

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Definition of the Term “Biological Product”

Docket No. FDA-2018-N-2732

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

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

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

B. Summary of Costs and Benefits

This proposed rule would codify the Food and Drug Administration’s (FDA or Agency) interpretation of the statutory terms “protein” and “chemically synthesized polypeptide” that the agency previously described in guidance (Ref. 1). Formalizing these interpretations would reduce regulatory uncertainty introduced by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). Specifically, the proposed rule would clarify the criteria for whether certain products will be regulated as drugs or biological products beginning on March 23, 2020. The “bright-line” approach under the proposed rule would reduce the amount of time spent by FDA staff and industry in support of making such determinations.

In this regulatory impact analysis, we identify the products most likely to require a case-by-case determination under the baseline scenario. Under the proposed rule, these determinations would be made by FDA according to the bright line standard proposed.

We calculate the cost savings from the amount of time saved by both 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 2017 dollars annualized over 10 years is \$340,766 using a 7% discount rate and \$321,506 using a 3% discount rate. We also calculate ranges of benefits of \$313,373 to \$355,690 and \$296,220 to \$335,282, respectively. The estimated annualized costs range from \$14,471 to \$18,089, with a primary estimate of \$16,079 using a 7% discount rate over a 10-year horizon. For a 3% discount rate, we estimate a range of \$12,378 to \$15,472, with a primary estimate of \$13,753. These figures are shown in Table 1 below.

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

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

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

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

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	\$110,574	\$99,517	\$124,396	\$114,868	\$103,382	\$129,227
Present Value of Cost Savings	\$2,891,315	\$2,993,948	\$2,702,931	\$4,556,396	\$4,671,456	\$4,345,200
Present Value of Net Costs	-\$2,780,741	-\$2,894,431	-\$2,578,534	-\$4,441,527	-\$4,568,074	-\$4,215,973
Annualized Costs	\$7,740	\$6,966	\$8,708	\$3,446	\$3,101	\$3,877
Annualized Cost Savings	\$202,392	\$209,576	\$189,205	\$136,692	\$140,144	\$130,356
Annualized Net Costs	-\$194,652	-\$202,610	-\$180,497	-\$133,246	-\$137,042	-\$126,479

II. Preliminary 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 Public Health Service Act (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 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) or, if applicable, Abbreviated New Drug Applications (ANDAs) 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. Such an application may, for example, be withdrawn and resubmitted under section 351(a) or 351(k) of the PHS Act, as appropriate (Ref. 2).

B. Market Failure Requiring Federal Regulatory Action

The amended definition of a “biological product” in the BPCI Act added a new regulatory burden to drug and biological product manufacturers and the FDA. Specifically, by introducing the scientific terms “protein” or “chemically synthesized polypeptide” in the statutory definition of “biological product,” Congress introduced uncertainty into the regulatory process. Without additional regulatory action by the FDA to clarify the terms in this definition, manufacturers and the FDA would need to spend time and resources to determine whether individual products are regulated as drugs under section 505 of the FD&C Act or as biological products under section 351 of the PHS Act.

C. Purpose of the Proposed Rule

The proposed rule would directly address the uncertainty introduced into the regulatory process by the BPCI Act by interpreting “protein” and “chemically synthesized polypeptide.” The proposed rule would codify the statutory interpretations FDA previously described in guidance (Ref. 1). Specifically, the proposed rule would interpret “protein” to mean “any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size,” and “chemically synthesized polypeptide” to mean “any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is greater than 40 amino acids but less than 100 amino acids in size.”

These interpretations would 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 proposed 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 proposed 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 August 2018 version of the FDA’s Orange Book contains 4,915 approved NDAs (Ref. 3). From these, the FDA has identified a preliminary list of 89 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 (“preliminary transition list”). Based on comments submitted to FDA through the public docket, there may be changes to the preliminary list of approved applications for biological products under the FD&C Act that will be affected by the transition provision.

Among these 89 approved applications, 23 have been discontinued according to the FDA Orange Book (Ref. 3). To give a sense of the market size of the affected products, we matched the remaining 66 non-discontinued products with IQVIA sales data¹. We estimate that for 2016, the total combined revenue was approximately \$32.5 billion dollars, or an average of \$492 million per product.

Without a regulation that codifies FDA’s interpretation of the terms “protein” and “chemically synthesized polypeptide,” as proposed in this rule, drug and biological product manufacturers may challenge agency classification decisions on a product-by-product basis. Under this baseline scenario, the agency expects that the 89 existing approved NDAs would transition to BLAs. We also forecast an additional 3 new approved applications per year would fall into the same size category as the 89 products described above. This is approximately equal to the average annual number of approvals of existing NDA products over both the last 5 years, and over the last 20 years, that will be transitioning to BLAs. Without the rule, we anticipate these applications would need a case-by-case analysis to determine whether the product is a drug product or a biological product.

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. 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 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.

¹ 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 February, 2018.

Any unexpired period of 5-year or 3-year exclusivity associated with a product approved in an NDA would 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 proposed rule would not significantly affect which biological products would be eligible for 12 years of exclusivity under the PHS Act because the size threshold for a product to be classified as a “biological product” would remain the same as described in guidance. 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 would transition from NDA to BLA. The Sensitivity Analysis (Section III) calculates the effects of the BPCI Act statutory changes and the proposed rule against this alternative baseline scenario.

E. Benefits of the Proposed Rule

Under the proposed rule, FDA would be able to 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 would 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 proposed rule from this streamlined review process.

For our primary estimate, we expect that these 89 currently approved products and 3 additional products per year would 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 would take at least 114 hours by FDA staff and 78 hours by industry for each product. These are conservative estimates, so the resulting cost-savings estimates are likely understated. For our lower-bound estimate of cost savings, we assume that no time would have been spent for the 23 discontinued products 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 proposed rule would require a case-by-case determination. FDA requests comment and data on our assumptions.

To calculate the cost savings of the proposed 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. 4). We double the wage estimate of \$65.69 to \$131.38 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 proposed rule would 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 \$1.5 million in 2020 to FDA and \$1.0 million to industry, with estimate ranges of \$1.5 million to \$1.6 million and \$0.8 million to \$1.1 million, respectively. Combining these estimates yields total cost savings in 2020 of \$2.5 million, or between \$2.3 million and \$2.6 million. In future years, the FDA would experience cost savings of \$46,000 and industry of \$31,000, for a total of about \$77,000. 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
2018	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
2019	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
2020	\$1,512,532	\$1,512,532	\$1,589,702	\$1,004,269	\$768,573	\$1,055,507	\$2,516,801	\$2,281,105	\$2,645,209
2021	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2022	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2023	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2024	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2025	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2026	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2027	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
PDV, 3%	\$1,648,176	\$1,648,176	\$1,718,798	\$1,094,332	\$878,637	\$1,141,222	\$2,742,508	\$2,526,813	\$2,860,019
PDV, 7%	\$1,438,371	\$1,438,371	\$1,501,365	\$955,029	\$762,631	\$996,854	\$2,393,400	\$2,201,002	\$2,498,219
Annualized, 3%	\$193,217	\$193,217	\$201,496	\$128,289	\$103,003	\$133,786	\$321,506	\$296,220	\$335,282
Annualized, 7%	\$204,792	\$204,792	\$213,761	\$135,975	\$108,581	\$141,930	\$340,766	\$313,373	\$355,690

F. Costs of the Proposed Rule

We assume that all firms that manufacture drug products would need to read this proposed rule. The current version of the proposed rule contains about 6,500 words. If the average adult reads between 200 and 250 words per minute, we estimate that it would take approximately 0.5 hours to read the proposed rule at the midpoint of 225 words per minute. Using data from the FDA Orange Book (Ref. 3), we count that there are 1,578 firms that manufacture drug products. We assume that the person reading the proposed 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. 4). Doubling this wage to account for overhead, we assume that the individuals reading the proposed rule earn a mean fully loaded hourly wage of \$159.04. Multiplying the number of firms by the time to read the proposed rule, and then multiplying that product by the mean fully loaded hourly wage, we estimate that the total cost to read the proposed rule would be about \$121,000 using 2017 wage figures. We also estimate a lower-bound of \$108,000 and an upper-bound of \$136,000, corresponding to faster and slower reading speeds. This would be a one-time cost that occurs in the first year.

G. Net Benefits of the Proposed Rule

To calculate the net benefits of the proposed 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 2017 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
2018	\$0	\$0	\$0	-\$120,835	-\$135,939	-\$108,752	-\$120,835	-\$135,939	-\$108,752
2019	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
2020	\$1,512,532	\$1,512,532	\$1,589,702	\$1,004,269	\$768,573	\$1,055,507	\$2,516,801	\$2,281,105	\$2,645,209
2021	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2022	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2023	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2024	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2025	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2026	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
2027	\$46,302	\$46,302	\$46,302	\$30,743	\$30,743	\$30,743	\$77,045	\$77,045	\$77,045
PDV, 3%	\$1,648,176	\$1,648,176	\$1,718,798	\$977,016	\$746,657	\$1,035,638	\$2,625,192	\$2,394,833	\$2,754,435
PDV, 7%	\$1,438,371	\$1,438,371	\$1,501,365	\$842,099	\$635,585	\$895,217	\$2,280,470	\$2,073,956	\$2,396,582
Annualized, 3%	\$193,217	\$193,217	\$201,496	\$114,536	\$87,531	\$121,408	\$307,753	\$280,747	\$322,904
Annualized, 7%	\$204,792	\$204,792	\$213,761	\$119,896	\$90,493	\$127,459	\$324,688	\$295,285	\$341,219

H. Analysis of Regulatory Alternatives to the Proposed Rule

For purposes of this analysis, in addition to the proposed interpretation described above, FDA considered and analyzed two regulatory alternatives to the proposed 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, other than molecules made entirely by chemical synthesis (i.e., a chemically synthesized polypeptide), 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, only 29 of the 89 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 60 applications that transition without a costly review by FDA and industry.

Under the primary baseline, we forecasted 3 new applications per year would 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 67%.

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 proposed 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 proposed 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
2018	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
2019	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
2020	\$1,019,684	\$1,019,684	\$1,071,709	\$677,035	\$518,139	\$711,578	\$1,696,720	\$1,537,824	\$1,783,287
2021	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2022	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2023	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2024	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2025	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2026	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
2027	\$31,215	\$31,215	\$31,215	\$20,726	\$20,726	\$20,726	\$51,940	\$51,940	\$51,940
Proposed Rule									
PDV, 3%	\$1,648,176	\$1,648,176	\$1,718,798	\$1,094,332	\$878,637	\$1,141,222	\$2,742,508	\$2,526,813	\$2,860,019
PDV, 7%	\$1,438,371	\$1,438,371	\$1,501,365	\$955,029	\$762,631	\$996,854	\$2,393,400	\$2,201,002	\$2,498,219
Annualized, 3%	\$193,217	\$193,217	\$201,496	\$128,289	\$103,003	\$133,786	\$321,506	\$296,220	\$335,282
Annualized, 7%	\$204,792	\$204,792	\$213,761	\$135,975	\$108,581	\$141,930	\$340,766	\$313,373	\$355,690
Alternative									
PDV, 3%	\$1,111,130	\$1,111,130	\$1,158,740	\$737,752	\$592,339	\$769,363	\$1,848,882	\$1,703,469	\$1,928,103
PDV, 7%	\$969,689	\$969,689	\$1,012,156	\$643,840	\$514,133	\$672,037	\$1,613,528	\$1,483,822	\$1,684,193
Annualized, 3%	\$130,258	\$130,258	\$135,840	\$86,487	\$69,440	\$90,193	\$216,745	\$199,699	\$226,032
Annualized, 7%	\$138,062	\$138,062	\$144,108	\$91,668	\$73,201	\$95,683	\$229,730	\$211,263	\$239,791
Difference									
PDV, 3%	\$537,046	\$537,046	\$560,058	\$356,580	\$286,297	\$371,859	\$893,626	\$823,344	\$931,916
PDV, 7%	\$468,683	\$468,683	\$489,209	\$311,189	\$248,498	\$324,818	\$779,872	\$717,180	\$814,027
Annualized, 3%	\$62,958	\$62,958	\$65,656	\$41,802	\$33,563	\$43,593	\$104,760	\$96,521	\$109,249
Annualized, 7%	\$66,730	\$66,730	\$69,652	\$44,306	\$35,380	\$46,247	\$111,036	\$102,110	\$115,899

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, and the statutory term “chemically synthesized polypeptide” would be interpreted to mean any alpha amino acid polymer

that (1) is made entirely by chemical synthesis; and (2) is greater than 50 amino acids but less than 100 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 the same 89 existing approved NDAs for biological products would transition to BLAs as under the approach described in the proposed rule. We do, however, identify one approved NDA product that is composed of 44 amino acids. Although this product is above the rule’s proposed threshold of 40 amino acids, it is made entirely by chemical synthesis and does not meet the definition of a biological product because it is a chemically synthesized polypeptide. Under this alternative proposal, it would also not meet the definition of a biological product because it is a peptide (i.e., composed of 50 or fewer amino acids), rather than a chemically synthesized polypeptide.

Since the preliminary list of products that would transition are identical under this alternative, we expect the cost and benefits of such a policy would be similar or identical to comparable estimates of the effects of the rule. However, it is possible that additional products submitted in the future could be made up of between 41 and 50 amino acids. Thus, there is the potential for one or more products in the future to be classified as drugs under this proposal that would be classified as biological products under the proposed rule.

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 terms “protein” and “chemically synthesized polypeptide” as reflected in FDA’s guidance (Ref. 1) would 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 rather than this proposed rule and expect the final outcome of such case-by-case determination for each individual product would 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 would not occur without the BPCI Act statutory changes and the rule.

We expect the bulk of the effects of the statute under this baseline are driven by two, interrelated factors: (1) the differences in 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 statutory changes and the rule would 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 would 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. According to August 2018 Orange Book exclusivity data (Ref. 3), only 6 NDAs on the transition list have exclusivity expiration dates beyond the March 23, 2020 transition date. Of these applications, 5 products have exclusivity expiration dates in late 2020, and 1 product has exclusivity that expires in mid-2021. Though any unexpired exclusivity for these applications and any other NDAs for biological products approved before the transition date would 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 would extend beyond these unexpired exclusivity expiration dates.

In contrast, in accordance with the BPCI Act statutory changes and the rule, applications for similar products submitted under section 351(a) of the PHS Act before, on, or after the March 23, 2020 transition date would 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 would 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 80 of the 89 applications on the preliminary transition list have no 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. We 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 would lead to greater competition (compared with follow-on products approved through the 505(b)(2) pathway) for the types of applications that would transition under the proposed rule.

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 and invite the public to comment on our 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. 7). 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 recent press release, 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. 8). These estimates are consistent with a recent report published by the RAND Corporation (Ref. 9) 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, 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 89 products on the transition list accounted for \$32.5 billion dollars in 2016, which is about \$365 million per product, including discontinued products. 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 would be regulated as biological products under the BPCI Act statutory changes and the rule. In years beyond 2016, 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 existing 89 products, plus 3 additional products approved in 2019 and 3 more approved in 2020. We assume that all products approved in 2020 will occur after the transition date of March 23, 2020. Under this forecast, there will be 95 products, of which 92 would have no unexpired exclusivity potentially facing biosimilar

competition and 3 products that will have 12 years of exclusivity. We therefore expect 97% of these products would receive discounts in the magnitudes described above in 2020. Under our forecast, the total number of products would continue to grow by 3 per year. This means that, beginning in 2032, the number of products without exclusivity would increase by 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 \$45.5 billion. We estimate that the BPCI Act statutory changes and the rule will generate between \$88 million and \$4.6 billion in savings relative to this baseline in 2020, with a primary estimate of \$1.3 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

Year	Products	Baseline Expenditures	Products without Exclusivity	% of Products	Reduced Expenditures		
					Low	Primary	High
2018	89	\$37,202,751,252			0	0	0
2019	92	\$41,148,750,936			0	0	0
2020	95	\$45,464,897,094	92	97%	\$88,058,327	\$1,364,904,069	\$4,623,062,168
2021	98	\$50,183,674,834	92	94%	\$94,222,410	\$1,460,447,353	\$4,946,676,519
2022	101	\$55,340,303,462	92	91%	\$100,817,979	\$1,562,678,668	\$5,292,943,876
2023	104	\$60,972,960,092	92	88%	\$107,875,237	\$1,672,066,175	\$5,663,449,947
2024	107	\$67,123,021,163	92	86%	\$115,426,504	\$1,789,110,807	\$6,059,891,443
2025	110	\$73,835,323,279	92	84%	\$123,506,359	\$1,914,348,564	\$6,484,083,844
2026	113	\$81,158,444,888	92	81%	\$132,151,804	\$2,048,352,963	\$6,937,969,713
2027	116	\$89,145,010,438	92	79%	\$141,402,430	\$2,191,737,670	\$7,423,627,593
PDV, 3%		\$501,298,007,485			\$739,460,933	\$11,461,644,468	\$38,821,699,003
PDV, 7%		\$400,428,646,787			\$575,054,603	\$8,913,346,346	\$30,190,366,657
Annualized, 3%		\$58,767,419,378			\$86,687,380	\$1,343,654,387	\$4,551,087,441
Annualized, 7%		\$57,012,030,750			\$81,874,838	\$1,269,059,994	\$4,298,429,011

The expenditure reductions relative to the alternative baseline described above would 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. 10) 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 92 products available for biosimilar competition see one additional biosimilar entrant, this would come at the cost of between \$9.2 billion and \$23 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 would 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 would 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 would 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 would instead flow to the biosimilar competitor or competitors. If lower prices result in greater access to products and higher market quantities, this would reduce the deadweight loss associated with monopoly pricing, which would 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. 11). For example, in fiscal year 2017, an NDA with clinical data for a new molecular entity cost \$5.3 million, whereas a BLA cost \$4.6 million. If these figures remained constant over time, this would represent \$743,000 less for each of the three applications per year as BLAs than NDAs, or about \$2.1 million per year. This does not include any additional costs from additional biosimilar applications. 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 would 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.

We once again request public comment on additional factors or data that FDA should consider in further evaluating the effects of the rule using an alternative pre-BPCI Act baseline. We also seek public comment on other alternative approaches that should be considered in evaluating the effects of the rule.

IV. Small Entity Effects

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities when “the agency publishes a general notice of proposed rulemaking” (5 U.S.C. § 601(2)). We have analyzed this proposed rule under the Regulatory Flexibility Act and propose to certify that, because we expect that the only cost of this proposed rule is the opportunity cost to read and understand the rule, which is estimated to be about \$77 for a typical firm, this proposed rule would 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. 5)), 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. 6), 1,615 of 1,775 firms classified in the pharmaceutical and medicine manufacturing industry employed fewer than 500 workers (Ref. 4). 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 proposed rule would be considered small businesses, these costs are limited to the time burden of reading the proposed 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 \$159. Our primary estimate is that each small business would incur \$77 in time costs associated with reading the rule. We also estimate a lower bound of \$69 and upper bound of \$86, which corresponds to faster or slower reading paces. This range of costs would likely not have a significant economic impact on a substantial number of small entities.

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