flexibility. For instance, the Canadian regulation allows use of a non-Canadian reference product, provided that it is shown to be a suitable proxy for the version actually licensed in Canada. However, this requirement cannot be met in countries that do not have a nationally licensed reference. The WHO guidance considers this possibility and, accordingly, makes some recommendations for the choice of the reference product: the reference product should be marketed for a suitable duration in a jurisdiction that has a well-established regulatory framework, and its original licensing should be based on the submission of full quality, nonclinical and clinical data, and so on.

### 5.2.2 Quality Package

Just as for any normal MAA, a complete quality/CMC section (CTD Module 3) is to be provided in a biosimilar application, addressing the manufacture, characterization, specifications, adventitious agent safety, stability, and the like, of the drug substance and drug product. These data need to be supplemented with a more specific package aimed at demonstrating comparability with the reference medicinal product. The assessment of similarity is viewed as a distinct collection of data supplementing the normal requirements. Accordingly, it may be recommended that this additional information be presented in a separate section such as Section 3.2.R in the EU application.

It is noteworthy that the reduction of the nonclinical and clinical data packages needs to be counterbalanced by a significant extension of the quality part.

#### 5.2.2.1 The Manufacturing Process

The adage "the process is the product" is often quoted to indicate that the quality attributes of biological products are the results of the manufacturing process by which they are produced. Differences in the manufacturing process may impact the quality profile of the product, affecting its safety and/or efficacy. Manufacturers of biosimilars have a very limited view of the manufacturing process of the reference product, only based on the information publicly available in the Scientific Discussion of the European Public Assessment Report (published by the EMA) and/or in the Chemistry Review of the Drug Approval Package (published by the FDA), for instance. The manufacturing processes of the biosimilar and its reference are thus not expected to be the same. This is particularly the case inasmuch a decade or more may separate the application for a biosimilar from its reference. The manufacturing process technology will most likely have evolved during this period of time.

The biosimilar is thus developed on its own, produced by a different manufacturing process (e.g., different starting materials, raw materials, equipment, process, in-process control, acceptance criteria). On some occasions, even the host cell type may be different. For example, in 2006, Valtropin was granted a marketing authorization in the EU under the legal base of similar biological medicinal product (EMA, 2012). The reference medicinal product for this application was Humatrope (EMA, 2014b). Both products contain somatropin (recombinant human growth hormone) as an active substance. Remarkably, whereas the active substance of Humatrope is produced in *Escherichia coli*, that of Valtropine is produced in *Saccharomyces cerevisiae*. This is quite an unusual situation, however. Guidelines generally recommend