EPO antibodies. Analysis of case series showed that the spike in cases of PRCA was temporally related to the replacement of human serum albumin by polysorbate 80 as stabilizer. It was suggested that polysorbate 80 could have increased the immunogenicity of EPREX by either forming micelles with epoetin or reacting with uncoated rubber stoppers to form leachates. The manufacturer also noted that the use of polysorbate 80 made the formulation less stable and therefore more vulnerable to degradation, which may have also resulted in increased immunogenicity (Boven et al., 2005; McKoy et al., 2008).

More recently, an increase in reports of thrombotic microangiopathy was observed with use of REBIF, an interferon beta product, in patients with multiple sclerosis (Hunt, 2014). Four cases of serious, some fatal thrombotic microangiopathy (TMA) were reported in patients in south Scotland. Six additional cases of TMA were reported to regulatory authorities in the United Kingdom (UK). There were very few cases reported globally for the initial 9 years from the launch of the product. It was noted that the increase in cases of TMA was seen in only those countries that used the same serum-free formulation as that being used in the UK formulation of REBIF (Giovannoni et al., 2009; Hunt, 2014). In this study, a strong correlation was seen to one manufacturing source and one formulation, thereby emphasizing that change in formulations can alter the safety profile of a product in such a way that may have clinically significant effects.

In order to address the limitations of the clinical trials in terms of the safety profile of biotherapeutics, including biosimilar drugs, regulators have made it mandatory to submit a risk management plan that has to be agreed upon by the regulatory authorities and by the manufacturer at the time of authorization of the drug. The risk management plan includes safety specifications, and based on these specifications, a detailed pharmacovigilance plan and risk minimization plan are developed by the marketing authorization holder (MAH). Based on the risk profile of the drug, the pharmacovigilance plan may include routine activities, which involve the collection, analysis, and reporting of spontaneous adverse event reports, or certain additional safety studies may be requested postauthorization to address efficacy or specific safety concerns. A risk minimization plan includes steps to be taken by the MAH to provide all relevant information regarding benefits and risks associated with the product to the stakeholders. In Canada, this information is disseminated as part of the product label in the Canadian product monographs and also as patient leaflets for every authorized drug. In cases where additional risk minimization activities are deemed necessary to mitigate specific risks, the MAH may be required to provide educational material and alert cards. Adverse drug reactions have to be reported as required by the Food and Drug Regulations in the same way as for any other medicinal product. Once the product is authorized, the MAH is required to provide periodic safety update reports (PSURs) as per ICH E2E guidelines in order to follow up on the already known and/or new or rare adverse events and to assess the overall benefit risk profile of the drug.

In the EU, specific guidance documents for biosimilars have been developed, based on the complexity of the molecule, to address the safety issues that are unique to that product class and to focus on the requirement for testing and monitoring of the product (EMA, 2006b,c, 2009a,b, 2010, 2012, 2013a,b, 2015). Any specific safety