1.3.6 The Problem of Immunogenicity

Since all biological products are biologically active molecules derived from living cells and have the potential to evoke an immune response, immunogenicity is probably the most critical safety "uncertainty" for the assessment of biosimilarity of follow-on biologics. The commonly seen possible causes of immunogenicity include, but are not limited to: (1) sequence differences between a therapeutic protein and endogenous proteins, (2) nonhuman sequences or epitopes, (3) structural alterations, (4) storage conditions, (5) purification during the manufacturing process, (6) formulation (e.g., surfactants), (7) route, dose, and frequency of administration, (8) patient status such as concomitant therapy (e.g., immunosuppressants) or genetic background. Thus, the following questions should be asked when assessing biosimilarity between biological products: (1) What is the immunogenic potential of the therapeutic protein? (2) What is the impact of the generating antibodies to the self-protein or to the therapeutic drug? (3) What is the impact of immunogenicity on preclinical toxicity (e.g., pharmacokinetic levels and dose-limiting toxicity)? (4) What is the impact of immunogenicity of the therapeutic protein on safety? (5) What are the risk evaluation and mitigation strategy processes required by regulatory agencies?

The immune responses to biological products can lead to: (1) anaphylaxis, (2) injection site reactions, (3) flu-like syndromes, and (4) allergic responses. Note that one of the most serious adverse events occurs when neutralizing antibodies to the drug cross-react with endogenous proteins that have a unique physiological role. The risk of immunogenicity can be reduced through stringent testing of the product during its development. It should be noted, however, that immunogenicity in animals does not predict immunogenicity in clinical trials, and analytical techniques may not detect differences that may impact immunogenicity. Therefore, the immunogenicity of a biological product depends heavily on the attributes of product quality such as the physical, structural, and functional properties of the active pharmaceutical ingredients; as well as excipients, container closure, and delivery system. It turns out that similarity of the acceptable ranges of these quality attributes is crucial to the evaluation of similarity between the biosimilar and the reference product.

Problems of immunogenicity in the development of biosimilars are discussed in Chapter 12 of this book.

1.3.7 Drug Interchangeability

Basically, drug interchangeability can be classified either as drug prescribability or drug switchability. Drug prescribability is defined as the physician's choice for prescribing an appropriate drug product for his or her new patients between a brand-name drug product and a (number of) biosimilar drug product(s) that have been shown to be bioequivalent/biosimilar to the brand-name drug product. The underlying assumption of drug prescribability is that the brand-name drug product and its biosimilars can be used alternatively in terms of the efficacy and safety of the drug product. Drug switchability, in contrast, is related to the switch from