10.3.2 Switching and Alternating

As noted above, the BPCI Act refers to the switching and alternating of drug products. Switching refers to changing between the reference and biosimilar products, $R \rightarrow B$ and $B \rightarrow R$. In an initial phase, upon introduction of an approved biosimilar primarily the former ($R \rightarrow B$) will occur. However, subsequent to competitive incentives, over time $B \rightarrow R$ may also be considered, subsequently, also including alternating between R and B. However, in the long term, multiple biosimilars may be available and result in the alternating of multiple products as described above (e.g., $R \rightarrow B_1 \rightarrow B_2 \rightarrow B_1 \rightarrow B_3 \rightarrow R \rightarrow B_2$). The expectation of controlling the risks of safety and efficacy applies to every switching component in this chain of alternation.

One should raise the question of whether interchangeability (for patients under existing therapy) between different, independently developed biosimilars should even be considered. Indeed, since biosimilarity (a prerequisite for considering interchangeability according to the FDA) has not been demonstrated between two biosimilars, interchangeability for two or more products cannot even be considered unless biosimilarity between both products is shown followed by extensive clinical studies to prove interchangeability. It is obvious that in situations where multiple biosimilars are involved, the chances of impacts of drifts in quality attributes are much more pronounced.

10.4 INTERCHANGEABILITY IN CANADA

In Canada, the term *substitutability* is applied to two products that can be used in lieu of the other during and within the same treatment period, that is, for interchangeability as discussed in this chapter. The general guidance of Health Canada on biosimilars (or subsequent-entry biologics) does not consider explicitly interchangeability (Health Canada, 2010a). Still, the position of Health Canada on the substitution of biological products is clear but rather soft: "Health Canada does not support the automatic substitution of a subsequent-entry biologic for its reference biologic drug. Health Canada therefore recommends that physicians make only well-informed decisions regarding therapeutic interchange" (Health Canada, 2010b).

Health Canada's position does not have legal authority. Funds for the reimbursement of pharmaceutical expenses are dispensed by the provinces. They will be keen to promote introduction of new biosimilars, that is, their prescribability. Furthermore, they will also seek the status of interchangeability for biosimilar products. Thus, in Canada the positions on interchangeability of biologic products and the related conditions will be diverse and controversial.

10.5 INTERCHANGEABILITY IN THE EUROPEAN UNION

The EU was the first region in the world to set up a legal framework and regulatory pathways for biosimilars. In fact, the word "biosimilars" was coined during this legislative process.

The concept of a "similar biological medicinal product" was adopted in EU pharmaceutical legislation in 2004 and came into effect in 2005. The EMA was the first to lay down an abbreviated regulatory pathway for biosimilars. As of April 2016, 23 biosimilars were approved within the product classes of human growth hormone, granulocyte