(McVie-Wylie et al., 2008)] on the glycans that are chemically attached to several sites on Myozyme, were observed to differ between the two reactors. Although the biopharmaceutical from the 2000 L was already approved and licensed in a number of other countries, when Genzyme filed for a supplemental license for approval in the US to sell the biopharmaceutical from its 2000 L reactor under Myozyme's original BLA, the FDA would not grant Genzyme approval owing to the lack of comparability of the phosphorylated glycans and recommended that Genzyme apply for a new BLA license for the 2000 L drug (Foumier, 2015; Mack, 2008).

The second case concerns the FDA approval in 2010 of the first generic version of low molecular weight heparin (LMWH) called Enoxaparin, to an original LMWH RP called Lovenex (FDA, 2010a,b). Although LMWH is classified as a pharmaceutical and is not a protein, the complex nature of this drug (a heterogeneous collection of different-sized oligosaccharides that is derived from a biological source, e.g., porcine intestinal mucosa) presented challenges in developing a copy of this drug that were much more similar to what a biosimilar manufacturer faces in attempting to make a copy of a biopharmaceutical than what a generic manufacturer faces in attempting to make an identical copy of a small organic molecule. Indeed, Enoxaparin is not an identical copy of Lovenex; it is a "highly similar" copy (Guerrini et al., 2015; Mourier et al., 2015). Nevertheless, the FDA was able to develop a rigorous scientific approach (based on five critical criteria) to assess the sameness of Enoxaparin to Lovenex, which was heavily dependent on analytical, functional, and pharmacodynamics data to allow the approval of Enoxaparin without the need to conduct clinical trials (Lee et al., 2013).

These two cases should make it apparent that, even though they represent very different scenarios and do not uniquely answer our question, the key factors in the critical decision-making process of granting or denying these approvals rested on the combination of analytics with whatever underpinning knowledge was known about how these drugs worked at the time in which regulatory action was taken. Both examples highlight the totality of the evidence mantra and bring into focus the realization that each drug approval or denial stands to a large extent on its own merit, spawning the need to use the infamous "case-by-case" phrase in formulating an answer to the question "What's important and what's not important?"

2.12 CONCLUSION

In the years following the approval of those biopharmaceuticals that have or are now nearing their patent expiration date, great strides have been made in improving our ability to analytically characterize these complex drugs to better support their development and approval. These new analytical capabilities are now being called upon to play an even more intensive and critical role in the approval process of a form of biopharmaceutical that has over the last decade attracted significant attention from those who make, use, and regulate biopharmaceuticals, called biosimilars. This form of biopharmaceutical is not a new or improved version of the RP with better therapeutic performance attributes. Rather, they are simply a "highly similar" copy of the RP that can be made and sold at a much lower price. The approval of biosimilars should thus play an important role in reducing the financial burden that