no two batches are identical. Thus, each originator biologic varies somewhat from the original batch (drift), and in some cases the biosimilar is more similar to the original biologic than is the biologic itself. The FDA thus allows for a range within which the biosimilar must stay to be considered a biosimilar. Therefore, there is some variability in both the biologics and the biosimilar (Schneider, 2013). Also, there is the issue of the manufacturing process, whereby changes can cause drift in the process. As both biologics and biosimilars change their manufacturing process, variability between the processes can occur. For example, Remicade has had over 35 process changes since the original process. Indeed, Genzyme wanted to produce its originator biologic Myozyme in a larger facility, but the FDA ruled that the product was different from Myozyme, which was produced in a smaller facility. Achieving sufficient product uniformity can sometimes be difficult (Blackstone and Fuhr, 2010).

Since biosimilars are not identical but highly similar, they cannot be automatically substituted at the pharmacy level unless they are interchangeable. According to the FDA, "[a]n 'interchangeable' biological product is biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient. In addition, to be deemed an interchangeable biological product, it must be shown that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" (FDA, 2014).

Each country has its own unique regulatory requirements for biosimilars. The term *biosimilar* is often misused since many products referred to as biosimilars in some countries with less rigorous regulatory requirements do not meet the standard of being highly similar. Such biosimilars can be referred to as noncomparable biologics. We consider a biosimilar to be one approved in the US, EU, Canada, and Australia and one should be cautious in referring to other countries' noncomparables as biosimilars. Further, biosimilars are sometimes referred to as follow-on biologics.

Biobetters are products that are, as the name suggests, better than originator biologics. They could have greater efficacy, easier or more convenient administration, fewer side-effects, or a lower rate of potential immunogenicity (discussed below) which could lead to greater adherence. A second-generation biologic produced by the reference producer is one example of a biobetter. There has been considerable discussion concerning biobetters, but few are currently on the market except for second-generation originator products. However, many are reportedly being developed. In the US, an alternative to the 351(k) (biosimilars) created by the BPCIA is available, that is, the Biologic Licensing Application 351(a) of the Public Service Act, but it has not been used much for biobetters.

16.3 BENEFITS OF PHARMACEUTICAL INNOVATION

Innovation increases the quality of life and promotes economic growth. Pharmaceutical innovation has led to tremendous advances in the treatment of diseases and has