(1)(iii) and (b)(2)(i)). For example, the term *reference product* should be used in the IB only to refer to the single biological product licensed under section 351(a) of the Public Health Service Act against which the proposed biosimilar product is evaluated for purposes of submitting a 351(k) application. The IB and study protocol(s) should use consistent nomenclature that clearly differentiates the proposed biosimilar product from the reference product. The IB and study protocol(s) also should clearly describe whether the comparator used in each study is the U.S.-licensed reference product or a non-U.S.-licensed comparator product, and use consistent nomenclature that clearly differentiates these products. If a non-U.S.-licensed comparator product is being used in a study conducted in the United States, the IB and study protocol(s) should clearly convey that the product is not FDA-approved and is considered an investigational new drug in the United States. The IB and study protocol(s) also should avoid conclusory statements regarding regulatory determinations (e.g., "comparable," "biosimilar," "highly similar") that have not been made.

3.12.3 Provisions related to requirement to submit a BLA for a "biological product"

Q. II.1: How does the FDA interpret the category of "protein (except any chemically synthesized polypeptide)" in the amended definition of "biological product" in section 351(i)(1) of the PHS Act?

A. II.1: The BPCI Act amends the definition of "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)" and provides that an application for a biological product must be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020, described in section 7002(e) of the Affordable Care Act.

The FDA has developed the following regulatory definitions of "protein" and "chemically synthesized polypeptide" to implement the amended definition of "biological product" and provide clarity to prospective applicants regarding the statutory authority under which products will be regulated.

Protein—The term "protein" means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

For purposes of this definition, the size of the molecule is based on the total number of amino acids and is not limited to the number of amino acids in a contiguous sequence. However, compounds greater than 40 amino acids in size will be scrutinized to determine whether they are related to a