13.1.2 Biopharmaceuticals and Biosimilars

The increase in the development of biological products or biopharmaceuticals presents unique opportunities for monitoring and pharmacovigilance. Biopharmaceuticals are proteins that are generally used to treat a variety of severe and life-threatening diseases. They are fundamentally different from the usual generic products, owing to the size and complexity of the active agents and the manufacturing process. In some jurisdictions, some of these products are authorized for rare diseases as orphan drugs; therefore, information on their safety profile at the time of authorization may sometimes be very limited due to small clinical trial sample size. Although biological products are considered targeted therapeutic drugs, they are associated with several adverse events. The most common safety concerns with biological products include the potential risk of infectious disease transmission, lot-to-lot variability, issues around immunogenicity, hypersensitivity reactions, alterations of immune function; which may lead to increased risks of infection, autoimmunity and/or cancer development, long biological half-lives leading to prolonged pharmacodynamic effects even after cessation of treatment, and unknown short- and long-term risks.

The most frequently associated risks with biopharmaceuticals are attributable to their immune-modulatory actions. A number of these responses are difficult to identify in preclinical studies since such reactions tend to be species-specific and cannot always be extrapolated to humans. An example of such a reaction was seen with anti-CD28 antibody TGN1412 in healthy volunteers. All six volunteers who received TGN1412 had a systemic inflammatory response, characterized by a rapid induction of pro-inflammatory cytokines, accompanied by headache, myalgia, nausea, diarrhea, erythema, vasodilatation, and hypotension (Suntharalingam et al., 2006; Attarwala, 2010). These reactions were, however, not recorded in the preclinical studies of TGN1412. Due to the complexity of biotherapeutics and the difficulties in predicting the adverse reactions that may be seen when these products are introduced to the market, their postmarket surveillance is crucial. Postmarket surveillance for biological products poses many challenges. With the introduction of biosimilar products, which are biologicals that have demonstrated biosimilarity to the reference product with respect to structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness, the pharmacovigilance of these products has become even more challenging and complex (Zuniga and Calvo, 2010; Weise et al., 2012; Casadevall et al., 2013).

Biosimilars [also called subsequent-entry biologics (SEBs) or follow-on biologics] are biotherapeutics that have demonstrated similarity, but that are not identical to the approved reference biologics or biotechnology derived products. They are not considered identical because of differences in the inherent complexity of the protein molecule itself, the complex, multistep manufacturing processes that utilize live cells, and the difficulties in accurate characterization of the reference biological product. In addition, cell lines used in the manufacture of a given biotherapeutic constitute proprietary information about the reference biological product, which is not available to the manufacturer of the biosimilar product. It is recognized that even slight changes in the protein molecule may have an unexpected clinical impact and