DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Definition of the Term "Biological Product"

Docket No. FDA-2018-N-2732

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final 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." This final rule is a significant regulatory action under sec. 3(f) of E.O. 12866.

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 the Food and Drug Administration's (FDA or Agency) interpretation of the statutory term "protein" that the Agency previously described in guidance (Ref. 1). This final rule does not finalize the FDA's interpretation of "chemically synthesized polypeptide" because section 605 of the Further Consolidated Appropriations Act, 2020 (Public Law 116-94) (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 Public Health Service Act (PHS Act). Formalizing this interpretation will reduce regulatory uncertainty introduced by the Biologics Price Competition and Innovation Act of 2009 (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 and resources 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 $395,000 using a 7% discount rate and $348,000 using a 3% discount rate. We also calculate ranges of benefits of $357,000 to $411,000 and $316,000 to $363,000, respectively. The estimated annualized costs range from $14,000 to $17,000, with a primary estimate of $15,000 using a 7% discount rate over a 10-year horizon. For a 3% discount rate, we estimate a range of $12,000 to $16,000, with a primary estimate of $14,000. These figures are shown in Table 1 below.

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	$395,000	$357,000	$411,000	2018	7%	10	Cost savings to FDA and industry to avoid case-by-case review of applications.
		$348,000	$316,000	$363,000	2018	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $/year	$15,000	$14,000	$17,000	2018	7%	10	Costs of reading the rule
		$14,000	$12,000	$16,000	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 Executive Order (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, discounted relative to year 2016, the estimated annualized net cost-savings equal $163,000 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	$88,000
Present Value of Cost Savings	$2,421,000
Present Value of Net Costs	($2,334,000)
Annualized Costs	$6,000
Annualized Cost Savings	$170,000
Annualized Net Costs	($163,000)

C. Summary of Changes

In 2018, we published the proposed rule "Definition of the Term Biological Product" (83 FR 63817). Accompanying the proposed rule was a comprehensive preliminary regulatory impact analysis on which we requested public comments (Ref. 2). We received no comments regarding this analysis. Compared to the preliminary analysis, the final regulatory impact analysis makes a substantive change to reflect the subsequent enactment of the FCA Act and several technical changes. First, we no longer exclude "any chemically synthesized polypeptide" from the category of "protein" in our analysis of the effects of the rule because the final rule reflects the revised statutory definition of "biological product" following the enactment of the FCA Act. Second, we now analyze the monetized effects of the rule for calendar years 2020 through 2029. Third, we updated several inputs into our cost and cost savings model with more recent industry wage figures. Fourth, we incorporated the most recent data available on approved drug products, including an updated list of products affected by the BPCI Act that are the focus of the final rule.

II. Final Regulatory Impact Analysis

A. Background

The BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (ACA) on March 23, 2010. The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. The statute defines "biosimilarity" to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product. The statute defines "interchangeability" to mean that the biological product has been shown to be biosimilar and meet additional requirements, and may be substituted for the reference product without the intervention of the prescribing health care provider. The objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984, which established abbreviated pathways for the approval of drug products under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

In addition to creating an abbreviated pathway for licensure of biological products, the BPCI Act also amended the definition of a "biological product" to include a "protein (except any chemically synthesized polypeptide)." The FCA Act further amended the statutory definition of "biological product" to remove the parenthetical "(except any chemically synthesized polypeptide)" from the category of "protein." By including the category of "protein," the BPCI Act clarified the statutory authority under which protein products that are currently regulated as drugs under section 505 of the FD&C Act are to be regulated. The BPCI Act requires that new marketing applications for biological products, which previously would have been submitted under section 505 of the FD&C Act, must be submitted under section 351 of the PHS Act, with certain exceptions. The BPCI Act also includes a provision to transition approved applications for such products that fall under the revised definition of a biological product on March 23, 2020. On this date, applications for biological products that are approved under section 505 of the FD&C Act will no longer exist as New Drug Applications (NDAs) and will be deemed to be (and replaced by) approved Biologics License Applications (BLAs). Additionally, an application for a protein product that has been submitted under section 505 of the FD&C Act and is pending on March 23, 2020, will not be approved under the FD&C Act (unless the application falls within the exception described in section 607 of the FCA Act). Such an application may, for example, be withdrawn and resubmitted under section 351(a) or 351(k) of the PHS Act, as appropriate (Ref. 3).

B. Market Failure Requiring Federal Regulatory Action

This regulatory action is not intended to address a market failure *per se*. The regulation is intended to reduce regulatory confusion introduced into the existing regulatory system related to the statutory introduction of a new undefined regulatory term. Specifically, by introducing the undefined scientific term "protein" in the statutory definition of "biological product," Congress introduced uncertainty into the regulatory process. Without additional regulatory action by the FDA to clarify the term "protein" in this definition, manufacturers and the FDA would have needed to spend time and

resources to determine whether individual products are to be regulated as drugs under section 505 of the FD&C Act or as biological products under section 351 of the PHS Act. As such, the confusion surrounding the amended definition of a "biological product" in the PHS Act, as amended by the BPCI Act, and as subsequently amended by section 605 of the FCA Act, added a new regulatory burden to drug and biological product manufacturers and the FDA which this rule seeks to address.

C. Purpose of the Rule

The rule directly addresses the uncertainty introduced into the regulatory process by the BPCI Act and section 605 of the FCA Act by interpreting the term "protein." The rule codifies the interpretation of the statutory term "protein" that FDA previously described in guidance (Ref. 1). Specifically, the rule interprets "protein" to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size."

This interpretation will reduce the burden on drug and biological product manufacturers and the FDA by instituting a bright-line standard for classifying existing products and new product applications, providing regulatory clarity, and reducing the time spent on such determinations.

D. Baseline Conditions

OMB's Circular A-4 offers guidance to Federal agencies on the development of regulatory analysis. A first step in developing the analysis is to "[i]dentify a baseline. Benefits and costs are defined in comparison with a clearly stated alternative. This normally will be a 'no action' baseline: what the world will be like if the rule is not adopted." In our primary analysis, we adopt a baseline that we believe reflects the best forecast of the world without the rule. We also analyze the effects of the rule relative to a pre-statutory baseline, which allows us to explore more of the effects of the BPCI Act than the primary baseline. In this Section, we describe the two baselines. In the Sensitivity Analysis (Section III) of the regulatory impact analysis, we explore implications of this alternative pre-BPCI Act baseline.

a. Primary Baseline

The November 2019 version of the FDA's Orange Book contains 5,050 approved NDAs (Ref. 4). From these, the FDA has identified a list of 91 approved applications for products that FDA classifies as proteins under the interpretation described in Agency guidance (Ref. 1) and will be deemed BLAs on March 23, 2020, under the BPCI Act "transition" provision ("transition list"). The transition list also includes 4 approved applications that subsequently were administratively closed and do not appear in the Orange Book but are related to other approved applications on the transition list, for a total of 95 products that will transition from NDA to BLA.

Among the 95 applications on the transition list, 25 have been discontinued according to the FDA Orange Book (Ref. 4). Four applications are NDAs that were submitted for a new indication or claim for a product reviewed under a different NDA (the "parent" NDA) and subsequently were administratively closed. These NDAs do not appear in the Orange Book because they were administratively closed (submissions are made to the "parent" NDA, which also appears on the transition list), but are included here for completeness. To give a sense of the market size of the affected products, we matched the remaining 66 non-discontinued products[1] with IQVIA sales data.[2] We estimate that for the 12-month period from December 2018 to November 2019, the total combined revenue was approximately $38.0 billion dollars, or an average of $576 million per product.

Without a regulation that codifies FDA's interpretation of the term "protein," as described in this rule, drug and biological product manufacturers may be more likely to challenge Agency classification decisions made on a product-by-product basis. Under this baseline scenario, the Agency expects that the 95 existing approved NDAs will transition to BLAs. We also forecast an additional 3 new approved applications per year will fall into the same size category as the 95 products described above. This is approximately equal to the average annual number of approvals of existing NDA products in this size category over both the last 5 years, and over the last 20 years, that will be transitioning to BLAs. However, without the rule, we anticipate these applications will need a case-by-case analysis to determine whether the product is a drug product or a biological product.

We note that FDA received a comment recommending that the Agency reconsider the case-by-case approach for evaluating whether a proposed product is composed of amino acid chains that are associated with each other in a manner found in nature based on the commenter's view that this approach is inconsistent with the bright line standard that FDA has otherwise adopted. In response to this comment to the rule, FDA recognizes 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 bright-line rule. FDA does not expect to receive applications for many proposed products requiring such an a determination; however, to the extent that the agency will need to perform such analyses, these would be necessary under both the baseline and rule, and do not represent effects of the rule. FDA also received one comment requesting that FDA clarify its approach to assessing the appropriate application type for combination products, including peptide-protein combination products. However, this request is outside the scope of the rulemaking. This rulemaking applies to the evaluation of whether a product contains a biological product constituent part. The determination of the appropriate application type for a combination product that contains a biological product constituent part is a separate assessment conducted pursuant to different regulatory processes.

[1] One of these products is covered by two applications, one of which has been administratively closed. Therefore, these 66 non-discontinued products are covered by 67 applications in total.

[2] Sales history is dynamic and reflects the present view of the database at the time the information is provided. IQVIA, National Sales Perspective™, Calendar Year 2016, data extracted January 2020.

As a result of the BPCI Act's requirement to deem approved NDAs for biological products to be BLAs, affected products will be subject to requirements under the PHS Act that may differ in some respects from those under the FD&C Act. For example, in some instances, holders of deemed BLAs may be required to report or provide different information than was required under the FD&C Act. However, FDA expects that holders of an approved NDA for a biological product that is deemed to be a BLA will experience minimal disruption due to these differences in the applicable requirements.

Another effect of the BPCI Act is that certain products approved in NDAs and certain proposed products that seek licensure in a 351(a) BLA could see changes to their potential periods of exclusivity, and associated delays in approval of competitor products. Any unexpired period of 5-year or 3-year exclusivity associated with a product approved in an NDA will cease to have any effect when the NDA is deemed to be a BLA because FDA will not file or approve any application for a biological product under the FD&C Act after March 23, 2020. In contrast to products in approved NDAs that are deemed to be BLAs, proposed products falling under the amended statutory definition of a biological product and submitted under section 351(a) of the PHS Act could potentially receive a longer exclusivity period following approval. Biological products that are first licensed under section 351(a) of the PHS Act may be eligible to receive a 12-year period of exclusivity, whereas products approved in an NDA may be eligible to receive a 5-year period and, in some cases, one or more 3-year period(s) of exclusivity.

As noted before, our baseline forecasts 3 new applications per year that could potentially receive 12 years of exclusivity instead of 5- or 3-year exclusivity. If such applications are eligible for this longer period of exclusivity, it could potentially lead to a lengthened period of higher pricing for the affected products. After this exclusivity period expires, products may face additional competition due to the new abbreviated approval pathway for biological products included in the BPCI Act. FDA expects that the rule will not significantly affect which biological products will be eligible for 12 years of exclusivity under the PHS Act (compared to the baseline) because the size threshold for a product to be classified as a "biological product" will remain the same as described in guidance. Although FDA's interpretation no longer excludes "any chemically synthesized polypeptide" from the statutory category of "protein," we do not expect this to result in a significant increase in biological products that will be eligible for 12 years of exclusivity under the PHS Act (compared to the baseline). Therefore, in our primary estimate of benefits and costs, we do not forecast and quantify how these provisions of the BPCI Act will affect competition.

b. Alternative Baseline

While we believe the primary baseline described above reflects the best forecast of the world without the rule, we have identified a secondary baseline that allows us to explore more of the effects of the BPCI Act's amendment to the statutory definition of "biological product" and clarification of the statutory authority under which protein products that are currently regulated as drugs under section 505 of the FD&C Act are to be regulated ("BPCI Act statutory changes"). Under this alternative baseline, we assume

that no products will transition from NDA to BLA. The Sensitivity Analysis (Section III) calculates the effects of the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act against this alternative baseline scenario.

E. Benefits of the Rule

Under the rule, FDA will make determinations for each of the affected products based on the size of the molecule using the "bright-line" standard. Since the FDA already collects this information during the application review process, only minimal staff time will be required to classify all existing products under the proposed definition as a drug product or a biological product. Compared to the primary baseline scenario of case-by-case determinations for each of the affected products, we identify and monetize potential cost savings under the rule from this streamlined review process.

For our primary estimate, we expect that the 95 products on the transition list and 3 additional products per year will require the FDA to determine the classification of each product on a case-by-case basis with input from industry. Based on the FDA's experience with a single product, we estimate that such a determination will take at least 114 hours by FDA staff and 78 hours by industry for each product. These estimates are such that the resulting cost-savings estimates are likely understated. For our lower-bound estimate of cost savings, we assume that no time will have been spent for the 25 discontinued products and 4 administratively closed applications for industry only under the baseline scenario. For our upper-bound estimate of cost savings, based on FDA's experience, we approximate 5 additional products near the size threshold under the rule will require a case-by-case determination.

To calculate the cost savings of the rule, we multiply the FDA staff hours by a loaded wage of $135.39 per hour. For industry, we apply estimates from the Bureau of Labor Statistics (BLS) of the mean wage for a medical scientist working in the pharmaceutical and medicine manufacturing industry as grouped by the North American Industry Classification System (NAICS) (Ref. 5). We double the wage estimate of $62.77 to $125.52 to account for overhead and multiply this to the number of hours spent by industry. Using these hour and wage estimates, we estimate that each case-by-case review avoided under the rule will generate about $15,000 in cost savings to the FDA and $10,000 to industry.

We assume that these determinations will take place in 2020 for existing products, and during the submission year for determinations about future product submissions. This results in an initial cost savings of about $1.51 million in 2020 to FDA and $0.96 million to industry, with estimate ranges of $1.51 million to $1.59 million and $0.70 million to $1.0 million, respectively. Combining these estimates yields total cost savings in 2020 of $2.47 million, or between $2.19 million and $2.60 million. In future years, the FDA will experience cost savings of $46,000 and industry of $29,000, for a total of about $76,000. Table 3 reports the cost savings to FDA and industry by year, as well as the present discounted value (PDV) and annualized value of these cost savings. The PDV and annualized values cover a 10-year time horizon using a 3% and 7% discount rate.

Table 3. Cost Savings to FDA and Industry Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,512,532	$1,512,532	$1,589,702	$959,628	$675,656	$1,008,588	$2,472,160	$2,188,188	$2,598,290
2021	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2022	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2023	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2024	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2025	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2026	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2027	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2028	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2029	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,153,743	$878,043	$1,201,278	$2,972,233	$2,696,532	$3,094,690
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$1,075,721	$810,327	$1,121,479	$2,771,235	$2,505,841	$2,889,114
Annualized, 3%	$213,182	$213,182	$221,966	$135,254	$102,933	$140,826	$348,436	$316,116	$362,792
Annualized, 7%	$241,403	$241,403	$251,672	$153,158	$115,372	$159,673	$394,562	$356,775	$411,345

F. Costs of the Rule

We assume that all firms that manufacture drug products will need to read this rule. The rule contains about 6,500 words. If the average adult reads between 200 and 250 words per minute, we estimate that it will take approximately 0.5 hours to read the rule at the midpoint of 225 words per minute. Using data from the FDA Orange Book (Ref. 4), we count that there are 1,637 firms that manufacture drug products. We assume that the person reading the rule at each firm is a legal professional and obtain data on the pharmaceutical and medicine manufacturing industry-specific mean hourly wage from the BLS (Ref. 5). Doubling this wage to account for overhead, we assume that the individuals reading the rule earn a mean fully loaded hourly wage of $163.66. Multiplying the number of firms by the time to read the rule, and then multiplying that product by the mean fully loaded hourly wage, we estimate that the total cost to read the rule will be about $129,000 using 2018 wage figures. We also estimate a lower-bound of $116,000 and an upper-bound of $145,000, corresponding to faster and slower reading speeds. This will be a one-time cost that occurs in the first year.

G. Net Benefits of the Rule

To calculate the net benefits of the rule, we subtract the costs of reading the rule identified in Section F from the cost savings to the FDA and industry calculated in Section E. Table 4 displays these figures yearly and reports the PDV and annualized values in 2018 dollars using both a 3 percent and 7 percent discount rate.

Table 4. Net Benefits of the Rule Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,512,532	$1,512,532	$1,589,702	$830,633	$530,538	$892,493	$2,343,165	$2,043,070	$2,482,195
2021	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2022	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2023	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2024	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2025	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2026	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2027	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2028	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
2029	$46,302	$46,302	$46,302	$29,376	$29,376	$29,376	$75,678	$75,678	$75,678
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,028,506	$737,151	$1,088,564	$2,846,995	$2,555,640	$2,981,976
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$955,166	$674,702	$1,012,979	$2,650,680	$2,370,216	$2,780,614
Annualized, 3%	$213,182	$213,182	$221,966	$120,572	$86,417	$127,613	$333,755	$299,599	$349,579
Annualized, 7%	$241,403	$241,403	$251,672	$135,994	$96,062	$144,225	$377,397	$337,466	$395,897

H. Analysis of Regulatory Alternatives to the Rule

For purposes of this analysis, in addition to the proposed interpretation described above, FDA considered and analyzed two regulatory alternatives to the rule. Under the first alternative approach, rather than a single size cutoff, this option would apply an algorithm based on certain limits to isolate the size ranges over which there seems to be some scientific agreement about whether a molecule is a peptide or a protein. Under this option, molecules of 40 amino acids or less in size would be considered peptides, and those of 100 amino acids or more in size would be considered proteins. Molecules within the range of uncertainty would be analyzed case-by-case based on structural or functional characteristics.

Under this algorithm-based approach, products approved under an NDA with 40 or fewer amino acids would continue to be regulated as drug products. Products approved under an NDA with 100 or more amino acids would transition and be regulated as biological products. Under this policy option, 32 of the 95 applications would require a case-by-case review, similar to the process described in the baseline scenario. Initial cost savings under this option would come from the existing 63 applications that transition without a costly review by FDA and industry.

Under the primary baseline, we forecasted 3 new applications per year will require a determination by the FDA. Under the algorithmic approach, we predict that about 1 application per year would fall into the range of uncertainty and about 2 applications per year could be sorted as a drug or biological product by the size threshold alone. This figure assumes that the share of products with at least 100 amino acids remains constant at around 66%.

Table 5 presents the benefits in the form of cost savings to FDA and Industry under this algorithm alternative. The estimated cost savings under this proposal are lower than those described in the analysis of the rule. We do not estimate the costs of reading this policy proposal, because we do not have the word count of such a policy; however, we expect that these costs are likely to be similar in magnitude to the costs of reading the rule.

Table 5. Benefits to FDA and Industry Under the Algorithm Alternative Over a 10-year Time Horizon

Year	FDA			Industry			Total		
	Primary	Low	High	Primary	Low	High	Primary	Low	High
2020	$1,003,048	$1,003,048	$1,054,223	$636,385	$448,067	$668,853	$1,639,432	$1,451,114	$1,723,077
2021	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2022	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2023	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2024	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2025	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2026	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2027	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2028	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
2029	$30,706	$30,706	$30,706	$19,481	$19,481	$19,481	$50,187	$50,187	$50,187
Proposed Rule									
PDV, 3%	$1,818,490	$1,818,490	$1,893,412	$1,153,743	$878,043	$1,201,278	$2,972,233	$2,696,532	$3,094,690
PDV, 7%	$1,695,514	$1,695,514	$1,767,636	$1,075,721	$810,327	$1,121,479	$2,771,235	$2,505,841	$2,889,114
Annualized, 3%	$213,182	$213,182	$221,966	$135,254	$102,933	$140,826	$348,436	$316,116	$362,792
Annualized, 7%	$241,403	$241,403	$251,672	$153,158	$115,372	$159,673	$394,562	$356,775	$411,345
Alternative									
PDV, 3%	$1,205,946	$1,205,946	$1,255,631	$765,114	$582,281	$796,637	$1,971,060	$1,788,227	$2,052,268
PDV, 7%	$1,124,394	$1,124,394	$1,172,222	$713,373	$537,375	$743,717	$1,837,767	$1,661,769	$1,915,939
Annualized, 3%	$141,374	$141,374	$147,198	$89,695	$68,261	$93,390	$231,068	$209,635	$240,588
Annualized, 7%	$160,088	$160,088	$166,898	$101,568	$76,510	$105,889	$261,657	$236,598	$272,787
Difference									
PDV, 3%	$612,544	$612,544	$637,781	$388,629	$295,762	$404,641	$1,001,173	$908,306	$1,042,422
PDV, 7%	$571,121	$571,121	$595,414	$362,348	$272,952	$377,761	$933,469	$844,073	$973,175
Annualized, 3%	$71,809	$71,809	$74,767	$45,559	$34,672	$47,436	$117,368	$106,481	$122,204
Annualized, 7%	$81,315	$81,315	$84,774	$51,590	$38,862	$53,785	$132,905	$120,177	$138,558

As a second alternative, we consider a different bright-line standard that FDA considers to be an alternate scientifically supported approach, based on the Agency's evaluation of the scientific literature. Under this option, the statutory term "protein" would be interpreted to mean any alpha amino acid polymer with a specific, defined sequence that is greater than 50 amino acids in size. Accordingly, products approved under an NDA with 50 or fewer amino acids would be considered "peptides" and continue to be regulated as drug products.

Under this alternative, bright-line standard, the Agency expects that 92 of the 95 approved NDAs for biological products would transition to BLAs. However, 3 approved NDA products are composed of between 41 and 50 amino acids. Under this alternative proposal, these 3 products would not meet the definition of a biological product because each of these products would be a peptide (i.e., composed of 50 or fewer amino acids), rather than a protein, and would not transition to BLAs. According to the Orange Book, one of these products has an exclusivity expiration date of July 27, 2021. For this product, this regulatory alternative could delay the time it may face a competitor product. For all three products, not transitioning to a BLA would also prevent potential competitor products from using the 351(k) pathway.

III. Sensitivity Analysis

In our main analysis of the costs and cost savings of this rule, our primary baseline assumes that the interpretation of the statutory term "protein" as reflected in FDA's guidance (Ref. 1) will continue to guide FDA's determinations on a case-by-case basis. Therefore, we attribute the transition of certain products from an NDA to a BLA to the BPCI Act and the FCA Act rather than this rule and expect the final outcome of such case-by-case determination for each individual product will remain unchanged with or without this rule. Under our secondary baseline, we evaluate the effects of the transition itself using a pre-statutory baseline as if the transition will not occur without the BPCI Act statutory changes.

We expect the bulk of the effects of the statutes under this baseline are driven by two, interrelated factors: (1) the differences in the length of available exclusivity periods between NDA and BLA products, and (2) competition from the abbreviated licensure pathway for biological products licensed as biosimilar to or interchangeable with a reference product after the March 23, 2020, transition date, as compared with competition from "follow-on" products approved prior to March 23, 2020 through the pathway described in section 505(b)(2) of the FD&C Act.

Compared to the pre-statutory baseline, the BPCI Act's statutory changes and subsequent statutory changes made by the FCA Act will affect the existing periods of exclusivity for the products on the preliminary transition list, and any exclusivity granted to approved applications for similar products in the future. As described earlier, any unexpired period of 5-year or 3-year exclusivity associated with a product approved as an NDA will cease to have any effect when the NDA is deemed to be a BLA because FDA will not file or approve any application for a biological product under the FD&C Act after March 23, 2020 (unless the application falls within the exception described in section 607 of the FCA Act, which specifies that any such applications remain subject to any unexpired period of exclusivity for a relied-upon listed drug). According to November 2019 Orange Book exclusivity data (Ref. 4), only 7 NDAs on the transition list have exclusivity expiration dates beyond the March 23, 2020 transition date. Of these applications, 3 products have exclusivity expiration dates in late 2020, 2 products have exclusivity that expires in mid-2021, and 1 product has exclusivity that expires in 2022. Though any unexpired exclusivity for these applications and any other NDAs for

biological products approved before the transition date will cease to have any practical effect at the time of the transition, this effect is minimal because the standard review timeframe for a competitor product submitted in a BLA on or after March 23, 2020, generally will extend beyond these unexpired exclusivity expiration dates.

In contrast, in accordance with the BPCI Act's statutory changes, applications for similar products submitted under section 351(a) of the PHS Act before, on, or after the March 23, 2020 transition date will be potentially be eligible to receive a 12-year period of exclusivity. Taken by itself, the extra years of exclusivity afforded to biological products first licensed in a 351(a) BLA relative to the periods of exclusivity available for NDA approvals will likely be seen as an incentive to prioritize development and submission of additional products similar to those on the preliminary transition list. However, because these differences in exclusivity coincide with a switch from potential follow-on product competition to biosimilar or interchangeable product competition, this prediction is less clear cut.

Orange Book (Ref. 1) data show that very few of the applications on the preliminary transition list have unexpired periods of exclusivity; however, competition is currently limited to certain follow-on products approved through the 505(b)(2) pathway and other products in the product class. Historically, applications for follow-on products in this category have been submitted pursuant to section 505(b)(2) of the FD&C Act generally due to past scientific challenges and statutory limitations on the scope of data that can be relied upon in abbreviated new drug applications (ANDAs). There are no currently marketed biological products that were approved through the ANDA pathway. The framework created by section 351(k) of the PHS Act provides a pathway under which increased competition has the potential to emerge.

In addition to the advantages of regulatory certainty with respect to the approval pathway for these products, the 351(k) pathway also creates new possibilities for the product development of biosimilar and interchangeable products, where sponsors can leverage FDA's finding of safety and effectiveness for the reference product to support approval of follow-on products. In this context, there may be a reduced need for multiple large clinical outcomes studies as part of biosimilar product development, which can significantly lower development costs. We therefore assume that it may be possible that the statutory requirements for obtaining a license under the 351(k) pathway for a biosimilar product or an interchangeable product will lead to greater competition (compared with follow-on products approved through the 505(b)(2) pathway) for the types of applications that will transition under the rule. We note that it would be difficult to evaluate any additional administrative burden that may be associated with the regulation of some of these products as biological products under section 351 of the PHS Act as compared to section 505 of the FD&C Act, in part because the relative administrative burden associated with one pathway versus another may vary by product. However, in the aggregate, FDA expects that any additional administrative burden that may be associated with regulation of products as biological products under the PHS Act as compared to the FD&C Act would be outweighed by the benefits associated with the

availability of the 351(k) pathway, which provides a clear path to market for follow-on biological products, including products that may be substitutable at the pharmacy level.

To quantify how competition may differ for these products, it is necessary to identify the probability and timing of one or more biosimilar or interchangeable competitors and the difference in price following competition. Evidence on these factors is scarce, so we attempt to use the best information available for inputs and estimates.

With respect to pricing, we note an earlier study of the biosimilar pathway as a whole by the Congressional Budget Office (Ref. 6). They predicted the following: “that during the first year of competition, the sales-weighted market average discount on FOBs relative to brand-name innovator drugs would be about 20 percent, reaching 25 percent in the most competitive markets. By the fourth year of competition, we anticipate that the sales-weighted average discount of the FOB relative to the brand-name price would reach about 40 percent.” In a press release, former FDA Commissioner Scott Gottlieb referenced an FDA finding “that entry of a single biosimilar product in non-U.S. OECD markets lowers prices relative to the reference product by 30 percent; markets with three to four biosimilar entrants have prices 35 to 43 percent lower than their reference biologics” (Ref. 7). These estimates are consistent with a recent report published by the RAND Corporation (Ref. 8) describing a literature review “that assumptions on biosimilar price relative to original price ranged from 10 to 51 percent (mean 27 percent).” These figures, when combined with estimates of biosimilar market shares, result in estimated “cost savings as a share of total biologic spending rang[ing] from 0.2 to 10.5 percent (mean 3.1 percent).” We adopt these estimates as our predicted cost savings for products potentially facing biosimilar competition following the transition date.

We note that the RAND report, in its own estimates of cost savings from biosimilars, makes an additional assumption about products that represent the largest revenue in the transition list: "We expect the biosimilar market for insulins and human growth hormones—where there are already multiple competing products—to look different than the market for other biologics," and further assumed that these products would see "one-half the biosimilar penetration and price discounts of other markets." While we do not adopt a comparable assumption in our primary estimate of total cost savings, and note that there may be reason to believe competition from biosimilar or interchangeable versions of many transition products may provide substantial cost savings relative to competition in the current market, this approach is well within the range of uncertainty that we do estimate.

To generate a dollar value of total cost savings, we need to define a baseline forecast for total expenditures on the affected products. As described earlier, we estimate that the products on the transition list accounted for $38 billion dollars, which is about $576 million per product. Noting that differences in incentives from additional years of potential exclusivity and from the newly available pathway for biosimilar or interchangeable products may have meaningful impacts on this estimate, we adopt an earlier forecast of 3 additional products approved per year that are currently regulated as

drugs under the baseline and will be regulated as biological products under the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act. In years beyond 2019, we assume that, under the baseline scenario, revenues of existing products will grow at an annual 7% rate, which is consistent with the RAND study's approach. For the additional 3 products approved per year, we impute sales revenue equal to the average sales revenue of existing products.

After calculating the annual revenue for each existing and projected product, we multiply these by the estimated cost savings for products that are potentially subject to biosimilar competition and have no unexpired exclusivity. For example, in the year 2020, we expect there to be the products that are the subject of the 95 applications on the transition list, plus 3 additional applications approved in 2020. We assume that all additional applications approved in 2020 will occur after the transition date of March 23, 2020. Under this forecast, there will be 98 products, of which 95 will have no unexpired exclusivity potentially facing biosimilar competition and 3 products that will potentially have 12 years of exclusivity. We therefore expect 97% of these products will receive discounts in the magnitudes described above in 2020. Under our forecast, the total number of products will continue to grow by 3 per year. This means that, beginning in 2032, the number of products without exclusivity will increase by up to 3 per year, reflecting a 12-year delay before biosimilar competition for products approved after 2020. We note that exclusivity is not the only factor that can limit competition in a particular market.

In 2020, the projected spending under the alternative baseline is about $51.4 billion. We estimate that the BPCI Act statutory changes and subsequent statutory changes made by the FCA Act will generate between $100 million and $5.2 billion in savings relative to this baseline in 2020, with a primary estimate of $1.5 billion. Table 6 reflects our estimated savings for the first ten years and reports the presented discounted value and annualized figures over the same time horizon using a 3% and 7% discount rate.

Table 6. Reduced Expenditures on Affected Products Relative to Alternative Baseline ($ Million)

Year	Products	Baseline Expenditures	Products without Exclusivity	% of Products	Reduced Expenditures		
					Low	Primary	High
2020	98	$51,448	95	97%	$100	$1,546	$5,237
2021	95	$56,734	95	94%	$107	$1,654	$5,603
2022	98	$62,509	95	91%	$114	$1,770	$5,995
2023	101	$68,814	95	89%	$122	$1,894	$6,415
2024	104	$75,695	95	86%	$131	$2,027	$6,864
2025	107	$83,203	95	84%	$140	$2,168	$7,345
2026	110	$91,391	95	82%	$150	$2,320	$7,859
2027	113	$100,317	95	80%	$160	$2,483	$8,409
2028	116	$110,045	95	78%	$171	$2,656	$8,998
2029	119	$120,644	95	76%	$183	$2,842	$9,627
PDV, 3%		$684,359			$1,156	$17,924	$60,712
PDV, 7%		$547,056			$932	$14,449	$48,941
Annualized, 3%		$80,228			$136	$2,101	$7,117
Annualized, 7%		$77,888			$133	$2,057	$6,968

The expenditure reductions relative to the alternative baseline described above will only occur if firms invest in developing biosimilar products, which is expensive. In a broader review of the economics of biosimilars, Blackstone and Joseph (Ref. 9) cite "a cost of between $100 million and $250 million" to develop a biosimilar, and also note that these products involve high manufacturing costs. If these figures are accurate, and all 91 products available for biosimilar competition see one additional biosimilar entrant, this will come at the cost of between $9.0 billion and $22.5 billion just on product development. Similarly, when products approved after the transition date begin to lose exclusivity in 2032, this could result in costs of $300 million to $750 million per year if one biosimilar is developed for each of the 3 forecasted biological products with expiring exclusivity. It is possible that some of these biological products may not face biosimilar competition even after the expiration of exclusivity, suggesting that these costs may be overestimates. On the other hand, it is also possible that products with higher revenues will eventually compete with more than one biosimilar. Additionally, these only reflect the cost of developing a biosimilar and do not reflect the recurring costs of manufacturing these products.

We also note that firms will not be expected to make investments in developing biosimilars unless they are able to recover the costs of development, manufacturing, and marketing of these products. Therefore, firms considering developing biosimilars will likely make such decisions based on predictions about market share and product markups. Table 6 also presents the present discounted value and annualized values of total expenditures on the affected products over a 10-year time horizon, which are likely to be relevant factors to entry. The estimates of cost savings following biosimilar competition reflect important distributional effects, however we are not able to fully measure the net social benefits. Instead, these represent a transfer of income from the

manufacturer of the reference product to patients and other purchasers. Additionally, some of the sales revenue from the reference product will instead flow to the biosimilar competitor or competitors. If lower prices result in greater access to products and higher market quantities, this will reduce the deadweight loss associated with monopoly pricing, which will result in greater total surplus. We have not estimated the welfare effects of these potential increases in utilization.

In addition to the effects of the exclusivity periods and abbreviated licensure pathways described above, the FDA also has experienced different costs in reviewing NDA and BLA applications (Ref. 10). Finally, we note that biological products are subject to certain provisions of both the FD&C Act and the PHS Act, and there are some differences in the regulatory requirements for biological products, which we do not attempt to monetize.

We have identified several additional factors that could affect the estimates in this section. First, we note that there is no pathway under the PHS Act that directly corresponds to the 505(b)(2) pathway under the FD&C Act. Since several of the products on the transition list were approved through this pathway, this suggests that the forecasted number of new products per year could be overstated. Additionally, if this pathway is currently resulting in competition and price reductions, then our primary estimate of cost savings under the rule will also likely be overstated. A second issue is that other factors besides exclusivity can limit competition. Patent protection can also delay marketing of competitor products, regardless of whether the reference product may have received 3 or 5 or 12 years of exclusivity. If patent-related issues were not considered in the timing of biosimilar or interchangeable product entrants or the estimates of market shares of biosimilar products, this would suggest that the resulting primary cost-savings estimates are also overstated.

Finally, we again note that following publication of the preliminary analysis, the statute was modified to no longer exclude "any chemically synthesized polypeptide" from the category of “protein” in the statutory definition of "biological product," and FDA revised the final rule accordingly. Removing this exception now allows for potential competition if a developer were to chemically synthesize a protein product (e.g., a follow-on insulin) because the developer would now be able to seek licensure of such product and bring it to market through the abbreviated biosimilar or interchangeable pathway, which would be less resource-intensive than submitting a new drug application. We are unable to quantify the effects of removing this exception on competition because we do not know how many such products may be developed.

IV. Final Small Entity Analysis

The Regulatory Flexibility Act requires us to analyze regulatory options that will minimize any significant impact of a rule on small entities when “the agency publishes a general notice of rulemaking” (5 U.S.C. § 601(2)). We have analyzed this rule under the Regulatory Flexibility Act and propose to certify that, because we expect that the only cost of this rule is the opportunity cost to read and understand the rule, which is estimated

to be about $79 for a typical firm, this rule will not have a significant economic impact on a substantial number of small entities.

Under the current Small Business Size Standards published by the U.S. Small Business Administration (Ref. 11), pharmaceutical and medicine manufacturing (NAICS code 325400) firms qualify as small businesses if they employ fewer than 1,000 employees. This threshold is higher for certain sub-industries, such as pharmaceutical preparation manufacturing (NAICS code 325412), for which the SBA applies a 1,250-employee cut-off. According to the most recent Statistics of U.S. Business (Ref. 12), 1,615 of 1,775 firms classified in the pharmaceutical and medicine manufacturing industry employed fewer than 500 workers (Ref. 5). We observe that at least 91% of firms in this sector qualify as small businesses, which is understated due to data limitations.

Although most of the firms that are affected by this rule will be considered small businesses, these costs are limited to the time burden of reading the rule. As discussed earlier, we predict that this could be done by a legal professional in about 0.5 hours, earning a loaded hourly wage of about $164. Our primary estimate is that each small business will incur $79 in time costs associated with reading the rule. We also estimate a lower bound of $71 and upper bound of $89, which corresponds to faster or slower reading paces. This range of costs will likely not have a significant economic impact on a substantial number of small entities.

V. References

1. Food and Drug Administration (2015). "FDA guidance for industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009." Silver Spring, MD: U.S. Food and Drug Administration. http://www.regulations.gov (Docket No. FDA-2011-D-0611).

2. Food and Drug Administration (2018). "Definition of the Term "Biological Product" (Proposed Rule) Preliminary Regulatory Impact Analysis." Silver Spring, MD: U.S. Food and Drug Administration. https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.

3. Food and Drug Administration (2016). "FDA draft guidance for industry: Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009." Silver Spring, MD: U.S. Food and Drug Administration. http://www.regulations.gov (Docket No. FDA-2015-D-4750).

4. Food and Drug Administration (2019). "Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)." Silver Spring, MD: U.S. Food and Drug Administration. https://www.fda.gov/Drugs/InformationOnDrugs/ucm129689.htm

5. Bureau of Labor Statistics (2018). May 2018 National Industry-Specific Occupational Employment and Wage Estimates: NAICS 325400 – Pharmaceutical and Medicine Manufacturing. http://www.bls.gov/oes/current/naics4_325400.htm.

6. Congressional Budget Office (2007). "S. 1695, Biologics Price Competition and Innovation Act of 2007: Cost estimate for the bill as ordered reported by the Senate Committee on Health, Education, Labor, and Pensions on June 27, 2007." Washington, DC: Congressional Budget Office. https://www.cbo.gov/sites/default/files/110th-congress-2007-2008/costestimate/s16950.pdf

7. Food and Drug Administration (2018). "Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilars Action Plan." Silver Spring, MD: U.S. Food and Drug Administration.
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm

8. Mulcahy, Andrew W., Jakub P. Hlávka, and Spencer R. Case (2018). "Biosimilar Cost Savings in the United States: Initial Experience and Future Potential." Arlington, VA: RAND Corporation.
https://www.rand.org/content/dam/rand/pubs/perspectives/PE200/PE264/RAND_PE264.pdf

9. Blackstone, Erwin A., and P. Fuhr Joseph, Jr. (2013). "The Economics of Biosimilars." American Health and Drug Benefits 2013 Sept-Oct 6(8): pp. 469-478.

10. Food and Drug Administration (2018). "Standard Costs (in thousands of dollars) for Components of the Process for the Review of Human Drug Applications." Silver Spring, MD: U.S. Food and Drug Administration.
https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm093484.htm

11. Small Business Administration (2017). "Summary of Size Standards by Industry Sector." Washington, DC: U.S. Small Business Administration.
https://www.sba.gov/content/summary-size-standards-industry-sector.

12. Census Bureau (2015). 2015 Statistics of U.S. Businesses Annual Data Tables by Establishment Industry. https://www.census.gov/data/tables/2015/econ/susb/2015-susb-annual.html.