of severe thrombocytopenia.

All biosimilar products are evaluated based on the regulatory guidelines such as the FDA guidance for binding antibodies and neutralizing antibodies. Binding antibodies bind to the protein but usually have no effect. Neutralizing antibodies can inhibit the function of the protein in the body. The FDA is more concerned with neutralizing antibodies because they are more likely to have clinical consequences. Because older products may have limited immunogenicity data based on tests with inadequate sensitivity, immunogenicity between a biosimilar and its reference product cannot be compared using data from the package insert of the reference product. Any comparison of immunogenicity will need a side-by-side clinical test of the biosimilar and its reference to