DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Biologics License Applications and Master Files

Docket No. FDA-2019-N-1363

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 small entities affected by this rule would incur a net cost savings, 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 $154 million, using the most current (2018) 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.

The proposed rule, if finalized, would allow certain biological products, originally approved in a new drug application (NDA) under the Federal Food, Drug & Cosmetic Act (FD&C Act), to continue marketing by referencing in the application a drug master file (DMF) for information on a drug substance, drug substance intermediate, or drug product (DS/DSI/DP) after the NDA is deemed to be a license for a biological product under the Public Health Service Act (PHS Act) on March 23, 2020 (approved NDAs that will be deemed to be licensed under the PHS Act on March 23, 2020, are referred to in this document as "deemed BLAs"). The proposed rule, if finalized, would also codify our existing practice that a biological product licensed in a biologics license application (BLA) under the PHS Act may incorporate by reference a master file, except for information regarding DS/DSI/DP. Finally, if finalized, the proposed rule would codify our existing practice that information from a master file, including DS/DSI/DP information, may be relied on in an investigational new drug application (IND) to investigate any biological product to enable the submission of a marketing application.

We estimate that the proposed rule, if finalized, would generate net cost savings for industry and FDA. Applicants with deemed BLAs would avoid the costs associated with a change to contract manufacturing or disruption in supply that would occur if the applicant could no longer reference a DMF for the DS/DSI/DP information. For example, such costs may include the cost of preparing a supplement that contains information the applicant would have referenced from a DMF. FDA would also avoid the cost of reviewing corresponding supplements that contain the DS/DSI/DP information. Industry

and consumers would also avoid potential disruption in the market that would occur if the products were removed from the market because DS/DSI/DP information was not available for incorporation by reference for these products.

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule.

B. Summary of Costs and Benefits

The proposed rule, if finalized, would clarify that deemed BLAs that originally referenced DMFs for DS/DSI/DP information in an approved NDA can continue to do so after March 23, 2020. The proposed rule, if finalized, would also codify the requirements for the use of master files by current and future BLA holders and sponsors of INDs for biological products. The proposed rule, if finalized, would codify existing practice with respect to biological products in BLAs and INDs, would allow the deemed BLAs to continue to reference DMFs for DS/DSI/DP information, and would generate net cost-saving benefits for the private and government sectors. Furthermore, the proposed rule, if finalized, would promote continuity and avoid potential disruptions in the supply of biological products deemed BLAs on March 23, 2020. Table 1 summarizes our estimate of the annualized costs and the annualized cost-saving benefits of the proposed rule.

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 $millions/year	$2.48	$0.33	$4.64	2017	7%	10	Cost savings
		$2.56	$0.32	$4.80	2017	3%	10	Cost savings
						7%		

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	Annualized Quantified					3%		
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.00	$0.00	$0.00	2017	7%	10	
		$0.00	$0.00	$0.00	2017	3%	10	
	Annualized Quantified					7%		
						3%		
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year					7%		
						3%		
	From/ To	From:			To:			
	Other Annualized Monetized $millions/year					7%		
						3%		
	From/To	From:			To:			
Effects	State, Local or Tribal Government: None Small Business: None Wages: None Growth: None							

Consistent 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 ($ million in 2016 dollars over an infinite horizon)

	Primary (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	$0.02	$0.02	$0.02	$0.02	$0.02	$0.03
Present Value of Cost Savings	$18.66	$2.49	$34.83	$22.47	$2.80	$42.14
Present Value of Net Costs	($18.64)	($2.47)	($34.81)	($22.45)	($2.77)	($42.12)
Annualized Costs	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00

Annualized Cost Savings	$1.31	$0.17	$2.44	$0.67	$0.08	$1.26
Annualized Net Costs	($1.30)	($0.17)	($2.44)	($0.67)	($0.08)	($1.26)

C. Key Terms

In Table 3, we define the key terms used in our analysis. We note that these definitions only apply to this document.

Table 3. Key Terms in the Regulatory Impact Analysis

Applicant	Firm, individual, or institution that submits application materials for review and approval of a drug product.
BLA	Biologics License Application
BPCI Act	Biologics Price Competition and Innovation Act of 2009. Title VII, Pub. L. 111-148.
Consumer Surplus	Value to consumers measured as the difference between the maximum amount a consumer would be willing to pay for a product and the full cost the consumer bears.
Deemed BLA	An approved application for a biological product under section 505 of the FD&C Act that shall be deemed to be a license for a biological product under section 351 of the PHS Act on March 23, 2020.
DMF	A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under 21 CFR part 312 or submits an application or an abbreviated application or an amendment or supplement to them under 21 CFR 314, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person.
DS/DSI/DP	Drug substance, drug substance intermediate, or drug product
NDA	New Drug Application.
Present Value	Discounting monetary values that occur at different times to a current value.

Producer Surplus	Social measure of added value producers receive above the cost of production.

II. Preliminary Regulatory Impact Analysis

A. Background

The BPCI Act amended the definition of a "biological product" in the PHS Act to include a "protein (except any chemically synthesized polypeptide)." The BPCI Act also 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 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 NDAs and will be deemed to be approved BLAs. However, we have generally not allowed BLAs approved under the PHS Act to incorporate by reference DS/DSI/DP information contained in master files. To date, we have identified 89 applications that meet this condition and will be deemed BLAs; 17 of the 89 applications incorporate by reference DS/DSI/DP information contained in nine DMFs. However, 7 of the 17 deemed BLAs are discontinued.

The proposed rule would codify the requirements for the use of master files in BLAs for current and future biological products.

B. Market Failure Requiring Federal Regulatory Action

The BPCI Act amended the statutory definition of "biological product" and provided that certain applications approved under section 505 of the FD&C Act "shall be deemed to be a license for the biological product under" section 351 of the PHS Act on March 23, 2020, but did not specify how this change would be implemented. This lack of specificity introduced uncertainty into the regulatory process. Because we do not allow biological products in BLAs to incorporate by reference DS/DSI/DP information contained in master files, deemed BLAs would not be able to incorporate by reference the DS/DSI/DP information contained in DMFs after March 23, 2020. Without regulatory action, applicants of these deemed BLAs would have to acquire direct knowledge of and control over the DS/DSI/DP information to continue marketing their products. These applicants could face potentially significant expenses and might decide to withdraw the products from the market. This would result in a disruption in the market for these medical products, affecting patient access to these products.

C. Purpose of the Proposed Rule

The proposed rule, if finalized, would allow certain biological products originally approved under the FD&C Act to continue referencing a DMF for DS/DSI/DP information after March 23, 2020, and would codify our existing practice that a biological product licensed under the PHS Act may incorporate by reference information in a master file, except the DS/DSI/DP information. The proposed rule, if finalized, would also codify our practice that any IND can rely on any information in a DMF, including the DS/DSI/DP information.

D. Baseline Conditions

We expect BLA holders to have knowledge of and direct control over the manufacturing process for the DS/DSI/DP of a biological product. Thus, without regulation, an applicant of an

NDA that is deemed a BLA could not continue to incorporate by reference DS/DSI/DP information from a DMF and would have to establish direct control over and knowledge of the manufacturing process of DS/DSI/DP. In this case, we expect that the applicant would attempt to enter into a contract manufacturing agreement with the holder of the DMF referenced in the NDA or enter into a contract manufacturing agreement with a different contract manufacturer who has experience with biological products. Alternatively, some applicants may decide not to continue to manufacture their biological product. The following sections examine the baseline costs under different scenarios.

1. *Lower Bound Estimate of Baseline Costs--Deemed BLA holders enter into a contract manufacturing agreement with the holders of the DMFs*

When a deemed BLA holder enters into a contract manufacturing agreement with the DMF holder, the deemed BLA holder would submit a supplemental application to update the DS/DSI/DP information. This would result in a one-time cost for industry to prepare the supplement, and a one-time cost for us to review the supplement. The holders of the DMFs might also require payment to provide their DS/DSI/DP information, although any payment would represent a transfer and not a cost of the proposed rule. Although there would be no resources expended to develop a new manufacturing process, there may be transaction costs for preparing and reviewing the contract manufacturing agreements.

The number of holders of DMFs who would be willing to enter into contract manufacturing agreements and allow the sponsor of the deemed BLA access to the DMF is uncertain. To deal with this uncertainty, as a lower-bound estimate of costs under the baseline, we assume that each of the 17 affected applicants would have a contract manufacturing agreement with a DMF holder and the DMF holder would allow the applicant direct access to

their DS/DSI/DP information. Because a biological product with a deemed BLA was already approved as an NDA, the applicant would only submit a supplement to the deemed BLA to replace the information in the DMF incorporated by reference. The applicant would incorporate by reference most or all the clinical information they submitted for their approved NDA and would not have to perform new clinical investigations for the approval of the supplement.

The cost for industry to prepare a supplement without clinical data is uncertain. However, our estimate for the cost to review a supplement without clinical data is $87,000 per application (Ref. 1). We assume this would be also the cost to industry to prepare a supplemental application. In addition, industry would incur the costs to enter into a contract manufacturing agreement with the DMF holder. Based on our records, we estimate that there would be 17 contract manufacturing agreements, one for each deemed BLA that relies on a DMF for DS/DSI/DP information and that the total labor hours to prepare and review each contract manufacturing agreement is 40 hours. We use a wage rate for an attorney of $71.13 (Ref. 2) from the median hourly wage in the BLS May 2017 National Occupational Employment and Wage Estimates for lawyers, Occupation code 23-1011, (NAICS code 541100). To account for benefits and overhead, we double this wage rate to $142.26 (= $71.13 x 2). We ask for comment about our assumptions.

We estimate the cost to industry for each contract manufacturing agreement would equal $92,690 per supplemental application, $5,690 to prepare and review the agreement (= $142.26 hr. x 40 hrs.) and approximately $87,000 to prepare the supplement. For the 17 biological products with applications that will be deemed BLAs and that incorporate by reference DS/DSI/DP information contained in DMFs, the total industry costs under this scenario would total $1,575,737 (= $92,690 application x 17 applications). Applying our assumption that the

industry cost to prepare the supplement would equal the government cost to review the supplement, we estimate the total cost to government of approximately $1,479,000 (= $87,000 application x 17 applications).

For this scenario, the one-time costs would equal $3,054,737. We estimate that in the absence of the rule these costs would be incurred in 2020. Thus, the present value equals $2.80 million discounted at 3 percent and $2.49 discounted at 7 percent. The total annualized costs discounted over 10 years equal $0.32 million at 3 percent and $0.33 million at 7 percent. In Table 4, we show a summary of our estimates for the costs.

Table 4. Lower Bound Estimate Summary Table (2017 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3 %
PV of Costs	$3,054,737	$2,493,576	$2,795,517
Annualized Costs[1]		$331,803	$318,175

[1] Assume annualized costs incurred at the end of the period.

2. *Upper Bound Estimate of Baseline Costs--Deemed BLA holders enter into a contract manufacturing agreement with a different contract manufacturer that has experience with biological products.*

Without the rule, applicants that reference a DMF could potentially enter into contract agreements with contract manufacturers to produce their DS/DSI/DP. In this scenario, we assume that no DMF holder would be willing to enter into a contract with an applicant and we assume the applicant would find alternative contract manufacturers. In this case, we assume there would be one-time transaction costs to prepare and review the agreements and one-time costs to develop a new manufacturing process and comparability data for submission in a supplement. We would also need to inspect the contract manufacturing facilities, and review comparability data. We further assume it could take three years to find a suitable contract manufacturer, enter into a contract manufacturing agreement with that manufacturer, and develop the manufacturing

process. While these activities occur, the available inventory of the product may be exhausted, or the product might expire. Until we approve the supplement, these affected biological products would not be commercially available. During that time, the market would be disrupted, generating lost consumer and producer surplus (e.g., medical benefit of products, and lost profits).

In this scenario, which forms our upper-bound cost estimate under the baseline, we assume on average that each applicant would approach contract manufacturers (not the DMF holder) and contract out with one of them to supply their drug ingredients. We assume that each of these deemed BLAs would contract with a separate manufacturer. We also assume the total labor hours to prepare and review the contract manufacturing agreements is 80 hours. We use the median hourly wage for lawyers, $71.13 from the BLS May 2017 National Occupational Employment and Wage Estimates for lawyers, Occupation code 23-1011, (NAICS code 541100) (Ref. 2). To account for fringe benefits and overhead, we double this wage rate to $142.26 (= $71.13 x 2). We estimate the total cost to prepare the contract manufacturing agreements would equal $193,474 (= $142.26 per hour x 80 hours per agreement x 1 contract per applicant x 17 applicants). This cost does not include search costs of approaching multiple contract manufacturers. We request comment on these potential costs.

The expenses for each contract manufacturer and biologic product applicant to transfer the production of the DS/DSI/DP are uncertain. Thus, for this analysis we assume the one-time cost to transfer the production of the DS/DSI/DP to a comparable facility would equal about $2 million to design and modify the facility. We assume the variable production costs would remain comparable to the prior processes. We estimate the total one-time total cost to transfer production would equal $34 million (= $2 million per contract manufacturing agreement x 1

agreement per applicant x 17 applications). We request comment on the cost to design and modify facilities to accommodate additional production.

Because the deemed BLAs are approved applications, the applicant would only need to submit a supplemental application to establish product comparability. For purposes of establishing an upper bound, we assume that the applicant would submit clinical data to support comparability in the supplement and that we would review the comparability data in the supplement and inspect the facilities.

Our cost to review a supplement with clinical data is $286,200 per application (Ref. 1). For the upper bound estimate, we assume that it takes industry double the effort to gather, evaluate and organize the information as it does for us to review the information. Therefore, we assume the cost to industry to prepare an application would equal $572,400 per application. The total estimate to prepare and review each supplement equals approximately $858,600. With 17 biological products that will be deemed BLAs, the total cost of submitting and reviewing supplements with clinical data would equal about $14.6 million (= $858,600 per application x 17 applications).

We would also inspect the facilities of the contract manufacturers. A recent estimate for the average labor hours for FDA consumer safety officers to inspect facilities is 34 hours (Ref. 3). For government wages, FDA estimates a fully loaded wage of $242,838 for an ORA inspector in 2018. With an average of 2,080 hours worked per year, the fully loaded hourly wage equals about $116.75. We estimate the costs to us to inspect would equal approximately $67,481 (= $116.75 per hour x 34 hours per facility x 1 facility per applicant x 17 applicants). We request comment on our estimate.

The total one-time upper bound cost would equal about $48.9 million (= $14.6 million to review and submit supplements + $193,474 to prepare contract manufacturing agreements + $34 million to transfer the production processes to different manufacturing facility + $67,481 for us to inspect the facilities). Moreover, the lost benefit to consumers of these products during the period they might not be available, or the manufacturers' lost profits could substantially exceed this amount depending on the time it takes to obtain approval of these supplements.

We assume the total one-time cost of $48.9 million would be incurred in year 2022. We estimate the present value of the total costs is $42.1million discounted at 3 percent; and $34.8 million discounted at 7 percent. The total annualized cost discounted over 10 years would equal $4.8 million at a 3 percent discount rate and $4.6 million at a 7 percent discount rate. In Table 5, we show a summary of our upper bound estimate.

Table 5. Upper Bound Estimate Summary Table (2017 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3%
PV of Costs	$48,857,155	$34,834,476	$42,144,611
Annualized Costs [1]		$4,635,183	$4,796,732

[1] Assume annualized costs incurred at the end of the period.

3. Primary Estimate of Baseline Costs--Deemed BLA holders enter contract manufacturing agreements with some holders of the DMFs containing the DS/DSI/DP information.

As our primary estimate of the baseline costs in the absence of regulation, we assume only some of the DMF holders would enter into a contract manufacturing agreement with the applicants holding the deemed BLAs. In our lower-bound estimate, we assumed all DMF holders would contract with the applicants. In our upper-bound estimates, we assumed that no DMF holder would contract with the applicants, and that applicants would have to search for alternative contract manufacturers. Lacking information on the likelihood of these two scenarios, we use an average of our lower and upper bound estimates for our primary estimate, assuming

the same timing as the lower and upper bound scenarios. We estimate an average one-time cost of $26.0 million (= ($48,857,155+ $3,054,737) ÷ 2). We estimate the present value of the total cost is $22.5 million at 3 percent discount rate and $18.7 million at 7 percent discount rate. The total annualized cost discounted over 10 years equals $2.6 million at 3 percent discount rate and $2.5 million at 7 percent discount rate. In Table 6, we show a summary of our primary cost estimate.

Table 6. Primary Estimate Summary Table (2017 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3 %
PV of Costs	$25,955,946	$18,664,026	$22,470,064
Annualized Costs [1]		$2,483,493	$2,557,453

[1] Assume annualized costs incurred at the end of the period.

E. Benefits of the Proposed Rule

The primary effect of the proposed rule would be to allow manufacturers of certain products that reference DMFs to continue marketing these products after certain applications transition from approved NDAs to approved BLAs on March 23, 2020. The baseline described above outlines scenarios intended to capture the primary, lower-bound, and upper-bound costs in the absence of a rule. The bulk of the benefits of the proposed rule, if finalized, are cost savings accrued from avoiding any costs and disruptions to manufacturing that would occur because of the transition from NDAs referencing DMFs to deemed BLAs.

Table 7 summarizes our estimate of the total cost-saving benefits. The present value of our primary estimate is $22.5 million using a 3% discount rate or $18.7 using a 7% discount rate.

Table 7. Cost-Savings Benefits of the Proposed Rule (2017 dollars)

	Lower bound at 7%	Lower bound at 3%	Primary bound at 7%	Primary bound at 3%	Upper bound at 7%	Upper bound at 3%

	discount rate	discount rate	discount rate	discount rate	discount rate	discount rate
Present Value	$2,493,575	$2,795,517	$18,664,026	$22,470,064	$34,834,476	$42,144,611
Annualized over 10 years	$331,803	$318,175	$2,483,493	$2,557,453	$4,635,183	$4,796,732

We anticipate that the proposed rule, if finalized would generate additional benefits. However, we lack sufficient data to quantify or monetize these benefits. For example, applicants with deemed BLAs would have regulatory certainty that they could reference DMFs because their biological products were originally approved as NDAs. Although we cannot estimate the value of this regulatory certainty, we believe this certainty has value to industry. We request comment on how industry values this regulatory certainty.

F. Costs of the Proposed Rule - The Time to Learn Rule

We anticipate that current and potential future applicants of biologic products would incur a one-time cost to learn the requirements of the rule. Department of Health and Human Services guidance (Ref. 4) specifies that the time to learn about a rule is determined by the number of words in the rule divided by an average reading speed of 200 to 250 words per minute, which allows enough time for review and interpretation.

The proposed rule has approximately 7,000 words. We estimate that a firm would devote one manager's time to learn the requirements of the rule. The amount of time to learn about the requirements for each manager would range from 0.5 hours to 0.6 hours (= 7,000 words / (200 to 250 words) / minute). The US Census Bureau reports that in 2012 there were 301 establishments within the Biological Product (except diagnostic) Manufacturing NAICs code 325414 (Ref. 5).

To estimate the cost of a manager's time, we use the median hourly wage in the pharmaceutical and medical manufacturing industry for a General and Operations Manager (North American Industry Classification, NAICS, code 325400) from the Bureau of Labor Statistics (BLS) May 2017 National Occupational Employment and Wage Estimates for General and Operations managers Occupation code 11-1021, which is approximately $78.13 (Ref. 6). To account for benefits and overhead, we double this value to roughly $156.26 (= $78.13 x 2).

We estimate that the one-time cost to learn about the rule for those establishments potentially affected by the rule would range from $21,900 (= 301 establishments x 0.47 hour x $156.26 per hour) to $27,400 (= 301 establishments x 0.58 hour per establishment x $156.26 / hour). Although the number of words, reading speed, and number of affected entities may change slightly, we believe these estimates properly reflect the potential cost of learning the rule. We ask for comment about our estimate and assumptions.

G. Uncertainty Analysis

The biggest uncertainty in our analysis is whether the DS/DSI/DP information would be available to the applicants with deemed BLAs that had incorporated such information by reference in the approved NDA. If no DMF holders contract out or license their information to deemed BLA holders or if no alternative contract manufacturers with manufacturing experience with comparable biological products are available, the social cost to develop new manufacturing facilities could be very large. Moreover, the time lag to develop new manufacturing plants could create a situation where a deemed BLA product could cease to be commercially marketed. When a deemed BLA product disappears from the market, the social cost includes lost consumer and producer surplus. In practical terms, this represents the public health and other

benefits of consuming a product, as well as the lost economic profits to manufacturers during the period that the biological products were not commercially marketed. Without the rule, we expect the social costs could be in the hundreds of millions of dollars although we lack sufficient information to quantify this cost; with the rule, we would expect equally large cost savings.

We also lack information about how much time it would take to construct the new manufacturing facilities and the period after March 23, 2020, when certain deemed BLA products would not be commercially available. The costs of construction and the consumer and producer surplus losses could be significant.

For our cost-saving estimates, we relied on the assumption that industry would require at least the same and possibly twice the cost to prepare a BLA than we require to review a BLA supplement. If industry requires more time and effort, then we underestimated the cost-savings benefit and if industry requires less time, then we over-estimated the cost-savings benefit. We request comment on potential costs to applicants to prepare and submit a supplement with and without clinical data.

One last consideration are the transition products themselves. We matched the list of 17 products with the August 2018 version of FDA's Orange Book (Ref. 7) and identified 7 products that are currently discontinued. In the main analysis, we treat active and discontinued products the same because discontinued products can become active if the application has not been withdrawn. Table 8 reports the benefits of the proposed rule in the form of cost savings under the alternative assumption that these products will withdraw from the market rather than incur any costs associated with transitioning from NDA to BLA.

Table 8. Cost-Savings Benefits of the Proposed Rule Excluding Discontinued Products (2017 dollars)

	Lower bound at 7% discount rate	Lower bound at 3% discount rate	Primary bound at 7% discount rate	Primary bound at 3% discount rate	Upper bound at 7% discount rate	Upper bound at 3% discount rate
Present Value	$1,466,809	$1,644,422	$10,978,839	$13,217,685	$20,490,868	$24,790,948
Annualized over 10 years [1]	$195,178	$187,162	$1,460,878	$1,504,384	$2,726,578	$2,821,607

[1] Assume annualized costs incurred at the end of the period.

H. Distributional Effects

The rule would preserve the marketing of certain deemed BLA products. Without the rule, the distributional effects may include transfers from applicants to DMF holders. For example, currently, NDAs referencing the DMF may pay low or fixed fees to reference the DMF, but without the rule, DMF holders could extract higher rents from applicants either by licensing such information or by manufacturing for them. In case markets are disrupted, either by temporary reduction in the supply or by permanent exit, alternative products could gain market power and increase prices. The rule seeks to avoid these potential distributional effects.

I. Analysis of Regulatory Alternatives to the Proposed Rule

In addition to the rule, we also analyze an alternative policy that would extend the compliance period by five years. Under this approach, existing NDA products that transition to BLAs on March 23, 2020, could continue to reference DMFs for DS/DSI/DP information until March 23, 2025. Following a 5-year compliance period, these BLA holders would then have to assume direct knowledge and control over such information rather than referencing a DMF.

Relative to the scenarios described in the baseline, this policy to extend the compliance period by five years would similarly shift the costs by five years into the future. This difference in timing generates cost savings through the discount rate. Table 9 summarizes the present value of the cost-savings under the proposed rule and under the regulatory alternative.

Table 9. Summary of the present value of the cost-savings under the proposed rule and with a 5-year compliance period.

	Lower bound at 7% discount rate	Lower bound at 3% discount rate	Primary bound at 7% discount rate	Primary bound at 3% discount rate	Upper bound at 7% discount rate	Upper bound at 3% discount rate
PV of Cost Savings Under the Rule	$2,493,575	$2,795,517	$18,664,026	$22,470,064	$34,834,476	$42,144,611
PV of Cost Savings with a 5-year compliance period [1]	$1,777,885	$2,411,437	$15,106,597	$20,489,863	$28,435,309	$38,568,289

[1] Assume annualized costs incurred at the beginning of the period.

III. Initial Small Entity Analysis

We examined the economic implications of the proposed rule as required by the Regulatory Flexibility Act. If a proposed rule would have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires us to analyze regulatory options that would lessen the economic effect of the rule on small entities. The proposed rule would generate net cost savings for current applicants of deemed BLA products that reference master files by avoiding transition costs relating to contract manufacturing or disruption in supply, including shortages and price increases. As described in the Baseline

section, one scenario includes the possibility that, without the rule, DMF holders could extract additional rents from applicants with deemed BLAs. Although these payments would be considered transfers in evaluating the rule, they could represent foregone rent for DMF holders. It is unclear how large or how likely these payments could be without the rule. Since we cannot identify any other potential costs of the proposed rule on these firms, we propose to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities. This analysis, together with other relevant sections of this document, serves as the proposed regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

IV. References

The following references are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. We have verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Standard Costs for Components of the Process for the Review of Human Drug Applications (2014-2017), https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/ucm093484.htm, accessed October 22, 2018.
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