"peptides" have 40 or fewer amino acids and are not "proteins." The FDA also proposed to define *chemically synthesized polypeptide* as an alpha amino acid polymer that is entirely made by chemical synthesis and that has fewer than 100 amino acids. Until the draft guidance is finalized, these definitions must be considered proposals. Nevertheless, they signal that the FDA might be shifting from its traditional, ad hoc approach to jurisdictional decisions to a new approach guided by bright-line rules.

The differentiation of products from being therapeutically interchangeable pharmaceuticals to biosimilar biopharmaceuticals had its roots in the size of active molecules; compared with synthetic small molecules, biologics are 100 to 1000 times larger, having several hundred amino acids (average molecular weight of 150 per amino acid), which are biochemically joined together in a defined sequence by peptide bonds to form a polypeptide. Thus, structurally, biologics are more complex than low–molecular weight drugs, consisting of primary (amino acid sequence) and secondary (α-helix and β-pleated sheet) structures, which are folded into complicated 3D tertiary structures. In some biopharmaceuticals, stable associations of tertiary structures of individual proteins form a quaternary structure. After synthesis, these structures are often further modified by PTMs such as glycosylation or sialylation, which may be crucial for biological activity. Furthermore, due to a larger size and structural complexity, the characterization of a biopharmaceutical presents an enormous challenge.

2.2 The rise of biosimilars

The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Barack Obama on March 23, 2010, amends the PHSA to create an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be biosimilar if data show that, among other things, the product is "highly similar" to an already-licensed biological product.

2.2.1 Legislative history

The history of the developments leading to the signing of the agreement and the progress so far in implementing a biosimilar pathway are discussed in the following.

March 2009—Californian Democrat Henry Waxman introduces a bill in the House that would clear a regulatory path for generic manufacturers to produce biosimilars after a five-year period of market exclusivity. Major biotech companies were hoping for 14 years of exclusivity.