different physicochemical or biological principles enlarge the possibility of detecting variants with one method, whereas the others do not.

Analytical characterization for biosimilars is discussed in greater detail in Chapter 2. A typical list of tests and methods is provided in Table 5.2.

5.2.2.4 The Comparability Exercise

The comparability exercise is defined in the WHO guideline as a "head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures" (WHO, 2013). The quality part is of decisive importance. Indeed, demonstration of a high degree of similarity as determined by robust quality data allows reducing the nonclinical and clinical requirements for licensing. It should be emphasized that the similarity is to be shown primarily at the level of the finished product. However, in guidelines, it is clearly stipulated or implicitly recognized that the active substances must also be similar, especially as the head-to-head comparison of formulated drug products is not always feasible, either because of the low concentration of the active substance or because of the presence of interfering excipients. Thus, the drug substance must be isolated from the reference medicinal product in order to be analyzed on its own. In this case, the isolation process should be outlined and carried out in such a way that the relevant quality attributes of the originator drug substance are not significantly altered, for example, by comparing the active substance before and after formulation/deformulation preparation.

The guideline ICH Q5E is aimed at providing principles for the comparability of biotechnological/biological products subject to changes in their manufacturing process (ICH, 2004). Although the scope of this guideline does not cover the comparison of two different products, a number of principles discussed in ICH Q5E may be applicable to the comparability exercise aimed at demonstrating similarity at the quality level between the biosimilar and its reference. However, it should be stressed that developing a biosimilar is different from introducing a change in the manufacturing process of a same product. In the latter case, the manufacturer has acquired solid knowledge of the product and of its manufacturing process and control. Drug substance as well as a range of values coming from historical data are available to the manufacturer. In contrast, the biosimilar manufacturer has access neither to the originator drug substance nor to the product information which remains proprietary, a hindrance referred to as the "knowledge gap" (Declerck et al., 2016). It has to rely on the originator drug product that is available on the market. The development of a biosimilar thus starts with the finished reference product and proceeds backwards.

Data collected during the comparability exercise from both the biosimilar and the reference product will be used to establish the range of variability of quantitative quality attributes. Apart from general statements on the need to follow an appropriate statistical approach, the guidelines provide little guidance on the number of lots to be analyzed and the statistical approach to be used in order to establish equivalence between the biosimilar and its reference for a given quality attribute and to set limits to its ranges. The answer to this question is not straightforward. The need for more detailed guidance was acknowledged by the authorities and should materialize through publication of a Reflection Paper on statistical methodology for the