DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Biologics License Applications and Master Files

Docket No. FDA-2019-N-1363

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

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

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Executive Summary

The Food and Drug Administration (FDA) is issuing a final rule to amend its regulations to address the use of master files by applications licensed under the Public Health Service Act (PHS Act). The final rule codifies FDA's existing approach that former approved applications for certain biological products under the Federal Food, Drug, and Cosmetic Act (FD&C Act) that have been deemed to be licenses for the biological products under the PHS Act may continue to incorporate by reference drug substance, drug substance intermediate, or drug product (DS/DSI/DP) information contained in a drug master file (DMF) if such information was being referenced at the time the application was deemed to be a license. This final rule also codifies FDA's general practices regarding the referencing of information in master files by applications licensed under the PHS Act, including applications for combination products licensed under the PHS Act, and by investigational new drug applications (INDs) for products that would be subject to licensure under the PHS Act.

This Final Regulatory Impact Analysis discusses the economic impacts of the final rule, including costs, cost savings, and benefits. The final rule will generate net cost-saving benefits for the private and government sectors. Furthermore, the final rule will promote continuity and help avoid potential disruptions in the supply of certain biological products.

I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 14094, the Regulatory Flexibility Act (5 U.S.C. 601-612), the Congressional Review Act/Small Business Regulatory Enforcement Fairness Act (5 U.S.C. 801, Pub. L. 104-121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4).

Executive Orders 12866, 13563, and 14094 direct us to assess all benefits, costs, and transfers 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). Rules are "significant" under Executive Order 12866 Section 3(f)(1) (as amended by Executive Order 14094) if they "have an annual effect on the economy of $200 million or more (adjusted every 3 years by the Administrator of the Office of Information and Regulatory Affairs (OIRA) for changes in gross domestic product); or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, territorial, or tribal governments or communities." OIRA has determined that this final rule is not a significant regulatory action under Executive Order 12866 Section 3(f)(1).

Because this rule is not likely to result in an annual effect on the economy of $100 million or more or meets other criteria specified in the Congressional Review Act/Small

Business Regulatory Enforcement Fairness Act, OIRA has determined that this rule does not fall within the scope of 5 U.S.C. 804(2).

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 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 estimates of anticipated impacts, 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 $177 million, using the most current (2022) 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

The Food and Drug Administration is issuing a final rule to amend its regulations to address the use of master files by biologics license applications (BLAs). The final rule codifies FDA's existing approach that former approved applications for certain biological products under the FD&C Act that were deemed to be licenses for the biological products under the PHS Act may continue to incorporate by reference DS/DSI/DP information contained in DMFs if such information was being referenced at the time the application was deemed to be a license. This final rule also codifies FDA's general practices regarding the referencing of information in

master files by applications licensed under the PHS Act, including applications for combination products licensed under the PHS Act, and by INDs for products that would be subject to licensure under the PHS Act.

Allowing deemed BLAs for biological products to continue referencing DMFs for DS/DSI/DP information will generate net cost-saving benefits for the private and government sectors. Furthermore, the final rule will provide certainty, promote continuity, and help avoid potential disruptions in the supply of certain biological products that were approved in applications under section 505 of the FD&C Act that were deemed, pursuant to section 7002(e)(4) of the BPCI Act, to be licenses for the biological products under section 351 of the PHS Act.

By allowing certain BLAs to continue referencing a DMF for DS/DSI/DP information, FDA avoids imposing a potential new regulatory burden. Affected entities will incur minimal costs to read and understand the rule. FDA estimates that over 10 years at a discount rate of 7 percent, the final rule will generate annualized net cost savings ranging from $0.40 million to $5.19 million with a primary estimate of $2.80 million; at a discount rate of 3 percent, the final rule will generate annualized net cost savings ranging from $0.37 million to $5.17 million with a primary estimate of $2.77 million. Table 1 summarizes our estimate of the annualized costs and the annualized cost-saving benefits of the final rule.

Table 1. Summary of Benefits, Costs and Distributional Effects of the Final Rule
(Millions of 2022 Dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits		$2.81	$0.41	$5.20	2022	7%	10	Cost savings

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
	Annualized Monetized $millions/year	$2.78	$0.38	$5.18	2022	3%	10	Cost savings
	Annualized Quantified					7%		
						3%		
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.01	$0.01	$0.01	2022	7%	10	
		$0.01	$0.01	$0.01	2022	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							

C. Key Terms

In Table 2, we define the key terms used in our analysis. We note that these definitions only apply to this document.

Table 2. Key Terms in the Regulatory Impact Analysis

BLA	Biologics License Application
BPCI Act	Biologics Price Competition and Innovation Act of 2009 (Pub. L. 111-148), as amended by the Further Consolidated Appropriations Act, 2020 (Pub. L. 116-94).
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	A former approved application for a biological product under section 505 of the FD&C Act that has been deemed, pursuant to section 7002(e)(4) of the BPCI Act, to be a license for the biological product under section 351 of the PHS Act.
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.

D. Comments on the Preliminary Economic Analysis of Impacts and Our Responses

We received comments on our preliminary regulatory impact analysis of the proposed rule. We group comments with similar themes together. Some comments address more than one theme. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or the order in which it was received.

(Comment 1) Several commenters stated that the proposed rulemaking will prevent shortages of biological products that are the subject of deemed BLAs.

(Response 1) We agree with these comments. FDA's longstanding practice of not allowing BLAs to incorporate by reference DS/DSI/DP information contained in master files raised questions about whether the former approved applications under the FD&C Act that had

referenced DMFs for such information before March 23, 2020, could continue to do so once those NDAs were deemed to be BLAs. The final rule codifies an exception for deemed BLAs that, as former approved applications under the FD&C Act, incorporated by reference DS/DSI/DP information in DMFs. Without the clarity provided in the final rule, there would be uncertainty about whether this exception would continue. Holders of deemed BLAs that reference a DMF for DS/DSI/DP information might assume that they need to attempt to enter into a contract manufacturing agreement with the holder of the DMF referenced in the former approved applications under the FD&C Act or with a different contract manufacturer who also has experience with biological products. Alternatively, some deemed BLA holders could decide to stop manufacturing their biological product altogether. By avoiding uncertainty, and delays and costs relating to contract manufacturing, the rule will help avoid supply disruptions and any potential resulting shortages or price increases for biological products that are the subject of deemed BLAs.

(Comment 2) One commenter suggested that the economic analysis should more clearly define small entities and describe the effects on these entities in greater detail.

(Response 2) In response to this comment, we have provided clarification of the effects on small businesses in the final economic analysis. We observe that at least 84% of firms in the biological product manufacturing sector qualify as small businesses. Although most of the firms that are affected by this rule will be considered small businesses, their costs are limited to the time burden of reading the rule. Furthermore, as described in the Baseline section, one scenario includes the possibility that, without the rule, DMF holders could

extract additional rents from deemed BLA holders. 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 likely these payments could be without the rule. The final rule would otherwise generate net cost savings for current holders of deemed BLAs that reference DMFs by avoiding the costs of transferring to contract manufacturing or disrupting supply through shortages and price increases. Since we cannot identify any potential costs of the final rule on these firms other than the time burden of reading the rule, we certify that the final rule will not have a significant economic impact on a substantial number of small entities.

(Comment 3) One commenter suggested that language in the economic analysis proposing to certify that the proposed rule will not have a significant effect on small entities implies that there would be no impact on small entities.

(Response 3) We have provided clarification in the final economic analysis to make clear the distinction between no impact and no significant impact on small businesses. Although most of the firms affected by this rule will be considered small businesses, their costs are limited to the time burden of reading the rule. Since we cannot identify any potential costs of the final rule on these firms other than the time burden of reading the rule, we certify that the final rule will not have a significant economic impact on a substantial number of small entities. We note that the Regulatory Flexibility Act permits an agency to certify that a proposed rule would not have a significant economic impact on a substantial number of small entities, if the preliminary analysis supports such a decision.

(Comment 4) One commenter noted that economic factors should be considered in the development of this rulemaking.

(Response 4) We believe that the preliminary economic analysis clearly outlined the economic factors of most relevance to this rulemaking, including cost savings to holders of deemed BLAs that reference a DMF, as well as costs of reading and understanding the rule.

(Comment 5) One commenter stated that by regulating deemed BLAs that reference a DMF for DS/DSI/DP information differently from other BLAs, the proposed rule would introduce unnecessary bureaucratic burdens.

(Response 5) We disagree with this comment. Allowing deemed BLAs to continue referencing DMFs for DS/DSI/DP information that was referenced in the former approved NDAs at the time that they were deemed BLAs imposes no new requirements. The rule aims to prevent unnecessary burdens on these deemed BLA holders.

(Comment 6) One comment stated that it would be costlier to incorporate by reference DS/DSI/DP information contained in master files for the non-biological product constituent parts of combination products approved under the PHS Act, as permitted in this rule, than to submit all necessary information for the non-biological product constituent parts. The commenter suggests that such a process would be costlier because the BLA applicant would also need to demonstrate how the non-biological product constituent part(s) and the biological product constituent part(s) interact.

(Response 6) FDA does not mandate the use of master files in this rule or elsewhere in its regulations; applicants may always submit information directly in their applications. In addition, we do not agree that incorporating by reference DS/DSI/DP information contained in a master file would be costlier than submitting that information in the application itself. For combination products, the applicant needs to provide information demonstrating any interactions between constituent parts, including between non-biological product constituent parts and biological product constituent parts, regardless of whether a master file is used.

E. Summary of Changes

Compared to the preliminary analysis, the final regulatory impact analysis makes two technical changes. First, we incorporated the most recent information available on biological products that are the subject of deemed BLAs. One NDA that was deemed to be a license was initially approved as an NDA after publication of the proposed rule. FDA also withdrew approval of one NDA at the application holder's request. The number of deemed BLAs for biological products that referenced DMFs remained at 17 while the number of DMFs referenced increased from 9 to 10. Second, we updated several inputs into our cost and cost savings model with the most recent industry data. The final regulatory impact analysis also provides more detail as to how the rule reduces uncertainty for holders of deemed BLAs that reference DS/DSI/DP information contained in DMFs.

We note that the final rule codifies FDA's general practice of permitting applications submitted under the PHS Act to incorporate by reference information other than DS/DSI/DP information contained in a master file for any biological product

constituent part of a combination product. The final rule also codifies that a biologics license application under section 351 of the PHS Act is not restricted from incorporating by reference DS/DSI/DP information contained in a master file for any non-biological product constituent part of a combination product. Because language regarding combination products was newly incorporated in the final rule, we incorporated these changes into the final regulatory impact analysis. The total number of affected products remained the same because FDA did not identify additional deemed BLAs that incorporate by reference DS/DSI/DP information contained in a DMF for a constituent part of a combination product.

II. Final Economic Analysis of Impacts

A. Background

Section 7002(b)(1) of the BPCI Act revised section 351(i) of the PHS Act, in part, to amend the definition of a "biological product" to include a "protein (except any chemically synthesized polypeptide)." Section 605 of the Further Consolidated Appropriations Act, 2020 (FCA Act), later amended this definition to remove the parenthetical "(except any chemically synthesized polypeptide)." FDA issued a final rule on February 21, 2020, regarding its interpretation of the term ''protein'' as used in section 351(i)(1) of the PHS Act (Definition of the term 'Biological Product,' 85 FR 10057). After March 23, 2020, the BPCI Act requires that a marketing application for a biological product (that previously could have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act.

Section 7002(e)(4) of the BPCI Act provided that, on March 23, 2020, an approved application for a biological product 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. Section 607 of the FCA

Act, 2020, amended section 7002(e)(4) of the BPCI Act to provide that FDA will continue to review an application for a biological product under section 505 of the FD&C Act after March 23, 2020, so long as that application was submitted under section 505 of the FD&C Act, was filed not later than March 23, 2019, and was not approved as of March 23, 2020. If such an application is approved under section 505 of the FD&C Act before October 1, 2022, it will be deemed to be a license for the biological product under section 351 of the PHS Act upon approval (see section 7002(e)(4)(B)(iii) and (vi) of the BPCI Act).We identified 97 applications that were deemed to be BLAs under section 7002(e)(4) of the BPCI Act (as amended by section 607 of the FCA Act); we further identified 17 of the 97 applications that incorporated by reference DS/DSI/DP information contained in 10 DMFs. Of these, 8 of the 17 deemed BLAs are discontinued.

B. Need for Federal Regulatory Action

The BPCI Act and the FCA Act amended the statutory definition of "biological product" in the PHS Act. The BPCI Act requires that a marketing application for a biological product (that previously could have been submitted under section 505 of the FD&C Act) must be submitted under section 351 of the PHS Act; this requirement was subject to certain exceptions during a 10-year transition period ending on March 23, 2020. On March 23, 2020, the BPCI Act required that an approved application for a "biological product" 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, but did not specify how this change would be implemented. This lack of specificity introduced uncertainty into the regulatory process. FDA's longstanding practice of not allowing BLAs to incorporate by reference DS/DSI/DP information contained in master files raised questions about whether the former approved applications under the FD&C Act that had referenced DMFs for

such information before March 23, 2020 could continue to do so once those applications were deemed to be BLAs. This rule provides regulatory clarity for deemed BLA holders. Without regulatory action, holders of deemed BLAs face uncertainty regarding potentially significant expenses and might decide to withdraw those 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 Rule

The final rule codifies FDA's existing approach to permit applications for certain biological products originally approved in NDAs under the FD&C Act to continue referencing DMFs for DS/DSI/DP information after the applications were deemed to be BLAs. The final rule also amends the regulations to address the use of master files for the constituent parts of combination products licensed under section 351 of the PHS Act. The final rule also codifies our practice that any IND, including INDs for products that would be subject to licensure under the PHS Act, can rely on any information in a master file, including DS/DSI/DP information.

D. Baseline Conditions

Without regulation, deemed BLA holders face uncertainty as to whether their applications may continue to incorporate by reference DS/DSI/DP information from a DMF. Given this uncertainty, deemed BLA holders may attempt to enter into a contract manufacturing agreement with the holder of the DMF referenced in the former approved NDA or enter into a contract manufacturing agreement with a different contract manufacturer who also has experience with biological products. Alternatively, some deemed BLA holders 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*

If a deemed BLA holder chooses to enter 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 final 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 deemed BLA holders 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 deemed BLA holders would have a contract manufacturing agreement with a DMF holder, and the DMF holder would allow the deemed BLA holder direct access to their DS/DSI/DP information. Because a biological product with a deemed BLA was the subject of a former approved NDA, the deemed BLA holder would only submit a supplement to the deemed BLA to replace the information in the DMF that was incorporated by reference. The deemed BLA holder likely would continue to reference most or all of the clinical information in the underlying deemed BLA and would not be expected 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 $100,725 per application, after converting 2017 costs to 2022 dollars (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 $98.38 (Ref. 2) from the median hourly wage in the BLS May 2022 National Occupational Employment and Wage Estimates for lawyers, Occupation code 23-1011, (NAICS code 325400). To account for benefits and overhead, we double this wage rate to $196.76 (= $98.38 x 2).

We estimate the cost to industry for each contract manufacturing agreement would equal $108,595 per supplemental application, summing $7,870 to prepare and review the agreement (= $196.76 hr. x 40 hrs.) and approximately $100,725 to prepare the supplement. For the 17 biological products with applications that have been deemed to be BLAs and that incorporate by reference DS/DSI/DP information contained in DMFs, the total industry costs under this scenario would total $1,846,122 (= $108,595 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 $1,712,325 (= $100,725 application x 17 supplemental applications).

For this scenario, the one-time costs would equal $3,558,447. We estimate that in the absence of the rule these costs would be incurred in 2025. Thus, the present value equals $3.26 million discounted at 3 percent and $2.90 discounted at 7 percent. The total annualized costs discounted over 10 years equal $0.38 million at 3 percent and $0.41 million at 7 percent. In Table 3, we show a summary of our estimates for the costs.

Table 3. Lower Bound Estimate Summary Table (2022 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3 %
PV of Costs	$3,558,447	$2,904,753	$3,256,483
Annualized Costs[1]		$413,571	$381,759

[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, deemed BLA holders 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 a deemed BLA holder, and we assume the deemed BLA holder 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 might be exhausted, or the product might expire. Once the necessary supplement was filed, but before it was approved, there would be uncertainty as to whether these biological products would be commercially available. If they were not available, the market would be disrupted during that time, 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 deemed BLA holder would approach contract manufacturers (not the DMF holder) and contract out with one of them to manufacture the DS/DSI/DP. We assume

that each of these deemed BLA holders would contract with a separate manufacturer. Using the same fully-loaded wage for a lawyer as in our lower-bound scenario, we estimate the total cost to prepare the contract manufacturing agreements would equal $267,594 (= $196.76 per hour x 80 hours per agreement x 1 contract per deemed BLA holder x 17 deemed BLA holders). This cost does not include search costs of approaching multiple contract manufacturers.

The expenses for each contract manufacturer and deemed BLA holder 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 deemed BLA holder x 17 supplemental applications).

Because the deemed BLAs are approved applications, to the extent product comparability is feasible and sufficient, the deemed BLA holder would only need to submit a supplemental application to establish product comparability. For purposes of establishing an upper bound, we assume that the deemed BLA holder 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 $331,349 per application, after converting 2017 costs to 2022 dollars (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 a supplement would equal $662,698 per application. The total estimate to prepare and review each supplement

equals approximately $994,047. With 17 biological products that are the subject of deemed BLAs, the total cost of submitting and reviewing supplements with clinical data would equal about $16.9 million (= $994,047 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 $270,349 for an average ORA employee in 2022. With an average of 2,080 hours worked per year, the fully loaded hourly wage equals $129.98. We estimate the costs to us to inspect would equal approximately $75,126 (= $129.98 per hour x 34 hours per facility x 1 facility per deemed BLA holder x 17 deemed BLA holders).

The total one-time upper bound cost would equal about $51 million (= $16.9 million to review and submit supplements + $267,594 to prepare contract manufacturing agreements + $34 million to transfer the production processes to different manufacturing facility + $75,126 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 deemed BLA holders' 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 $51.24 million would be incurred in year 2027. We estimate the present value of the total costs is $44.20 million discounted at 3 percent; and $36.53 million discounted at 7 percent. The total annualized cost discounted over 10 years would equal $5.18 million at a 3 percent discount rate and $5.20 million at a 7 percent discount rate. In Table 4, we show a summary of our upper bound estimate.

Table 4. Upper Bound Estimate Summary Table (2022 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3 %
PV of Costs	$51,241,518	$36,534,494	$44,201,384
Annualized Costs [1]		$5,201,690	$5,181,751

[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 deemed BLA holders. In our lower-bound estimate, we assumed all DMF holders would contract with the deemed BLA holders. In our upper-bound estimates, we assumed that no DMF holder would contract with the deemed BLA holders, and that deemed BLA holders 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 $27.40 million (= ($3,558,447 + $51,241,518) ÷ 2). We estimate the present value of the total cost is $23.73 million at 3 percent discount rate and $19.72 million at 7 percent discount rate. The total annualized cost discounted over 10 years equals $2.78 million at 3 percent discount rate and $2.81 million at 7 percent discount rate. In Table 5, we show a summary of our primary cost estimate.

Table 5. Primary Estimate Summary Table (2022 dollars)

	Undiscounted	Discounted at 7 %	Discounted at 3 %
PV of Costs	$27,399,983	$19,719,624	$23,728,933
Annualized Costs [1]		$2,807,631	$2,781,755

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

E. Benefits of the Rule

The primary effect of the final rule would be to allow deemed BLA holders to be certain that their applications could continue referencing DMFs. 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 final rule are cost savings accrued from avoiding any costs and disruptions to manufacturing for the deemed BLA products.

Table 6 summarizes our estimate of the total cost-saving benefits. The present value of our primary estimate is $23.73 million using a 3% discount rate or $19.72 using a 7% discount rate.

Table 6. Cost-Savings Benefits of the Final Rule (2022 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	$2,904,753	$3,256,483	$19,719,624	$23,728,933	$36,534,494	$44,201,384
Annualized over 10 years	$413,571	$381,759	$2,807,631	$2,781,755	$5,201,690	$5,181,751

We anticipate that the final rule could generate additional benefits. However, we lack sufficient data to quantify or monetize these benefits. For example, future BLA applicants would have regulatory certainty regarding their BLAs' ability to reference certain information in master files. Although we cannot estimate the value of this regulatory certainty, we believe this certainty has value to industry.

F. Costs of the Rule

We anticipate that current and potential future BLA holders 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 preamble and codified of final rule are approximately 13,600 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 0.91 hours to 1.13 hours (= 13,600 words / (200 to 250 words) / minute). The US Census Bureau reports that in 2020 there were 373 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 Manager (North American Industry Classification, NAICS, code 325400) from the Bureau of Labor Statistics (BLS) May 2022 National Occupational Employment and Wage Estimates for Occupation code 11-1021, which is approximately $80.60 (Ref. 6). To account for benefits and overhead, we double this value to roughly $161.20 (= $80.60 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 $54,516 (= 373 establishments x 0.91 hour x $161.20 per hour) to $68,145 (= 373 establishments x 1.13 hour per establishment x $161.20 / 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.

G. Distributional Effects

The rule codifies FDA's existing approach in order to provide certainty about the continued marketing of certain deemed BLA products. Without the rule, the distributional effects might include transfers from deemed BLA holders to DMF holders. For example, before March 23, 2020, the holders of these former approved NDAs may have paid low or fixed fees to reference the DMFs, but, without the rule, DMF holders could now extract higher rents from these application holders 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.

H. Uncertainty and Sensitivity Analysis

The biggest uncertainty in this analysis is how deemed BLA holders would acquire and incorporate DS/DSI/DP information into their applications if they can no longer reference DMFs. If deemed BLA holders believe they must find alternatives to the use of DMFs, and if no DMF holders 1) contract out, 2) share their information with deemed BLA holders, or 3) 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. If a deemed BLA product disappeared from the market, the social cost would include 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 deemed BLA holders during the period that the biological products

are not commercially marketed. Without the rule, the social costs could be in the hundreds of millions of dollars, although we lack sufficient information to quantify this cost; with the rule, there may be equally large cost savings.

We also lack information about how much time it would take to construct new manufacturing facilities, if deemed BLA holders think this is necessary. 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 supplement 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.

One last consideration is the deemed BLAs themselves. Of the 17 deemed BLAs that rely on a DMF for DS/DSI/DP information, we identified 8 products that are currently discontinued. In the main analysis, we treat active deemed BLAs and those for which the products are discontinued the same because BLAs for discontinued products can become active. Table 7 reports the benefits of the final rule in the form of cost savings under the alternative assumption that the applicants of these deemed BLAs for discontinued products will request voluntary revocation of the license to manufacture the product rather than incur any costs associated with acquiring and incorporating the information in their respective applications.

Table 7. Cost-Savings Benefits of the Final Rule Excluding Discontinued Deemed BLAs (2022 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	$1,537,810	$1,724,020	$10,439,801	$12,562,377	$19,341,791	$23,400,733
Annualized over 10 years [1]	$218,950	$202,108	$1,486,393	$1,472,694	$2,753,836	$2,743,280

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

I. Analysis of Regulatory Alternatives to the Rule

In addition to the rule, we also analyze an alternative policy that would have extended the compliance period by two years. Under this approach, deemed BLAs could continue to reference DMFs for DS/DSI/DP information until 2025.

Relative to the scenarios described in the baseline, in which we assume that the costs of compliance occur at least two years following the final rule's effective date, this alternative policy would shift the costs by two additional years into the future. This difference in timing reduces cost savings through the discount rate. Table 8 summarizes the present value of the cost savings under the final rule and under the regulatory alternative.

Table 8. Summary of the present value of the cost-savings under the final rule and with a two-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	$2,537,123	$3,069,547	$17,223,883	$22,366,796	$31,910,642	$41,664,044
PV of Cost Savings with a 5-year compliance period [1]	$361,229	$359,845	$2,452,293	$2,622,071	$4,543,358	$4,884,297

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

III. Final Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We have analyzed this rule under the Regulatory Flexibility Act and 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 $159 for a typical firm, this rule will not have a significant economic impact on a substantial number of small entities.

We use the biological product (except diagnostic) manufacturing industry[1] to identify entities that would be impacted by the rule. For this industry, the U.S. Small Business Administration (SBA) defines small businesses as those with fewer than 1,250 employees.[2] From the U.S. Census Bureau's 2020 Statistics of U.S. Businesses (Ref. 5), approximately 82 percent of all biological product (except diagnostic) manufacturing firms employ fewer than 1,000 employees.[3] In 2017, the most recent year for which annual receipts data are available, small firms represented approximately 14 percent of total revenue in the biological product (except diagnostic) manufacturing industry (Ref. 7).

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 described in the

[1] North American Industry Classification System (NAICS) code 325414

[2] The most recent size standards for "Biological Product (except Diagnostic) Manufacturing" are available in SBA's 2022 Table of Small Business Size Standards (page 11): https://www.sba.gov/sites/default/files/2022-05/Table%20of%20Size%20Standards_Effective%20May%202%202022_Final.pdf

[3] The SUSB data define employment size cut-offs at 500-749 and 1,000-1,499 employees. The threshold for small businesses in this industry (fewer than 1,250 employees) falls within the 1,000-1,499 cut-off. We therefore use the under 1,000 cut-off as an approximation. Though this understates the number of small firms, only 6 firms were in the 1,000-1,499 group.

Baseline section, one scenario includes the possibility that, without the rule, DMF holders could extract additional rents from deemed BLA holders. 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 likely these payments could be without the rule. The final rule will otherwise generate net cost savings for holders of deemed BLAs that reference DMFs by avoiding the costs of transferring to contract manufacturing or disrupting supply which could result in shortages and price increases.

Since we cannot identify any potential costs of the final rule on these firms other than the time burden of reading the rule, we certify that the final rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Final Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

IV. References

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