

monitoring imposed on the reference product is required for biosimilar products as well. For example, all biosimilars for epoetin are required to monitor the incidence of PRCA. In the case of monoclonal antibodies, especially those authorized for cancer indication, the EU guidance states that additional long-term immunogenicity and safety data are required postauthorization. Health Canada recommends similar monitoring for specific safety concerns with biosimilar products.

In the EU, the MAH may also be required to conduct postauthorization safety studies (PASSs) in order to identify and characterize a safety hazard, confirm the safety profile of the medicines, and to assess the effectiveness of the risk management measures. Drug utilization studies (DUSs) are also used by regulatory authorities to identify the prescribing trends in clinical practice. In Canada, with the introduction of Bill C17, also known as Vanessa's Law, Health Canada now has the regulatory authority to order additional tests and studies from sponsors. Bill C17 is crucial in giving the authority to enhance the safety oversight of drugs throughout their life cycle (Health Canada, 2014).

### 13.3.2 ISSUES WITH INTERCHANGEABILITY/SUBSTITUTABILITY/SWITCHING

Another challenge in the pharmacovigilance of SEBs is interchangeability. As per the consensus document sponsored by the EU, the terms *switching*, *interchanging*, and *substitution* have distinct meanings. Switching refers to the treating physician's decision to exchange one medicine for another without the consent of the patient. Interchangeability is changing the reference product for the biosimilar by a health care professional, with the expectation of the same clinical outcome without the knowledge or consent of the patient. Substitution is the practice of dispensing one medicine instead of another that is equivalent, without the knowledge of the physician or the patient (European Commission, 2013). The initial clinical trials conducted to obtain authorization for a product are usually not powered to assess differences in adverse drug reactions between biosimilar product and reference product. As already described above, the complexity of the manufacturing process and changes in the formulations can lead to differences within batches of the same product. Not only are there differences between the reference product and the biosimilar product, but different lots of the biosimilar products may also vary. Therefore, tracking of each lot is important to ensure the traceability of the product, especially in cases where a particular batch may be associated with the adverse reaction (European Commission, 2013; Ebbers and Chamberlain, 2014).

There is a theoretical possibility that interchanging an innovator product with a biosimilar product may increase the immunogenicity to the drug product, which could potentially alter the efficacy and safety of both products. If the drugs are switched or substituted automatically, it is difficult to ascertain whether the adverse drug reactions are related to the innovator product or to the biosimilar product. Changes in formulation postauthorization can lead to substantially different product characteristics than the one approved. The studies required at the postapproval stage are not designed to be comparative to the reference product and therefore can create challenges for postmarket surveillance (Ebbers and Chamberlain, 2014). In Canada, the guidance document states that SEBs are not