indicate a need for adjustment after conducting additional clinical studies sponsored by the biosimilar manufacturer.

5.2.2.7 Stability

Since minor changes in a manufacturing process may affect the stability profile of a product, the stability claims of biosimilars cannot be extrapolated from their respective reference products. Instead, as is true of any medicinal product, the shelf life should be supported by real-time/real-conditions stability data, in compliance with the principles outlined in Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products and Q1A(R2) Stability Testing of New Drug Substances and Products (ICH, 1995, 2003). As a consequence, the shelf life of a biosimilar is not necessarily the same as that for the reference product. Whereas some guidelines prescribe undertaking comparative real-time stability studies on both the biosimilar and the reference, with the aim of detecting possible subtle differences that went unnoticed during the characterization studies (Health Canada, 2010), others don't (EMA, 2014a).

Yet all guidelines recognize the need to conduct accelerated stability and forced degradation studies not only on the biosimilar but also on the reference. In particular, forced degradation or stress conditions studies are standardly conducted on the medicinal products and their drug substance in order to reveal the pattern of degradation, to identify the likely degradation products, and, as a corollary, to gain insight into the analytical procedures that offer the best stability indicating potential (ICH, 1995, 2003). In the particular case of biosimilars, conducting comparative accelerated stability and stress conditions studies could reveal otherwise hidden properties of a product that warrant additional evaluation and/or controls.

5.3 APPARENT INCONSISTENCIES

The quality matter of biosimilars shows some singular features that merit emphasis. For instance, the complexity of biological medicinal products derives primarily from their drug substance. Accordingly, the emphasis of the quality comparability exercise is predominantly placed on the drug substance. However, it should be kept in mind that biosimilars are similar medicinal products, and not similar drug substances. Therefore, at the end of the day, biosimilarity is to be demonstrated at the level of the drug product. Guidelines are unambiguous in this regard. Considering the medicinal product as a whole in the comparability exercise makes sense at all levels, and the emphasis given to the drug substance may hide the consideration that the drug product deserves. For instance, safety issues related to inappropriate formulation were reported. The increased incidence of pure red cell aplasia linked to a change in the formulation of a recombinant human erythropoietin (EPO) is a notorious example. To comply with a new European regulation, human serum albumin used as an excipient was replaced by polysorbate 80. Through the action of polysorbate 80, organic compounds were leached from rubber stoppers, which in turn were eliciting a deleterious immune response to EPO (Sharma et al., 2004; Boven et al., 2005).