

the cost of biosimilar drugs. The FDA had taken a lead when it approved several complex and biological products without any clinical studies in patients and in all likelihood wanted to expand this practice based on the science of understanding the molecules.

The use of fingerprint-like similarity to obviate clinical trials is not new to the FDA. One of the better recent examples is the approval of enoxaparin. In approving enoxaparin, an LMWH, the FDA developed five criteria for fingerprinting evaluation of enoxaparin:

- Equivalence of physicochemical properties
- Equivalence of heparin source material and mode of depolymerization
- Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
- Equivalence in biological and biochemical assays
- Equivalence of in vivo PD profile

In approving enoxaparin, the FDA stated that

the five criteria ensure that generic enoxaparin will have the same active ingredient components as those of Lovenox's enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated. Therefore, pharmacological activity of the active ingredient of the generic enoxaparin and that of Lovenox can be expected to be the same.

While enoxaparin is not a protein, its complexity is perhaps more comparable to those some simpler proteins. For biosimilar products, the FDA lists fingerprint-like similarity requirements as shown in Figure 4.7.

The attributes that are significant to establish fingerprint-like similarity are shown in Figures 4.8 and 4.9.

4.7 Comparability versus similarity

It should be noted that biosimilarity is the outcome of various similarity exercises. We do not demonstrate structural and functional biosimilarities; it is merely analytical similarity. We also do not demonstrate structural or functional comparability; we demonstrate similarity. There is a difference between these two terms as *comparability* refers to postapproval changes requiring a comparison between the products before and after the changes are made. Generally, the term *comparability* is used in conjunction with *protocol* to define this exercise. We can use *comparison* but not *comparability* if we do not want to confuse the agencies about the intent of the exercise.

In light of the confusion created in the literature, in the regulatory guidance worldwide and by developers, it is important to understand the