in the pivotal phase III clinical trials. By so doing, Biogen hoped it could make use of the prior phase III clinical trial data in filing the IFNβ drug copy for approval without the need to conduct much additional clinical work. In the end, Biogen was successful in showing and convincing FDA regulators that their copy of IFNβ was adequately comparable (via extensive physicochemical and biological work) to the IFNβ material made by Rentschler and used in the original pivotal clinical phase III trials. The success of this undertaking led to the landmark approval of Biogen's first biopharmaceutical, IFNβ (Avonex), in 1996 with minimal additional clinical work, which ushered in the concept of comparability into the biopharmaceutical industry (Blaich et al., 2007). Today this achievement also stands as a milestone event in fostering and bridging the ideas of comparability (or internal comparability) with the concept of biosimilarity (or external comparability) (Kozlowski et al., 2011; Woodcock et al., 2007).

2.3 THE UNIQUE CHALLENGES IN MAKING BIOSIMILARS VERSUS GENERICS FROM A PHYSICOCHEMICAL PERSPECTIVE

The introduction to this chapter presented the main features of biopharmaceuticals (including biosimilars) that make them different from pharmaceuticals (including generics). These differences prevent a biopharmaceutical manufacturer from making its biopharmaceutical identical and the task of making it adequately comparable on a lot-to-lot basis very difficult (Geigert, 2004). As a consequence, it creates an even greater challenge for the biosimilar manufacturer trying to make a biosimilar of an innovator's biopharmaceutical. This is because the underlying additional fine detail of physicochemical structural heterogeneity of a biopharmaceutical, which a biosimilar manufacturer is trying to copy, goes beyond the commonly known main structural element of the innovator's biopharmaceutical—the linear sequential ordering of the amino acids in its polypeptide chain(s). It is this additional fine detail of physicochemical structural information and its heterogeneous distribution among the biopharmaceutical molecules in a given lot and the variation of this distribution on a lot-to-lot basis (which is known only to the innovator and to the regulators who evaluated and approved the innovator's biopharmaceutical) that makes the process of producing a biosimilar even more challenging than making a generic of a pharmaceutical.

Indeed, in the case of making a generic drug, one only needs to know the *unique documented and publicly known chemical structure* of the pharmaceutical (e.g., aspirin). Once that structure is known, one can then simply design the chemical synthetic route to make the *identical* molecule (see Figure 2.2A). In contrast, in the case of attempting to make a biosimilar of a biopharmaceutical, knowing the chemical structure of an innovator's biopharmaceutical's amino acid sequence is unfortunately not its complete final structure. From a physicochemical point of view, a biopharmaceutical's structure also involves a collection of additional chemical modifications to its polypeptide chain(s) (involving primary or covalent bonds) and physical structural changes to its folded state (resulting from chemical modifications or/and