in Figure 2.1B. However, in so doing significant debate and concern has been raised and to some extent still exists over the clarity as to what exactly is needed to establish and acquire regulatory approval of biosimilars, and about the potential problems or issues that biosimilars may create. Nevertheless, many biopharmaceutical and pharmaceutical companies are actively pursuing their development (Calo-Fernández and Martínez-Hurtado, 2012; Thayer, 2013) with the hope that it will bring the same success story (both as a new business opportunity and as an effective cost-reduction route to achieve better and increased access to these life-changing drugs) as that achieved by implementation of generics in the case of pharmaceuticals.

This chapter takes a close look at the scientific process of assessing the high comparability or similarity of a biosimilar to its corresponding innovator's biopharmaceutical from a structural perspective (which is associated with the biochemical and biophysical areas of the drug development process, highlighted as the darker areas in Figure 2.1B). In so doing, the following two areas will be emphasized: (1) the challenges that need to be overcome to successfully assess and characterize the physicochemical structure and properties of these complex drugs to obtain regulatory approval, which the FDA has already pointed out is dominated by the important issues and specific challenges concerning structural heterogeneity, HOS, and aggregation (FDA, 2009a) and (2) the analytical capabilities (in terms of tools and methods) that are available to establish adequate physicochemical structural comparability or similarity.

Before embarking on this discussion, it should again be pointed out that the analytical characterization of the structural or physicochemical component of the comparability or similarity process (which is the first and most fundamental step needed to be successfully executed in obtaining regulatory approval of a biosimilar) is only a part of a much broader process (which is largely the subject matter covered in this book). A process that has come to be referred to as the assessment of *biosimilarity*, which is assessed using the general concept referred to by the FDA as the *Totality of the Evidence* (Kozlowski et al., 2011; Woodcock et al., 2007), which in reality is a more general concept implemented in assessing and approving *all* drugs (Houde and Berkowitz, 2014a), as indicated in Figure 2.1A and B.

2.2 BIOSIMILARITY: AN EXTENSION OF THE CONCEPT OF COMPARABILITY

The underlying concept of biosimilarity is directly linked to what is now considered a common activity often carried out in developing and commercializing biopharmaceuticals called comparability studies; this activity was initiated by the FDA in 1996 (FDA, 1996) and formalized into the International Conference on Harmonisation (ICH) document designated as Q5C (ICH, 2004). Comparability studies are specifically associated with two important tasks: (1) assessing the ability of a biopharmaceutical manufacturer to be able to consistently make a biopharmaceutical on a lot-to-lot basis (which amounts to saying all lots are comparable in terms of meeting a set of established limits or specifications) and (2) enabling a biopharmaceutical manufacturer to introduce a change(s) into the process of making its biopharmaceutical (e.g., change in raw material, process step, site of manufacturing, etc.), as long