biosimilars are given in the overarching guidance document. In addition, the EU has implemented specific guidance documents to address the unique safety issues that may be associated with a particular product class. These include the guidelines for granulocyte-colony stimulating factor, somatropins, recombinant interferon alpha, low-molecular-weight heparins, recombinant erythropoietin, monoclonal antibodies, follicle stimulating hormones, interferon beta, and recombinant human soluble insulin (EMA, 2006a,b,c, 2009a,b, 2010, 2012, 2013a,b, 2015).

In Canada, the guidance for biosimilars or SEBs was developed around the same time as the WHO document and was implemented in 2010 to provide manufacturers and stakeholders with information regarding the quality, safety, and efficacy requirements for approval of biosimilar products (Health Canada, 2010).

The US Food and Drug Administration (US FDA) allows for abbreviated licensing of biosimilars under the Biologics Price Competition and Innovation Act (BPCIA) of 2009. The licensure pathway permits a biosimilar biological product to be licensed under Section 351(k) of the Public Health Service Act (PHS Act). As per the guidance document, the biosimilar products should be shown to be similar to or interchangeable with a previously licensed reference product. "A biological product is considered similar to the reference product if it is highly similar to the reference product, and if there are no clinically meaningful differences between the products in terms of safety and efficacy" (US FDA, 2015a).

13.3 CHALLENGES IN PHARMACOVIGILANCE OF BIOSIMILARS

13.3.1 Uncertainties with Safety Profile of the Product at Authorization

At the time of authorization of a biosimilar drug product, a reduced nonclinical and clinical data package is acceptable if similarity between the reference product and the biosimilar product is clearly demonstrated. Information on issues such as immunogenicity, which may lead to hypersensitivity, to infusion related reactions, and the like, have to be characterized for biosimilar products before approval.

A slight change in the manufacturing process can alter the safety profile of the protein product, resulting in the formation of antidrug antibodies (ADAs) that could alter the overall benefit–risk profile of the product. Therefore, safety issues, such as immunogenicity, are a major concern for biotherapeutic products (Chirino et al., 2004; Schellekens, 2002; Sharma, 2007). For example, such changes leading to unexpected adverse events were seen with the epoetin product EPREX and, more recently, with interferon beta, REBIF. EPREX (epoetin α) is a synthetic erythropoietin used to treat anemia in patients with chronic kidney failure. EPREX was first authorized in Europe in 1988. In 1998, there was a marked increase in cases of pure red cell aplasia (PRCA) reported with epoetin (EPO) alpha products, with the majority being in chronic kidney disease patients taking subcutaneous EPREX. PRCA is a rare disorder that manifests as sudden severe onset of anemia characterized by complete absence of red cell precursors in the bone marrow and a reticulocyte count below 10×10^9/L. Serum analyses of patients with PRCA showed the presence of