



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 600

[Docket No. FDA-2018-N-2732]

RIN 0910-AH57

Definition of the Term “Biological Product”

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is proposing to amend its regulation that defines “biological product” to incorporate changes made by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), and to provide its interpretation of the statutory terms “protein” and “chemically synthesized polypeptide.” Under that 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. A *chemically synthesized polypeptide* would mean any alpha amino acid polymer that is made entirely by chemical synthesis and is greater than 40 amino acids but less than 100 amino acids in size. This proposed rule is intended to clarify the statutory framework under which such products are regulated.

DATES: Submit either electronic or written comments on the proposed rule by **[INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before **[INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL***

REGISTER]. The <https://www.regulations.gov> electronic filing system will accept comments until midnight Eastern Time at the end of **[INSERT DATE 75 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions.")

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2018-N-2732 for “Definition of the Term ‘Biological Product.’” Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.”

Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Janice Weiner, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6270, Silver Spring, MD 20993, 301-796-3475, janice.weiner@fda.hhs.gov.

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I. Executive Summary

A. *Purpose of the Proposed Rule*

FDA proposes to amend its regulation that defines “biological product” to make a technical revision and to conform to the statutory definition enacted in the BPCI Act. The BPCI Act amended the definition of *biological product* in section 351(i) of the Public Health Service Act (PHS Act) to include a “protein (except any chemically synthesized polypeptide).” The proposed rule would make conforming changes to § 600.3 (21 CFR 600.3) to add “protein” and “chemically synthesized polypeptide.”

B. *Summary of the Major Provisions of the Proposed Rule*

Under the proposed rule, the term *protein* would mean any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size, and the term *chemically synthesized polypeptide* would mean any alpha amino acid polymer that: (1) is made entirely by chemical synthesis and (2) is greater than 40 amino acids but less than 100 amino acids in size. This is consistent with interpretations of these terms that FDA previously described in a final guidance document issued on April 30, 2015 (see 80 FR 24259 (announcing the availability of a guidance for industry entitled “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,” available at <https://www.regulations.gov> (Docket No. FDA-2011-D-0611) (Biosimilars Q&A Guidance))).

C. Legal Authority

FDA is proposing to amend its regulations to implement certain aspects of the BPCI Act. FDA’s authority for this rule derives from the biological product provisions in section 351 of the PHS Act (42 U.S.C. 262), and the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, *et seq.*) applicable to drugs. The rule is necessary to clarify the statutory authority under which biological products are regulated and to prevent inconsistent regulation.

D. Costs and Benefits

This proposed rule would codify FDA’s interpretation of the statutory terms “protein” and “chemically synthesized polypeptide” in a manner that is consistent with interpretations of these terms that FDA previously described in guidance (see Biosimilars Q&A Guidance). Formalizing these interpretations would reduce regulatory uncertainty over whether certain products are regulated as drugs or biological products. This reduced uncertainty, under the

“bright-line” approach described in the proposed rule, would allow both FDA and private industry to avoid spending hours and resources on case-by-case determinations for each product. Our primary estimate of the benefits from these cost savings in 2017 dollars annualized over 10 years is \$340,766 using a 7 percent discount rate and \$321,506 using a 3 percent discount rate. We also calculate ranges of benefits of \$318,137 to \$355,690 and \$300,617 to \$335,282, respectively. Additionally, drug manufacturers would need to spend time to read and understand the proposed rule. We monetize the time spent by industry and estimate an annualized cost range from \$14,471 to \$18,089, with a primary estimate of \$16,079 using a 7 percent discount rate over a 10-year horizon. For a 3 percent discount rate, we estimate a range of \$12,378 to \$15,472, with a primary estimate of \$13,753.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
BPCI Act	Biologics Price Competition and Innovation Act of 2009
CFR	Code of Federal Regulations
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
PHS Act	Public Health Service Act
U.S.	United States
U.S.C.	United States Code

III. Background

A. Introduction

The BPCI Act amended the definition of *biological product* in section 351(i) of the PHS Act to include a “protein (except any chemically synthesized polypeptide).” As amended by the BPCI Act, a *biological product* is defined as “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, or cure of a disease or condition of human beings” (see section 351(i)(1) of the PHS Act).

The BPCI Act clarified the statutory authority under which certain protein products are to be regulated. Although the majority of therapeutic biological products have been licensed under section 351 of the PHS Act, some protein products historically have been approved under section 505 of the FD&C Act (21 U.S.C. 355). The BPCI Act requires that a marketing application for a “biological product” (that previously would have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act, subject to certain exceptions during a 10-year transition period ending on March 23, 2020 (see sections 7002(e)(1) through (3) and (e)(5) of the BPCI Act).

The BPCI Act also amended the PHS Act and other statutes to create an abbreviated licensure pathway in section 351(k) of the PHS Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the BPCI Act). The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (commonly referred to as the “Hatch-Waxman Amendments”), which established abbreviated pathways for the approval of drug products under section 505(b)(2) and (j) of the FD&C Act. FDA is proposing to provide its interpretation of the terms “protein” and “chemically synthesized polypeptide” to clarify the statutory framework under which such products are regulated.

B. History of the Rulemaking

On October 5, 2010, the Agency published a notice of public hearing and request for comments concerning implementation of the BPCI Act (75 FR 61497). Information on this

public hearing, including the *Federal Register* notice, meeting transcripts, and public comments can be found at <https://www.regulations.gov> (Docket No. FDA-2010-N-0477). In the notice, FDA addressed “the absence of scientific consensus on the distinction between the categories of ‘protein’ and ‘polypeptide’ or ‘peptide,’ ” and requested comment concerning how these statutory terms should be interpreted. FDA also described its thinking on this topic and sought additional comments by opening a docket for the Agency’s draft guidance document on “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009” (see 77 FR 8885, February 15, 2012; available at <https://www.regulations.gov> (Docket No. FDA-2011-D-0611)) (Biosimilars Q&A Draft Guidance Docket). This draft guidance document issued in 2012 has been superseded by subsequent guidance documents.

FDA reviewed the relevant comments in these public dockets and conducted an extensive analysis of the scientific literature in considering how to interpret “protein (except any chemically synthesized polypeptide)” in the amended definition of “biological product” in section 351(i) of the PHS Act.

Some comments submitted to the public docket established for the Biosimilars Q&A Draft Guidance supported using the size of the alpha amino acid polymer as the basis for FDA’s interpretation of the statutory term “protein.” Other comments suggested that FDA should consider structural and/or functional attributes and, for example, interpret the statutory term “protein” to mean an alpha amino acid polymer with a specific defined sequence that requires a stable multidimensional conformation for its function and is manufactured by a process that utilizes a biological system. Several comments suggested that FDA interpret the statutory term “chemically synthesized polypeptide” to mean any linear chain of alpha amino acids that is made

entirely by chemical synthesis, irrespective of the size of the chain. Some, but not all, of these comments also suggested that a chemically synthesized polypeptide should not rely on higher order structure for functionality.

A review of the scientific literature and dictionaries demonstrates consensus on certain aspects of the definitions of the terms “protein,” “polypeptide,” and “peptide,” as well as how the definitions vary.

1. Dictionary Definitions

a. Protein:

- “A complex, high polymer containing carbon, hydrogen, oxygen, nitrogen, and usually sulfur, and composed of chains of amino acids connected by peptide linkages....” (Ref. 1)
- “Protein molecules consist of one or several long chains (polypeptides) of amino acids linked in a characteristic sequence.” (Ref. 2)
- “A high molecular weight polypeptide of L-amino acids that is synthesized by living cells. Proteins are biopolymers with a wide range of molecular weights, structural complexity, and functional properties.” (Ref. 3)
- “Any of a large class of complex organic chemical compounds that...consist of long chains of amino acids connected by peptide bonds and have distinct and varied three-dimensional structures.” (Ref. 4)

b. Polypeptide:

- “The class of compounds composed of acid units chemically bound together with amide linkages (-CO·NH-) with elimination of water. A polypeptide is thus a polymer of amino acids. The chain of amino acids (less than 100) are

linked by peptide bonds.” (Ref. 1)

- “A peptide comprising 20 or more amino acids. Polypeptides that constitute proteins usually contain 100-300 amino acids.” (Ref. 2)
- “The term [polypeptide] is most often used for proteins, which can consist of one or more polypeptide chains, but can also be used more generally for all amino acid polymers including peptides, polyamino acids, and chemically synthesized polymers of amino acids.” (Ref. 5)
- “A linear polymer of more than 10 amino acids that are linked by means of peptide bonds.” (Ref. 3)
- “A peptide which on hydrolysis yields more than two amino acids....See peptide.” (Ref. 6)

c. Peptide:

- “See polypeptide.” (Ref. 1)
- “Any of a group of organic compounds comprising two or more amino acids linked by peptide bonds....Polypeptides contain more than 20 and usually 100-300.” (Ref. 2)
- “A chemical compound that is composed of a chain of two or more amino acids and is usually smaller than a protein.” (Ref. 4)
- “Any member of a class of compounds of low molecular weight which yield two or more amino acids on hydrolysis....Peptides form the constituent parts of proteins.” (Ref. 6)
- “Peptides...are oligomers in which the repeating units are amino acids. Peptides have a defined sequence of amino acids that are linked together by

formation of peptide bonds. In contrast to polypeptides and proteins, peptides consist of a small number of amino acids. The distinction between a peptide and a polypeptide is somewhat arbitrary, but generally a peptide has between 2 and 50 amino acid residues....Most peptides are unstructured, described as having a random coil conformation, but others have highly ordered secondary and tertiary structure similar to that observed in larger proteins.” (Ref. 5)

2. Textbook Definitions

- “Most natural polypeptide chains contain between 50 and 2000 amino acid residues and are commonly referred to as proteins. Peptides made of small numbers of amino acids are called oligopeptides or simply peptides.” (Ref. 7)
- “Proteins are molecules that consist of one or more polypeptide chains. These polypeptides range in length from ~40 to ~33,000 amino acid residues.” (Ref. 8)
- “Proteins consist of one or more linear polymers called polypeptides...a minimum of 40 residues seems to be required for a polypeptide to adopt a stable three-dimensional structure in water.” (Ref. 9)
- “Many terms are used to denote the chains formed by the polymerization of amino acids. A short chain of amino acids linked by peptide bonds and having a defined sequence is called an oligopeptide, or just peptide; longer chains are referred to as polypeptides. Peptides generally contain fewer than 20-30 amino acid residues, whereas polypeptides are often 200-500 residues long.” (Ref. 10)

- “A protein molecule is made from a long chain of these amino acids, each linked to its neighbor through a covalent peptide bond. Proteins are therefore also known as polypeptides. Each type of protein has a unique sequence of amino acids.... Proteins come in a wide variety of shapes, and they are generally between 50 and 2000 amino acids long.” (Ref. 11)

As the previous examples demonstrate, sources disagree over certain aspects of the definitions of these terms, especially the term “polypeptide.”

At the same time, despite the lack of precise, agreed-upon definitions, most, if not all, sources agree about certain aspects of the meanings of these terms. These areas of agreement may be summarized in the following manner. First, all of the terms (*protein*, *polypeptide*, and *peptide*) refer to amino acid polymers (“chains”) made up of alpha amino acids linked by peptide bonds. Second, *protein* refers to chains containing a specific, defined sequence of amino acids, generally provided by a corresponding DNA or RNA sequence. As noted in one biochemistry textbook: “In 1953, Frederick Sanger determined the amino acid sequence of insulin, a protein hormone [figure omitted]. *This work is a landmark in biochemistry because it showed for the first time that a protein has a precisely defined amino acid sequence.*” (Ref. 7) (emphasis in original). Finally, *peptide* is a term distinct from *protein*. Most sources agree that the term *peptide* generally refers to smaller, simpler chains of amino acids, while *protein* is used to refer to longer, more complex chains. Based on these areas of agreement, the generally accepted meanings of *protein*, *polypeptide*, and *peptide* appear to include the following: all three terms refer to amino acid polymers. *Proteins* are long, complex polymers of alpha amino acids. Each protein has a specific, defined sequence. *Peptides* are distinct from proteins.

In applying its scientific expertise to interpret the statutory terms “protein” and “chemically synthesized polypeptide,” FDA seeks to establish a scientifically reasonable, bright-line rule that provides regulatory clarity and facilitates the implementation of the BPCI Act. A clear rule facilitates efficient use of time and resources by both FDA and applicants and reduces regulatory uncertainty.

Under the Agency’s proposed interpretation, the term “protein” in the amended definition of *biological product* would not include peptides. In general, most scientific sources describe the term *protein* as excluding “peptides” (i.e., amino acid polymers or “chains” that are generally shorter and simpler than proteins). Thus, to the extent that there is a generally accepted meaning of “protein,” peptides appear to be outside the scope of the term.

With these considerations in mind, FDA is proposing a size-based cutoff for distinguishing peptides from proteins that is supported by scientific sources. This approach reflects the Agency’s conclusion 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. Specifically, for purposes of interpreting the BPCI Act, the Agency is proposing to codify that “*protein* (except any chemically synthesized polypeptide)” would mean any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. This threshold, based on a single, well-defined criterion, would supply a clear, bright-line rule.

IV. Legal Authority

FDA’s authority for this proposed rule derives from the biological product provisions in section 351 of the PHS Act and the provisions of the FD&C Act (21 U.S.C. 321, *et seq.*) applicable to drugs. Under these provisions of the PHS Act and the FD&C Act, FDA has the authority to issue regulations designed to ensure, among other things, that biological products are

safe, pure, and potent and manufactured in accordance with current good manufacturing practices. FDA also has general authority to issue regulations for the efficient enforcement of the FD&C Act and the PHS Act, under section 701 of the FD&C Act (21 U.S.C. 371) and section 351(j) of the PHS Act.

V. Description of the Proposed Rule

This proposed rule would amend the definition of *biological product* in § 600.3(h) to make a technical revision and to conform to changes in the statutory definition of “biological product” made by the BPCI Act.

We are proposing to revise the definition of *biological product* in § 600.3(h) by replacing the phrase “means any” with the phrase “means a” to conform to the text of section 351(i)(1) of the PHS Act. This proposed technical revision to the definition of *biological product* is not intended to alter our interpretation of § 600.3(h).

We also are proposing to define a *biological product* in § 600.3(h) to include a “protein (except any chemically synthesized polypeptide).” We are proposing to add paragraphs (h)(6) and (7) to this section to provide our interpretation of the terms “protein” and “chemically synthesized polypeptide.”

Under the proposed rule, 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’s proposed interpretation of this statutory term is informed by several factors. The scientific literature describes a *protein* as a defined sequence of alpha amino acid polymers linked by peptide bonds and generally excludes “peptides” from the category of “protein.” Similarly, a *peptide* generally refers to polymers that are smaller, perform fewer functions, contain less three-dimensional structure, are less likely to be post-translationally modified, and, therefore, are generally

characterized more easily than proteins. Consistent with the scientific literature, FDA is proposing to codify its interpretation of the term “protein” in a manner that does not include peptides. To enhance regulatory clarity and minimize administrative complexity, FDA is proposing to codify an approach that distinguishes proteins from peptides based solely on size (i.e., number of amino acids).

In the absence of clear scientific consensus on definitive criteria that distinguish proteins from peptides, including the exact size at which a chain(s) of amino acids becomes a protein, FDA reviewed the pertinent literature and concluded that a threshold of 40 amino acids is appropriate for defining the upper size boundary of a peptide. Although there also is support in the scientific literature for a threshold of 50 amino acids, FDA believes that a threshold of 40 amino acids is more appropriate based on the scientific literature and alignment with current regulatory practice (see Refs. 5, 7, 8, 9, 11). FDA’s proposal to use a threshold of 40 amino acids for its “bright-line” approach reflects that amino acid polymers that are greater than 40 amino acids may often assume several of the structural and functional characteristics that are generally associated with proteins, lending a higher level of complexity to these products. Accordingly, FDA proposes to consider any polymer composed of 40 or fewer amino acids to be a peptide and not a protein. Therefore, unless a peptide otherwise meets the statutory definition of a “biological product,” it would be regulated as a drug under the FD&C Act.

Where an amino acid polymer is greater than 40 amino acids in size and is related to a naturally occurring peptide (i.e., a polymer that is 40 or fewer amino acids in size), such a polymer would be reviewed to determine whether the additional amino acids that cause the peptide to exceed 40 amino acids in size raise any concerns about the risk/benefit profile of the product.

Some amino acid polymers are composed of multiple amino acid chains that are associated with each other. To determine the size of such an amino acid polymer for purposes of FDA's interpretation of the terms "protein" and "chemically synthesized polypeptide," FDA would evaluate whether two or more of its amino acid chains are associated in a manner that is found in naturally occurring proteins. In proposed § 600.3(h)(6) and (7), FDA explains that when two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer would be based on the total number of amino acids in those chains, and would not be limited to the number of amino acids in a contiguous sequence. In other words, the amino acids in each such amino acid chain would be added together to determine whether the product meets the numerical threshold in FDA's interpretation of the terms "protein" and "chemically synthesized polypeptide." However, for products with amino acid chains that are associated with each other in a manner that is not found in nature (i.e., amino acid chains that are associated with each other in a novel manner that is not found in naturally occurring proteins), FDA would conduct a fact-specific, case-by-case analysis to determine whether the size of the amino acid polymer, for purposes of this definition, should be based on adding each of the amino acids in the amino acid chains together, or should be based on separate consideration of the amino acid chains (e.g., the number of amino acids in the largest chain). In such cases, FDA would consider in its analysis, among other things, any structural or functional characteristics of the product.

The proposed rule would define *chemically synthesized polypeptide* to mean any alpha amino acid polymer that: (1) is made entirely by chemical synthesis and (2) is greater than 40 amino acids but less than 100 amino acids in size. As amended by the BPCI Act, the term "protein" specifically excludes chemically synthesized polypeptides. Thus, chemically

synthesized polypeptides will continue to be regulated as drugs under the FD&C Act unless the product meets the statutory definition of a “biological product” on another basis.

Where an amino acid polymer is greater than 99 amino acids in size and is related to a naturally occurring peptide or polypeptide of shorter length, such a polymer would be reviewed to determine whether the additional amino acids that cause the polymer to exceed 99 amino acids in size raise any concerns about the risk/benefit profile of the product.

FDA’s proposed interpretation of this statutory term is informed by several factors. The statutory category of “protein” parenthetically excludes “any chemically synthesized polypeptide.” There are several definitions of *polypeptide* in the scientific literature. Some are broad (e.g., polypeptide means any amino acid polymer), while others are more narrow (e.g., polypeptide means any amino acid polymer composed of fewer than 100 amino acids). FDA believes that a narrow definition of polypeptide is most appropriate in this context because, among other reasons, this avoids describing an exception to the statutory category of protein that includes a broader category of molecules. In addition, FDA believes that any chemically synthesized polypeptide composed of more than 99 amino acids would have, among other characteristics, a level of structural and functional complexity and sensitivity to environmental conditions that makes regulating such a protein under the same statutory authority as the majority of proteins more appropriate. Moreover, a narrow definition of polypeptide means that larger and/or more complex proteins (i.e., amino acid polymers composed of more than 99 amino acids) are considered to be biological products regardless of their method of manufacture. This approach also addresses the concern raised in a public comment “that reliance on the mode of manufacture will create incentives for a manufacturer to choose a process that may be suboptimal solely to enable its product to be regulated under a particular statute” (Biosimilars

Q&A Draft Guidance Docket). Therefore, FDA proposes to interpret the statutory exclusion for *chemically synthesized polypeptide* narrowly to mean any molecule that is made entirely by chemical synthesis and that is composed of greater than 40 amino acids but less than 100 amino acids in size. 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 any portion of the peptide using cell-based or cell-free recombinant-DNA-directed synthesis or recombinant-RNA-directed synthesis. Chemically synthesized polypeptides would be regulated as drugs under the FD&C Act unless the molecule otherwise meets the statutory definition of a “biological product.” For example, vaccines are specifically identified as biological products under the statutory definition in section 351(i) of the PHS Act irrespective of their size, content, or method of manufacture. Accordingly, vaccines will continue to be regulated as such under the PHS Act, even if they contain, or are composed of, an amino acid chain of 40 or fewer amino acids and/or a chemically synthesized polypeptide composed of greater than 40 amino acids but less than 100 amino acids in size.

FDA seeks comment on any additional considerations for proposed products that are combination products or meet the statutory definition of both a “device” and a “biological product.” We also encourage prospective sponsors or applicants to contact FDA with product-specific questions. Any final rule that results from this proposed rule 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 (see sections 7002(e)(1) through (3) and (e)(5) of the BPCI Act).

VI. Proposed Effective Date

If finalized, this rule would take effect 60 days after publication in the *Federal Register* or on March 23, 2020, whichever is earlier.

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule does not impose new regulatory burden on small entities, other than administrative costs of reading and understanding the rule, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or

more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

This proposed rule would codify FDA’s interpretation of the statutory terms “protein” and “chemically synthesized polypeptide,” in a manner that is consistent with interpretations of these terms that FDA previously described in the April 30, 2015, guidance (see Biosimilars Q&A Guidance). Formalizing these interpretations would reduce regulatory uncertainty introduced by the BPCI Act. Specifically, the proposed rule would clarify the criteria for whether certain products are regulated as drugs or biological products. The “bright-line” approach under the proposed rule would reduce the amount of time spent by FDA staff and industry in support of making such determinations.

In this regulatory impact analysis, we identify the products most likely to require a case-by-case determination under the baseline scenario. Under the proposed rule, these determinations would be made by FDA according to the bright-line standard proposed. We calculate the cost savings from the amount of time saved by both FDA and industry by avoiding a case-by-case determination. We also calculate the incremental costs to industry that are the result of reading and understanding the rule.

The primary estimate of the benefits in 2017 dollars annualized over 10 years is \$340,766 using a 7 percent discount rate and \$321,506 using a 3 percent discount rate. We also calculate ranges of benefits of \$313,373 to \$355,690 and \$296,220 to \$335,282, respectively. The estimated annualized costs range from \$14,471 to \$18,089, with a primary estimate of \$16,079

using a 7 percent discount rate over a 10-year horizon. For a 3 percent discount rate, we estimate a range of \$12,378 to \$15,472, with a primary estimate of \$13,753. These figures are shown in table 1 below.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of Proposed Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$/year	\$340,766	\$313,373	\$355,690	2017	7%	10	Cost savings to FDA and industry to avoid case-by-case review of applications.
		\$321,506	\$296,220	\$335,282	2017	3%	10	
	Annualized Quantified					7%		
						3%		
Qualitative								
Costs	Annualized Monetized \$/year	\$16,079	\$14,471	\$18,089	2017	7%	10	Costs of reading the rule
		\$13,753	\$12,378	\$15,472	2017	3%	10	
	Annualized Quantified					7%		
						3%		
Qualitative								
Transfers	Federal Annualized Monetized \$/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized \$/year					7%		
						3%		
From/To	From:			To:				
Effects	State, Local or Tribal Government:							
	Small Business:							
	Wages:							
	Growth:							

In line with Executive Order 13771, in table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon. Based on these cost savings, this proposed rule would be considered a deregulatory action under Executive Order 13771.

Table 2.--EO 13771 Summary Table (in 2016 dollars, over a perpetual time horizon)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	\$110,574	\$99,517	\$124,396	\$114,868	\$103,382	\$129,227

Present Value of Cost Savings	\$2,891,315	\$2,993,948	\$2,702,931	\$4,556,396	\$4,671,456	\$4,345,200
Present Value of Net Costs	-\$2,780,741	-\$2,894,431	-\$2,578,534	-\$4,441,527	-\$4,568,074	-\$4,215,973
Annualized Costs	\$7,740	\$6,966	\$8,708	\$3,446	\$3,101	\$3,877
Annualized Cost Savings	\$202,392	\$209,576	\$189,205	\$136,692	\$140,144	\$130,356
Annualized Net Costs	-\$194,652	-\$202,610	-\$180,497	-\$133,246	-\$137,042	-\$126,479

C. Summary of Regulatory Flexibility Analysis

To determine the impact of the proposed rule on small entities, we first determined how many firms would be affected. We estimate that at least 1,615 firms classified in the Pharmaceutical and Medicine Manufacturing industry employ fewer than 1,250 employees and are therefore also classified as small businesses. Although a large number of small businesses will face costs under the proposed rule, the costs to these firms would be limited to the time burden of reading the proposed rule. We estimate that the time burden of reading the rule would be about \$77 per firm, with a lower bound of \$69 and upper bound of \$86. This range of costs is unlikely to have a significant adverse impact on a substantial number of small entities.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 12) and at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this proposed rule is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

XII. References

The following reference marked with an asterisk (*) is on display in the Dockets Management Staff (see ADDRESSES) and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at

<https://www.regulations.gov>. References without asterisks are not available for electronic viewing because they have copyright restriction, or they are available as published articles and books, but these references are available for viewing by interested persons at the Dockets Management Staff (see ADDRESSES) between 9 a.m. and 4 p.m., Monday through Friday.

FDA has verified the website address, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Larrañaga, M. D., R. J. Lewis Sr., and R. A. Lewis, *Hawley's Condensed Chemical Dictionary*, 16th ed., New Jersey: Wiley (2016), s.vv. "peptide," "polypeptide," "protein."

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5. Creighton, T. E., *Encyclopedia of Molecular Biology*, New Jersey: Wiley (1999), s.vv. "peptide," "polypeptide."

6. Newman, W. A., *Dorland's Illustrated Medical Dictionary*, 28th ed., Pennsylvania: W.B. Saunders Co. (1994), s.vv. "peptide," "polypeptide."

7. Berg, J., J. Tymoczko, and L. Stryer, *Biochemistry*, 5th ed., New York: W. H. Freeman (2002), pp. 52-53.

8. Voet, D. and J. Voet, *Biochemistry*, 3rd ed., New Jersey: Wiley (2004), p. 68.

9. Pollard, T., W. Earnshaw, et al., *Cell Biology*, New York: Elsevier (2002), p. 21.

10. Lodish, H., A. Berk, C.A. Kaiser, et al., *Molecular Cell Biology*, 6th ed., London, U.K., W. H. Freeman (2007), p. 66.

11. Alberts, B., A. Johnson, J. Lewis, et al., *Molecular Biology of the Cell*, 4th ed., New York: Garland Science (2002), pp. 129, 135.

*12. Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Definition of the Term “Biological Product”; Proposed Rule, 2018, available at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects in 21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

Therefore, under the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 600 be amended as follows:

PART 600--BIOLOGICAL PRODUCTS: GENERAL

1. The authority citation for part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 356c, 356e, 360, 360i, 371, 374, 379k-1; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

2. Amend § 600.3 by revising paragraph (h) introductory text and by adding paragraphs (h)(6) and (7) to read as follows:

§ 600.3 Definitions.

* * * * *

(h) *Biological product* means 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, or cure of a disease or condition of human beings:

* * * * *

(6) A protein is any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this paragraph (h)(6) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.

(7) A chemically synthesized polypeptide is any alpha amino acid polymer that is made entirely by chemical synthesis and is greater than 40 amino acids but less than 100 amino acids in size. When two or more amino acid chains in an amino acid polymer are associated with each other in a manner that occurs in nature, the size of the amino acid polymer for purposes of this paragraph (h)(7) will be based on the total number of amino acids in those chains, and will not be limited to the number of amino acids in a contiguous sequence.

* * * * *

Dated: December 6, 2018.

Scott Gottlieb,

Commissioner of Food and Drugs.

[FR Doc. 2018-26840 Filed: 12/11/2018 8:45 am; Publication Date: 12/12/2018]