

**Summary: Definition of the Term “Biological Product”
(FDA-2018-N-2732)**

Publication Date: December 12, 2018

Comments Due: February 25, 2019

On Dec 12, 2018 The Food and Drug Administration (FDA) issued a [new proposal](#) to amend its regulation that defines “biological product” to incorporate changes made by the Biologics Price Competition Act of 2009 (BPCI Act). The BPCI Act amended the definition of biological product to include a “protein (except any chemically synthesized polypeptide.” To clarify these terms, FDA is proposing to provide its interpretation of the terms “protein” and “chemically synthesized polypeptide.”

By codifying interpretations of the terms “protein” and “chemically synthesized polypeptide”, FDA seeks to reduce regulatory uncertainty over what products are regulated as drugs or biological products, therefore allowing FDA and private industry to spend less time and resources on case-by-case determinations. In its proposal, FDA states that these interpretations are consistent with terms that FDA previously described in a [final guidance document](#) issued on April 30, 2015. Comments on this proposal must be submitted to the FDA by February 25, 2019. Any final rule that results from this proposal will become effective 60 days after publication in the Federal Register or on March 23, 2020, the end of the 10-year transition period specified in the BPCI Act, whichever is earlier.

The following is a summary of FDA’s proposal:

The current definition of a “biological product” under the BPCI Act is, “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide,) or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, cure of disease or condition of human beings.”

FDA’s Interpretation of the Term “Protein”

Under FDA’s proposed interpretation, the term “protein” would mean any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. FDA notes that this interpretation of the term “protein” would not include peptides as most scientific sources exclude peptides when defining a protein. FDA concludes that, other than size, there does not appear to be a precise set of structural or functional attributes that would define a protein so as to clearly distinguish proteins from peptides. FDA determined that 40 amino acids is appropriate for defining the upper size boundary of a peptide after a pertinent literature review although there is support in the literature for a threshold of 50 amino acids.

FDA is proposing that for products with amino acids composed of multiple chains, each of which is less than 40 amino acids, FDA will evaluate such situations on a case-by-case basis. If this is the natural structure and the total is 40 amino acids or greater, the structure will be considered a “protein.” Additionally, there may be a peptide that is naturally less than 40 amino acids but the proposed

pharmaceutical drug substance may have additional amino acids added so that the total is 40 amino acids or longer. In such situations, FDA is proposing to assess the situation on a case-to-case basis.

FDA's Interpretation of the Term "Chemically Synthesized Polypeptide"

FDA would interpret a "chemically synthesized polypeptide" as any alpha amino acid polymer that is (1) made entirely by chemical synthesis and (2) is greater than 40 amino acids but less than 100 amino acids in size. FDA is choosing to define "chemically synthesized polypeptide" narrowly to mean any molecule that is made entirely by chemical synthesis and conforms to the size listed above.

The phrase, "made entirely by chemical synthesis" would mean that all amino acids in the peptide chain were added to the peptide by a synthetic process that does not involve any synthesis of portion of the peptide using cell-based and cell-free recombinant-DNA-directed synthesis or recombinant-RNA-directed synthesis. While not explicitly stated in the proposal, any polypeptide chain of 100 amino acids or longer would be considered a protein irrespective of the method in which it is made.