developing biosimilar products that are important for a biosimilar product developer to understand, more particularly, as this pertains to how the development of measurement science, standards, and related technologies might make it easier to characterize FDA-regulated biological products. Dr. Kozlowski recognized three specific properties of biological products that cannot be sufficiently measured, but are critical for understanding the behavior of biological protein products and suggested that better analytical methods that can measure these three properties would be extremely helpful in determining the similarity of similar biological protein products.

In approving biosimilar products, the FDA wants to understand the characterization and composition of these products, more specifically, what materials they are made up of, and how the materials are arranged (i.e., the structure) at a molecular level. For some products, particularly the nonbiological products, the characterization is relatively straightforward since adequate analytical technology currently exists that is capable of fully understanding the structural nuances of these products. However, in the era of molecular biology where many new therapies are manufactured by inserting novel genes into living cells so as to produce therapeutic proteins by biologic processes, a new challenge has come about that raises the bar on the technology of analytical testing.

3.13.1 Size and complexity of biological drugs: Protein therapeutics

Compared to assessing the structure of small-molecule drugs, which have generally fewer than 100 atoms, assessing the structure of biological drugs is a formidable task. Therapeutic proteins are much larger than typical small-molecule drugs. Using molecular weight as a measure of size, human growth hormone is more than 150 times larger than aspirin, and a mAb is more than five times larger still than human growth hormone. Therapeutic proteins are also much more complex than typical small-molecule drugs.

The manufacture of biological drugs is also quite complex. Most biological drugs are composed of many thousands of atoms linked together in a precise arrangement (called the primary structure). This organization of atoms is further organized into a 3D HOS by the folding of the linked atoms into a specific pattern that is held together by relatively unstable connections. A protein molecule consists of a long chain of building blocks called amino acids, of which there are 20 types—a single protein chain can be made up of hundreds of amino acids. The sequential order of these building blocks in the chain can be critical for medicinal activity. Protein chains with the same sequence of amino acids can fold in different ways—much like a single piece of rope can be tied to a variety of different knots. The specific folding of these chains is also very important in carrying out their therapeutic functions.