3.13.4.2 3D structure As previously described, proteins must be folded into a 3D structure to become functional (sometimes a 3D structure can be misfolded). The proteins within a biologic will have one major 3D structure along with a distribution of other variants differing in a 3D structure. Our current ability to predict the potency of biological drugs would be enhanced if we had improved ability to measure and quantify the correct (major) 3D structure, the aberrant 3D structures (misfolding), and the distribution of different 3D structures.

3.13.4.3 Protein aggregation Some biological products can stick to one another. When many protein molecules stick together, they are referred to as aggregates and have the potential to cause adverse immune responses in patients. There are many forms and sizes of aggregates, and many current methodologies have gaps in their ability to detect different types of aggregates. Our ability to minimize adverse immune reactions would be enhanced if we had improved ability to measure and quantify various types of aggregates.

The field of biopharmaceuticals is rapidly advancing—in many ways more quickly than analytical technologies. New measurement tools and standards would be of value in all areas, particularly, reliable and discriminating material standards that can enhance the use of current methodologies and encourage new technologies to fill current gaps. Moreover, as the field of biopharmaceuticals continues to advance, there is the potential for greater research and development in the evolving area of biosimilar products, which stand to save consumers billions of dollars over time.

3.14 The comparative EMA and FDA mind-set

An analysis of the differences between the FDA and the EMA forms a good basis to understand the complexity of developing biosimilars. While the emphasis in this book is on understanding what the FDA considers to be essential elements of biosimilarity, it is to be expected that companies filing for the FDA approval would also want to secure the EU markets, requiring a planning that will cover the expectations of both agencies. Given in the following is a cursory overview of the mind-sets of the two agencies.

Both the EMA and FDA are continuously evolving their approach to approving biosimilars; the changes in the approval standards will come as a result of the experience of approving these products, their safety market confidence, and also to a better understanding of the science involved in assessing the safety and the effectiveness of these products. It is for this reason that I am calling this *current* mind-set.

- The guiding principle of a biosimilar development program is to establish similarity between the biosimilar and the reference product by the *best possible means*, ensuring that the