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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: Final rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final rule 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 the Further Consolidated Appropriations Act, 2020 (FCA Act), and to provide its interpretation of the statutory term “protein.” Under this final rule, the term *protein* means any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. This final rule is intended to clarify the statutory framework under which such products are regulated.

DATES: This rule is effective March 23, 2020.

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the “Search” box and follow the prompts, and/or go to the Dockets

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I. Executive Summary

A. *Purpose of the Final Rule*

This final rule amends FDA’s regulation that defines “biological product” by making a technical revision and conforming to the statutory definition enacted in the BPCI Act, as further amended by section 605 of the FCA Act (Pub. L. 116-94). The BPCI Act amended the definition of “biological product” in section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)) to include a “protein (except any chemically synthesized polypeptide).” After publication of the proposed rule, section 605 of the FCA Act further amended the definition of “biological product” in section 351(i) of the PHS Act to remove the parenthetical “(except any chemically synthesized polypeptide)” from the statutory category of “protein.” The final rule makes conforming changes to § 600.3 (21 CFR 600.3) to add FDA’s interpretation of the statutory term “protein.”

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

Under the final rule, the term *protein* means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size. This is consistent with the interpretation of this term that FDA previously described in the notice of proposed rulemaking published in the *Federal Register* on December 12, 2018 (83 FR 63817) and 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) (2015 Biosimilars Q&A Guidance); see also “New and Revised Draft Q&As on Biosimilar Development and the Biologics Price Competition and Innovation Act (Revision 2)” (December 2018; 83 FR 63898)).

C. Legal Authority

This final rule amends FDA’s regulations to implement certain aspects of the BPCI Act and the FCA Act. FDA’s authority for this rule derives from the biological product provisions in section 351 of the PHS Act and the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, *et seq.*) applicable to drugs, as well as section 701 of the FD&C Act (21 U.S.C. 371). The rule is necessary to clarify the statutory authority under which biological products are regulated, to prevent inconsistent regulation of such products, and for the efficient enforcement of the FD&C Act.

D. Costs and Benefits

This final rule codifies FDA’s interpretation of the statutory term “protein” in a manner that is consistent with the interpretation of this term that FDA previously described in guidance (see 2015 Biosimilars Q&A Guidance) and the proposed rule. Formalizing this interpretation will 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, will allow both FDA and private industry to avoid spending time and resources on case-by-case determinations for each product. The primary estimate of the benefits in 2018 dollars annualized over 10 years is \$394,562 using a 7 percent discount rate and \$348,436 using a 3 percent discount rate. We also calculate ranges of benefits of \$356,775 to \$411,345 and

\$316,116 to \$362,792, respectively. The estimated annualized costs range from \$13,511 to \$16,889, with a primary estimate of \$15,012 using a 7 percent discount rate over a 10-year horizon. For a 3 percent discount rate, we estimate a range of \$12,471 to \$15,589, with a primary estimate of \$13,857.

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
EO	Executive Order
FCA Act	Further Consolidated Appropriations Act, 2020
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. *History of This Rulemaking*

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).” After publication of the proposed rule, section 605 of the FCA Act further amended the definition of “biological product” in section 351(i) of the PHS Act to remove the parenthetical “(except any chemically synthesized polypeptide)” from the statutory category of “protein.” As amended by the BPCI Act and the FCA Act, a “biological product” is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, 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 section 7002(e)(1) through (3) and (e)(5) of the BPCI Act). FDA is adding its interpretation of the term “protein” to the regulations to clarify the statutory framework under which such products are regulated.

The proposed rule includes a history of this rulemaking and cites several scientific resources, including textbooks and dictionaries, to illustrate the aspects of the meanings of the terms “protein,” “polypeptide,” and “peptide” on which there is or is not scientific consensus (see 83 FR 63817 at 63819-63820). As discussed in the proposed rule, despite the lack of precise, agreed-upon definitions, most, if not all, sources agree about certain aspects of the meanings of these terms. First, all of the terms (“protein,” “polypeptide,” and “peptide”) refer to amino acid polymers (also referred to as “amino acid chains”) made up of alpha amino acids that are 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. Finally, the term “protein” is distinct from and excludes the term “peptide” (i.e., amino acid chains that are generally shorter and simpler than a protein).

In the proposed rule, FDA described its proposed interpretation of the statutory terms “protein” and “chemically synthesized polypeptide,” which appeared in the definition of “biological product” in section 351(i) of the PHS Act prior to the enactment of the FCA Act.

FDA is now finalizing its interpretation of the statutory term “protein” without change. However, in light of the recently enacted FCA Act, which removed the parenthetical exception for “any chemically synthesized polypeptide” from the category of “protein” in the statutory definition of “biological product,” FDA is not finalizing its interpretation of “chemically synthesized polypeptide” because it is no longer necessary.

B. Summary of Comments on the Proposed Rule

We received four comments on the proposed rule. Two of the comments were general comments supporting FDA’s proposed interpretations; one of these comments specifically supports FDA’s proposal because the commenter stated that it enables insulin to be brought into the regulatory pathway for biological products, including biosimilar and interchangeable products. Two of the comments substantively addressed specific aspects of the proposed interpretations of “protein” and “chemically synthesized polypeptide.”

IV. Legal Authority

We are issuing this final rule under 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. See section 351(j) of the PHS Act. Under these provisions, FDA has the authority to issue regulations designed to ensure, among other things, that biological products are safe, pure, and potent and are 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 and section 351(j) of the PHS Act.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received four comments on the proposed rule by the close of the comment period, two of which contained one or more substantive comments on one or more issues. We received comments from trade organizations, a patient advocacy group, and a State bar association.

We describe and respond to the comments in section B of this rule. We have numbered each comment to help distinguish between different comments. We have grouped similar comments together under the same number, and in some cases, we have separated different issues discussed in the same comment and designated them as distinct comments for purposes of our responses. The number assigned to each comment or comment topic is purely for organizational purposes and does not signify the comment's value or importance or the order in which comments were received.

B. Specific Comments and FDA Response

We proposed to amend § 600.3(h) 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” was not intended to alter our interpretation of section 351(i) of the PHS Act. We also proposed to revise the definition of a “biological product” in § 600.3(h) to include a “protein (except any chemically synthesized polypeptide).”

We received no comments regarding these proposed revisions. However, after publication of the proposed rule, section 605 of the FCA Act further amended the definition of “biological product” in section 351(i) of the PHS Act to remove the parenthetical “(except any chemically synthesized polypeptide)” from the statutory category of “protein.” Therefore, we

are finalizing these revisions to the definition of “biological product” in § 600.3(h) with the following change: we are defining “biological product” in § 600.3(h) to include a “protein” instead of defining “biological product” in § 600.3(h) to include a “protein (except any chemically synthesized polypeptide).”

We also proposed to amend § 600.3(h) to add FDA’s interpretation of the statutory terms “protein” and “chemically synthesized polypeptide.” We proposed to interpret the term “protein” to mean any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. We proposed to interpret the term “chemically synthesized polypeptide” to 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. We explained 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 for purposes of our interpretations of the terms “protein” and “chemically synthesized polypeptide” 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.

In the following paragraphs, we discuss comments on these proposed interpretations. After considering these comments, we are finalizing our interpretation of “protein” without change. We are not finalizing our interpretation of “chemically synthesized polypeptide” as it is no longer necessary because of the change to the statutory definition of “biological product.”

1. Scientific Support for Interpretations of “Protein” and “Chemically Synthesized Polypeptide”

(Comment 1) One comment asserts that FDA’s interpretations of the statutory terms “protein” and “chemically synthesized polypeptide” do not reflect current science and maintains that there is more recent evidence that amino acid polymers composed of 40 or fewer amino

acids are capable of assuming secondary and tertiary structural conformations indicative of proteins. For these reasons, the commenter requested that we revise and reissue the proposed rule.

(Response 1) We disagree with the comment's suggestion that FDA's interpretation of the term "protein" as set forth in the proposed rule and the textbooks we cited in the proposed rule no longer reflects current science. The textbooks cited in the proposed rule have been in use for decades and continue to be in use (e.g., in college biochemistry classes). Moreover, the definitions and descriptions in these textbooks and dictionaries illustrate the point that there is not a scientific consensus on certain aspects of the definitions of the terms "peptide" and "protein," an observation that is not refuted by more recent editions of these textbooks.

This lack of consensus is also reflected in several of the articles cited by the comment. For example, the comment cites two articles to support its claim of the existence of "proteins" composed of as few as 11 amino acids. However, these two articles describe the 11-amino acid polymer differently. One describes it as an 11-amino-acid "protein" (see Ref. 1) and the other describes it as an 11-amino-acid "peptide" (see Ref. 2).

Given the lack of a clear scientific consensus that FDA could consider for adoption, the Agency is applying its scientific expertise to interpret the statutory term "protein" in a manner that establishes a scientifically reasonable, bright-line rule that provides regulatory clarity and facilitates the implementation of the BPCI Act, as further amended by the FCA Act. A clear rule facilitates efficient use of time and resources by both FDA and applicants and reduces regulatory uncertainty. In deciding where to draw this bright-line rule, one of the factors that FDA considered is the number of amino acids understood to be generally necessary for an amino acid

polymer to exhibit characteristics that are generally associated with “proteins,” lending a higher level of complexity to these products.

FDA considered whether to include structural or functional attributes (e.g., folding, provides structural support to cellular macrostructures, catalyzes a biochemical reaction, transports other molecules, aids in the folding of other proteins) in its interpretation of the term “protein,” but determined that this would not serve to make the line between peptides and proteins any brighter. Among other things, relying on a factor such as “folding” would not provide regulatory certainty because it would raise questions about how much folding is sufficient to differentiate between “peptides” and “proteins,” as many peptides can arguably be said to exhibit some folding. Therefore, adopting this approach would not provide for a bright-line rule and would result in regulatory uncertainty and inefficiency.

(Comment 2) One comment asserts that “proteins” are a subset of “polypeptides,” yet FDA’s interpretation of “chemically synthesized polypeptide” presumes that “polypeptides” are a subset of “proteins.”

(Response 2) With the FCA Act’s removal of the parenthetical exception for “any chemically synthesized polypeptide” from the category of “protein” in the statutory definition of “biological product” in section 351(i) of the PHS Act, all amino acid polymers that meet FDA’s interpretation of the term “protein” (including an amino acid polymer that previously would have fallen within the term “chemically synthesized polypeptide” as interpreted by FDA) will be considered to fall within the statutory definition of “biological product.”

(Comment 3) Two comments assert that the proposed interpretations that we have chosen were not supported by a scientific consensus and that there is a lack of scientific consensus for

distinguishing between “protein,” “polypeptide,” and “peptide” based on a particular number of amino acids.

(Response 3) While we agree that there may not be clear scientific consensus for a particular number of amino acids to use when distinguishing between the terms “protein” and “peptide,” there is strong support in scientific literature for distinguishing between types of amino acid polymers based on the number of amino acids they contain. Specifically, the definitions cited in the preamble to the proposed rule are clear that “peptides” are distinct from “proteins” and that the term “peptide” generally refers to smaller, simpler chains of amino acids, while the term “protein” is used to refer to longer, more complex chains (83 FR 63817 at 63819-63820). Moreover, there is scientific support for the fact that amino acid polymers greater than 40 amino acids in size exhibit at least some of the characteristics that are generally associated with proteins (83 FR 63817 at 63820).

The removal of the parenthetical exception for “any chemically synthesized polypeptide” from the category of “protein” in the statutory definition of “biological product” has eliminated any need to distinguish between these terms.

(Comment 4) One comment asserts that FDA’s example of insulin does not support the number of amino acids in FDA’s interpretation of “chemically synthesized polypeptide” because insulin is composed of 2 polypeptide chain subunits, one containing 21 amino acids and the other containing 30 amino acids.

(Response 4) We disagree with the comment because it confuses the terms “polypeptide” and “polypeptide chain.” Even though the need to avoid confusion between the terms “polypeptide” and “polypeptide chain” has been eliminated by the removal of the parenthetical exception for “any chemically synthesized polypeptide” from the category of “protein” in the

statutory definition of “biological product” in section 351(i) of the PHS Act, we note in passing that our interpretation of “protein” uses the phrase “amino acid chain” instead of the phrase “polypeptide chain.” In other words, instead of describing the two subunits of the insulin protein as polypeptides or polypeptide chains like the comment, we describe them as amino acid chains. It therefore follows that insulin clearly is a “protein” as interpreted in the final rule, because the total number of amino acids exceeds 40. In particular, insulin is an alpha amino acid polymer with a specific, defined sequence consisting of 2 amino acid chain subunits with 21 amino acids and 30 amino acids, respectively. As these amino acid chain subunits are associated with each other in a manner that occurs in nature, we add the number of amino acids in each amino acid chain together to determine whether insulin is an alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size. Specifically, by adding together the number of amino acids in each of the two amino acid chain subunits that comprise insulin, we conclude that insulin is an alpha amino acid polymer with a specific, defined sequence of 51 amino acids. Therefore, according to the interpretation we are finalizing, insulin is a protein because it is an alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size.

2. Alternate Proposals

(Comment 5) One comment requests that FDA adopt functional definitions for “protein” and “chemically synthesized polypeptides” that are principally focused on the method of manufacture as well as the conformation of the amino acid polymer rather than the size of the amino acid polymer, reflecting the comment’s view that the method of manufacture, not size, should be the determining factor.

(Response 5) We are not finalizing our interpretation of the term “chemically synthesized polypeptide” because of the removal, by section 605 of the FCA Act, of the parenthetical “(except any chemically synthesized polypeptide)” from the category of “protein” in the statutory definition of “biological product.” Also, we do not agree that we should adopt an interpretation of the statutory term “protein” that is principally focused on the method of manufacture for the following reasons.

First, we disagree with the comment’s premise that the statutory definition of “biological product,” which included “protein (except any chemically synthesized polypeptide)” prior to the enactment of the FCA Act, was principally focused on the method of manufacture. We need not address whether the fact that the earlier version of the statute described the method of manufacture in the parenthetical clause (excluding chemically synthesized polypeptides from the scope of the term “protein”) has any bearing on our current interpretation. However, we note in passing that, according to basic rules of statutory construction, if Congress wanted the term “protein” not to include any “chemically synthesized proteins,” then it seems unlikely that the statute would employ two different terms (“protein” and “polypeptide”). Accordingly, we had described the term “polypeptide” as it appeared in section 351(i) of the PHS Act prior to the enactment of the FCA Act as referring to a subset of “protein.”

Second, as noted in the response to Comment 1, FDA considered whether to include structural or functional attributes in its interpretation of the term “protein,” but determined that doing so would not be appropriate as it would lead to regulatory uncertainty due to the lack of a bright-line rule.

Third, adopting an interpretation that focused on the method of manufacture could improperly incentivize product developers to choose a suboptimal method of manufacturing a

product that may be less efficient and/or more costly, based on a perceived regulatory advantage under a particular regulatory scheme.

It is FDA's view that the optimal policy for determining which products are subject to regulation under the PHS Act is to apply a bright-line rule that provides regulatory certainty. Thus, in order to provide regulatory certainty and provide a bright-line interpretation of the term "protein," we are focusing on the number of amino acids in the amino acid polymer (irrespective of the method of manufacture).

(Comment 6) One comment urges the Agency to abandon the proposed case-by-case approach for determining whether a proposed product composed of amino acid chains that are associated with each other in a manner not found in nature constitutes a "biological product."

(Response 6) FDA is not persuaded by this comment because there are a number of ways in which amino acid chains could be associated with each other in a novel manner that is not found in naturally occurring proteins and we cannot predict all of these iterations. Although some of these combinations may result in amino acid polymers that exhibit characteristics generally associated with proteins, some may not.

We recognize that the application of the fact-specific, case-by-case analysis for proposed products composed of amino acid chains that are associated with each other in a manner not found in nature does not provide the same level of certainty that is provided by the other criteria in § 600.3(h)(6) (see 83 FR 63817 at 63821), but it appears that case-by-case analysis is currently the best means of addressing such cases. We encourage sponsors of these proposed products to reach out to FDA early in their development program to discuss issues related to product classification and the appropriate pathway for a marketing application.

3. Relationship to Other Regulatory Provisions

(Comment 7) One comment asserts that FDA’s proposed definitions are inconsistent with § 601.2(a)(4) and (c) (21 CFR 601.2(a)(4) and (c)).

(Response 7) We disagree with the comment’s assertion that our proposed interpretations are inconsistent with our current regulations in § 601.2(a)(4) and (c). The comment appears to interpret § 601.2(a)(4) and (c) to mean that if a product is a therapeutic recombinant DNA-derived product, then, regardless of size, the product is a biological product subject to licensure and should be regulated in accordance with § 601.2(c). However, that conclusion seems to be based on a misreading of these provisions. We interpret our regulation at § 601.2(a)(4) and (c) to mean that if the product meets the definition of “biological product” under § 600.3(h), and also is a therapeutic recombinant DNA-derived product, then the application would be regulated in accordance with § 601.2(c).

(Comment 8) One comment requests that FDA propose a regulatory definition of products that are “analogous” to a protein and therefore are biological products.

(Response 8) We appreciate the comment. A definition of products that are “analogous” to a “protein” for purposes of section 351(i)(1) of the PHS Act is outside the scope of this

rulemaking. We note, however, that it would not be appropriate for the statutory term “analogous product” to be interpreted in a way that would include products that are specifically excluded by this final rule.

(Comment 9) One comment requests that FDA clarify its approach to assessing the appropriate application type for combination products, including peptide-protein combination products.

(Response 9) We appreciate the comment. The Agency’s approach for determining the appropriate type of marketing application for certain combination products is outside the scope of this rulemaking. If a sponsor is unsure of the appropriate marketing application for its combination product containing a biological constituent part, we encourage the sponsor to reach out to FDA at an appropriate time in its development program to discuss issues related to product classification and the appropriate pathway for a marketing application.

VI. Effective Date

This final rule will become effective March 23, 2020.

VII. Economic Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order (EO) 12866, EO 13563, EO 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). EOs 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). EO 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.” This final rule is a significant regulatory action under sec. 3(f) of E.O. 12866. Based on the cost savings summarized below and discussed further in the regulatory impact analysis, this final rule is considered a deregulatory action under EO 13771.

Pursuant to the Congressional Review Act (5 U.S.C. 801 et seq.), the Office of Information and Regulatory Affairs designated this rule as not a “major rule,” as defined by 5 U.S.C. 804(2).

The Regulatory Flexibility Act requires us to analyze regulatory options that will 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 certify that the final 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 issuing “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 \$154 million, using the most current (2018) Implicit Price Deflator for the Gross Domestic Product. This final rule will not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

This final rule codifies FDA’s interpretation of the statutory term “protein” that the Agency previously described in guidance (see 2015 Biosimilars Q&A Guidance). This final rule

does not codify the FDA’s interpretation of the statutory term “chemically synthesized polypeptide” because section 605 of the FCA Act removed the parenthetical “(except any chemically synthesized polypeptide)” from the category of “protein” in the definition of “biological product” in section 351(i) of the PHS Act. Formalizing this interpretation will reduce regulatory uncertainty introduced by the BPCI Act and section 605 of the FCA Act. Specifically, the rule clarifies the criteria for whether certain products will be regulated as drugs or biological products. The “bright-line” approach under the rule will 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 rule, these determinations will be made by FDA according to the bright-line standard outlined in the final rule. We calculate the cost savings from the amount of time saved by both the 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 2018 dollars annualized over 10 years is \$394,562 using a 7 percent discount rate and \$348,436 using a 3 percent discount rate. We also calculate ranges of benefits of \$356,775 to \$411,345 and \$316,116 to \$362,792, respectively. The estimated annualized costs range from \$13,511 to \$16,889, with a primary estimate of \$15,012 using a 7 percent discount rate over a 10-year horizon. For a 3 percent discount rate, we estimate a range of \$12,471 to \$15,589, with a primary estimate of \$13,857. These figures are shown in table 1.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized \$/year	\$394,562	\$356,775	\$411,345	2018	7%	10	Cost savings to FDA and industry to avoid case-by-case review of applications.
		\$348,436	\$316,116	\$362,792	2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized \$/year	\$15,012	\$13,511	\$16,889	2018	7%	10	Costs of reading the rule
		\$13,857	\$12,471	\$15,589	2018	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 EO 13771, in table 2 we estimate present and annualized values of costs and cost savings over an infinite time horizon. With a 7 percent discount rate, the estimated annualized net cost-savings equal \$170,903 in 2016 dollars over an infinite horizon. Based on these cost savings, this final rule is considered a deregulatory action under EO 13771.

Table 2.--EO 13771 Summary Table (in 2016 Dollars, Over an Infinite Time Horizon)

	Primary Estimate (7%)
Present Value of Costs	\$91,971
Present Value of Cost Savings	\$2,533,439
Present Value of Net Costs	(\$2,441,468)
Annualized Costs	\$6,438
Annualized Cost Savings	\$177,341
Annualized Net Costs	(\$170,903)

C. Summary of Regulatory Flexibility Analysis

To determine the impact of the final 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 final rule, the costs to these firms would be limited to the time burden of reading the final rule. We estimate that the time burden of reading the rule would be about \$79 per firm, with a lower bound of \$71 and upper bound of \$89. This range of costs is unlikely to have a significant adverse impact on a substantial number of small entities. We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 3) 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 action 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

This final rule has an influence on previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of

Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR parts 601 and 610 for submission of BLAs and general biological standards have been approved under OMB control number 0910-0338; the collections of information in 21 CFR 600.80 through 600.90 for reporting of adverse experiences have been approved under OMB control number 0910-0308; and the collections of information in 21 CFR 201.56, 201.57, and 201.80 for labeling requirements of biological products have been approved under OMB control number 0910-0572.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in EO 13132. We have determined that the 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.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in EO 13175. We have determined that the rule does not contain policies that have substantial direct effects 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. Accordingly, we conclude that the rule does not contain policies that have tribal implications as defined in the EO and, consequently, a tribal summary impact statement is not required.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Su, M., Y. Ling, J. Yu, et al. "Small Proteins: Untapped Area of Potential Biological Importance," *Frontiers in Genetics*, vol. 4, p.286, 2013.
2. Galindo, M. I., J. I. Pueyo, S. Foux, et al. "Peptides Encoded by Short ORFs Control Development and Define a New Eukaryotic Gene Family" *PLoS Biology*, vol. 5, p. e106, 2007.
3. *FDA, Regulatory Impact Analysis, "Definition of the Term 'Biological Product,'" 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 Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 600 is 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.

2. Amend § 600.3 by revising paragraph (h) introductory text and adding paragraph (h)(6) 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, 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.

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Dated: February 18, 2020.

Stephen M. Hahn,

Commissioner of Food and Drugs.

