DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

List of Bulk Drug Substances that can be used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act

Docket No. FDA-2016-N-3464

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

Economics Staff
Office of Planning
Office of Policy, Planning, and Legislation
Office of the Commissioner

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I. Introduction and Summary

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations." We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that this final 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 we do not have enough information about the effect of the final rule on small entities, we find that the final rule will have a significant economic impact on a substantial number of small entities.

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

B. Summary of Costs and Benefits

We evaluated ten bulk drug substances for this final rule. We will place six bulk drug substances on the 503A Bulks List and we will not place four substances on the 503A Bulks List. We expect that the rule will affect compounding pharmacies and other producers that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected substances, and payers that cover these drug products or alternative treatments. Because we lack sufficient information to quantify most of the costs and benefits of this final rule, we also include a qualitative description of potential benefits and potential costs.

In Table 1, we summarize the impacts of the final rule. The present value of the costs of the final rule equals $3.33 million at a 7 percent discount rate and $3.00 million at a 3 percent discount rate. The final rule will result in annualized costs of $0.42 million at a 7 percent discount rate, or $0.31 million at a 3 percent discount rate.

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

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized ($m/year)							
	Annualized Quantified							
	Qualitative	Potential gains or losses in consumer surplus, depending on consumer preferences for compounded drugs. Potential public health benefits from increased use of other drug products that may be more effective.						
Costs	Annualized Monetized ($m/year)	$0.42	$0.27	$0.56	2016	7%	10 years	
		$0.31	$0.21	$0.42	2016	3%	10 years	
	Annualized Quantified							
	Qualitative	Costs to submit investigational new drug applications (INDs) for some compounded drug products.						
Transfers	Federal Annualized Monetized ($m/year)							
		From:			To:			
	Other Annualized Monetized ($m/year)							
		From:			To:			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

C. Comments on the Preliminary RIA and Our Responses

We received 4 comments on our preliminary regulatory impact analysis of the proposed rule. We group comments with similar themes together. 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 discussed by the commenter(s).

(Comment 1) Multiple commenters expressed concerns that we did not address the costs of applying the criteria for evaluating substances for inclusion in the 503A Bulks List.

(Response 1) We disagree with comments suggesting we include the full costs of the criteria for all nominated bulk drug substances in the economic analysis for this rule. We recognize that the criteria we use to evaluate bulk drug substances for the 503A Bulks List will affect the markets for bulk drug substances considered in future rulemakings. However, we cannot predict how the criteria will affect which bulk drug substances will be on the 503A Bulks List in the future.

Therefore, we will address the benefits and costs of applying the criteria to bulk drug substances not considered in this rulemaking as they arise in future rulemakings.

(Comment 2) A commenter suggested that we underestimated the cost of the proposed rule by excluding the costs to submit nominations for the 503A Bulks List in 2014. The commenter suggested that it took, on average, 6 hours to submit each nomination.

(Response 2) We agree with this commenter. Because we use the pre-statutory baseline for our analysis, the costs of the rule should include the costs to submit nominations. In our final regulatory impact analysis, we clarify our baseline in this analysis. Also, we have included the costs to nominate bulk drug substances for inclusion on the 503A Bulks List.

(Comment 3) A commenter suggested that by considering only the cost of completing the expanded access IND form, Form FDA 3926, we underestimated the cost of applying for an expanded access IND.

(Response 3) We agree that applying for an expanded access IND involves costs beyond the cost of completing Form FDA 3926. We lack data on the other costs of submitting an expanded access IND, and the commenter did not provide data for us to estimate these costs. Therefore, we qualitatively discuss the costs of submitting an expanded access IND, and quantify only the cost of completing Form FDA 3926.

D. Summary of Changes

In response to comments and newly available information, we made the following changes to the analysis. Using information provided by commenters, we added the costs to submit nominations for the 503A Bulks List. We also estimate the administrative costs of the final rule to compounding pharmacies. Because we lack information about the effect of the final rule on small entities, we find that the final rule will have a significant effect on small entities.

II. Final Regulatory Impact Analysis

A. Background

Compounding pharmacies[1] combine, mix, or alter a drug or components of a drug to create a medication tailored to the needs of an individual consumer. We call these medications "compounded drug products."

The Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes requirements for the marketing of drug products in the United States, including requirements for premarket approval of new drug products, labeling and current good manufacturing practices. Under section 503A of the FD&C Act, compounded drug products may be exempt from some of these requirements ("503A exemptions"), if they meet certain conditions. In November 2013, the Drug Quality and Security Act (DQSA) clarified that section 503A of the FD&C Act applies nationwide in the United States.

[1] "Pharmacy" or "pharmacies" refers to pharmacies compounding under section 503A of the FD&C Act.

A bulk drug substance[2] is an active pharmaceutical ingredient. Section 503A specifies the conditions for using bulk drug substances to compound drug products that qualify for the 503A exemptions. Compounders using a bulk drug substance to compound a drug product under section 503A can qualify for the 503A exemptions if the bulk drug substance is the subject of an applicable U.S. Pharmacopeia (USP) or National Formulary (NF) monograph. Official USP and NF drug substance monographs set standards for active pharmaceutical ingredients. If an applicable USP or NF monograph does not exist, compounders using a bulk drug substance to compound a drug product under section 503A can qualify for the 503A exemptions if the bulk drug substance is a component of a Food and Drug Administration (FDA or Agency)-approved drug product. Finally, if an applicable USP or NF monograph does not exist and the bulk drug substance is not a component of an FDA-approved drug product, compounders using a bulk drug substance to compound a drug product under section 503A can qualify for the 503A exemptions if the bulk drug substance appears on the 503A Bulks List, a list of bulk drug substances established by regulation.[3]

Compounders using a bulk drug substance that is not the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug product, cannot qualify for the 503A exemptions unless the bulk drug substance is on the 503A Bulks List. However, in June 2016, FDA published a guidance for industry that describes our interim policy for 503A compounders using bulk drug substances while we consider substances for the 503A Bulks List (Ref. 1). In this guidance, we stated our intent not to take regulatory action while we review bulk drug substances for the 503A Bulks List, unless we identify significant safety issues with drugs compounded using the bulk drug substances, provided the other conditions of section 503A are met. This interim policy applies only to bulk drug substances nominated with sufficient information for evaluation. Under this interim policy, compounders currently market drug products compounded with certain bulk drug substances nominated for the 503A Bulks List.

B. Market Failure Requiring Federal Regulatory Action

Although we subject new drug products to a rigorous approval process to determine whether a new drug product is safe and effective, drug products compounded with the bulk drug substances discussed in this final rule have not gone through this drug approval process. The availability of drug products compounded using these bulk drug substances may lead consumers to believe that we have approved these compounded drugs. Because we have more information about the bulk drug substances used to compound drug products than the average consumer of the compounded drugs, an information asymmetry may exist between us and the average consumer. With an information asymmetry, consumers may make choices they would not have made if they were better informed. Without this final rule, consumers may not have access to information about bulk drug substances that might influence their choice to use compounded drug products. Moreover, section 503A, which the DQSA clarified is applicable nationwide, directs us to create the 503A Bulks List by rulemaking. This final rule will fulfill this statutory requirement.

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[2] "Bulk drug substance" means active pharmaceutical ingredient as defined in 21 CFR 207.1.

[3] Section 503A(c) of the FD&C Act requires the Secretary of Health and Human Services to establish the 503A Bulks List by regulation.

C. Purpose of the Rule

In 2013 and 2014, following the signing of the DQSA, we solicited nominations of bulk drug substances for the 503A Bulks List (Ref. 2 and Ref. 3). We received nominations for over 2,000 substances in response to the first solicitation. After clarifying the information we needed to evaluate a bulk drug substance, we reopened nominations and received approximately 1,500 nominations for 740 unique substances. This final rule establishes the criteria that we use to evaluate bulk drug substances for inclusion on the 503A Bulks List. These criteria include:

1. The physical and chemical characterization of the bulk drug substance;
2. Any safety issues raised by the use of the bulk drug substance in compounded drug products;
3. The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the bulk drug substance; and
4. Historical use of the bulk drug substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

We used these criteria to review 10 of the nominated bulk drug substances (Table 3) for this final rule. Based on our review and our consultation with the Pharmacy Compounding Advisory Committee (PCAC) and the USP, we will place six of the reviewed substances on the 503A Bulks List. Under the final rule, provided they meet the other conditions of section 503A, compounding pharmacies may legally market drug products they compound with these 6 bulk drug substances.

Table 2. Bulk Drug Substances Reviewed for this Final Rule

Bulk Drug Substance	Included on the 503A Bulks List [1]
Brilliant Blue G	X
Cantharidin	X
Diphenylcyclopropenone (DPCP)	X
N-acetyl-D-glucosamine (NAG)	X
Oxitriptan	
Piracetam	
Silver Protein Mild	
Squaric Acid Dibutyl Ester (SADBE)	X
Thymol Iodide	X
Tranilast	

[1] An "X" indicates that we will include the substance on the 503A Bulks List. A blank entry indicates that we will not include the substance on the 503A Bulks List.

With this final rule, we will not place 4 substances on the 503A Bulks List. In general, under the final rule, compounding pharmacies may not compound drug products with these 4 substances without an IND.[4]

[4] "Expanded access IND application" refers to an application for expanded access to investigational drugs for treatment use covered in 21 CFR 312.300 – 312.320.

Placing or not placing a bulk drug substance on the 503A Bulks List serves as a signal to the consumer. This signal may help correct false impressions consumers may have had about drug products compounded from the bulk drug substances. Thus, the final rule may address market failures arising from information asymmetry in two ways. First, by taking regulatory action, we can prevent consumers from taking certain drugs compounded with bulk drug substances that we determine should not be used in compounded drugs. Second, this final rule will provide more information to consumers, reducing information asymmetry.

D. Baseline Conditions

In our analysis, we use a pre-statutory baseline. In the pre-statutory baseline, it was unlawful for compounders to market drug products compounded using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product. However, in practice, compounders compounded drug products using bulk drug substances that are not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product before the statute. Therefore, the baseline of this analysis is the world where compounders compounded drug products using the 10 bulk drug substances in this final rule. The final rule will place 6 of these substances on the 503A Bulks List.

1. Affected Firms and Substances

We have limited information about the market for drugs compounded using bulk drug substances in the United States. We do not have data on the number of firms that the final rule will affect, though we expect that the final rule could affect compounding pharmacies, manufacturers of bulk drug substances, wholesalers who distribute bulk drug substances, and repackagers of bulk drug substances who supply bulk drug substances to compounding pharmacies. In the absence of data about the number of affected entities, we use the limited available information to characterize the size of the market for each bulk drug substance.

First, we looked at the reported value of bulk drug substance imports for human use from 2011 to 2015. However, importers self-report the value of imported drug products and the reported import value may be subject to reporting errors. If there is no domestic production of a bulk drug substance, then the import value represents the total value of the bulk drug substance prior to distribution and compounding. If there is domestic production of a bulk drug substance, then the import value represents the lower bound on the total value of the bulk drug substance prior to distribution and compounding. In Table 4, we estimate the real value of imports of bulk drug substances from 2011 to 2015.

Table 3. Reported Value of Bulk Drug Substance Imports from 2011 to 2015

Bulk Drug Substance	2011	2012	2013	2014	2015	Total
Brilliant Blue G	$0	$9,890	$0	$0	$0	$9,890
Cantharidin	$0	$0	$0	$1,177	$795	$1,972
DPCP	$0	$0	$0	$0	$0	$0
NAG	$421,342	$253,261	$160,808	$119,092	$116,152	$1,070,656
Oxitriptan	$0	$0	$52	$0	$0	$52
Piracetam	$73,868	$48,160	$4,573	$3,515	$0	$130,116
Silver Protein Mild	$0	$0	$0	$0	$0	$0
SADBE	$0	$0	$0	$0	$0	$0
Thymol Iodide	$0	$0	$1,447	$0	$0	$1,447
Tranilast	$88,559	$124,005	$0	$23,511	$0	$236,075

All reported values expressed in 2016 dollars.

Second, we reviewed the nominator presentations and public comments on bulk drug substances at public meetings of the PCAC. In Table 5, we summarize any information about marketing discussed during these public meetings. Though only one nominator provided sales information for a bulk drug substance, the nominator presentations and public comments indicate that all 10 substances were marketed in 2015.

Table 4. Marketing Information from PCAC Public Meetings

Bulk Drug Substance	Marketing Information from PCAC Meeting
Brilliant Blue G[c]	Sold by members of Professional Compounding Centers of America and National Community Pharmacists Association. National Community Pharmacists Association reported that demand is limited.
Cantharidin[b]	Sold by members of Professional Compounding Centers of America.
DPCP[b]	Sold by members of Professional Compounding Centers of America.
NAG[c]	Sold by Fagron.
Oxitriptan[c]	Sold by representative of National Community Pharmacists Association.
Piracetam[b]	Professional Compounding Centers of America reported gross sales less than $13,000 in 2014.
Silver Protein Mild[a]	Sold by members of Professional Compounding Centers of America.
SADBE[b]	Sold by members of Professional Compounding Centers of America.
Thymol Iodide[b]	Sold by Fagron and members of Professional Compounding Centers of America.
Tranilast[c]	Sold by members of Professional Compounding Centers of America.

[a]Ref. 4 , [b]Ref. 5, [c]Ref. 6

By combining the information in Table 4, Table 5, and internet searches, we can draw limited conclusions about the size of the markets for the 10 bulk drug substances considered in this final rule. Of the 10 bulk drug substances evaluated, NAG and tranilast appear to be the most widely compounded. The reported value of NAG imports was above $100,000 annually

from 2011 to 2015. The reported value of tranilast imports was relatively large in 2011 and 2012, but fell in the following years, with no reported imports in 2013 or 2015. However, through internet searches, we found many pharmacies offering compounded tranilast products. The market for drug products compounded from piracetam appears to be small. The reported value of piracetam imports fell substantially from 2011 to 2015. Furthermore, at the February 2015 PCAC meeting, a firm that nominated piracetam for the 503A Bulks list reported that it sold $13,000 worth of bulk piracetam in 2014. Finally, we find some evidence that pharmacies compound drug products using the remaining 7 bulk drug substances, but we have limited information about the size of these markets.

2. Historical Uses and Alternative Treatments to Bulk Drug Substances Not Included on the 503A Bulks List

In Table 6, we describe the historical uses of the four substances not included on the 503A Bulks List. Alternative treatments exist for the conditions that were proposed to be treated by oxitriptan, piracetam, and silver protein mild. These alternative treatments are FDA-approved, and safe and effective under their approved conditions of use. FDA-approved alternatives to tranilast exist for the treatment of eczema, psoriasis, and scars. However, there are no FDA-approved drugs or biologics for the treatment of keloids and hypertrophic scars. While other treatments for keloids and hypertrophic scars exist, one tranilast nominator claimed that these treatments are "caustic, invasive, and expensive" (Ref. 6).

Table 5. Historical Uses of Substances Not Included on the 503A Bulks List

Bulk drug substance	Historical Uses
Oxitriptan	Insomnia; depression
Piracetam	Mild cognitive impairment
Silver Protein Mild	Conjunctivitis; preoperative chemical preparation of the eye
Tranilast	Eczema; psoriasis; scar treatment; keloids; hypertrophic scars

E. Benefits of the Rule

We lack sufficient data to quantify many of the potential benefits of the final rule. For those benefits that we cannot quantify, we qualitatively describe the benefits of including an ingredient on the 503A Bulks List and the benefits of not including an ingredient on the 503A Bulks List.

We expect that the final rule could have some effect on consumers of drug products compounded using bulk drug substances that we will include on the 503A Bulks List. For example, the final rule could give prescribers more confidence prescribing a drug product compounded using such bulk drug substances. Thus, some consumers, on the advice of their prescriber, may switch from alternative treatments to drug products compounded using bulk substances on the 503A Bulks List.

We consider the effect of the final rule on consumers of bulk drug substances that we will not include on the 503A Bulks List. The effect of the final rule on these consumers depends on the availability of alternative treatments and consumer preferences.

Consumers choose compounded drug products based on the advice of their prescriber because the consumer may prefer these drugs to alternative treatments. However, consumers may have incomplete information about the risks and benefits of the compounded drug product. We expect that the final rule will indirectly provide consumers with additional information[5] about the risks and benefits of the compounded drug product. Once consumers and their prescribers become aware of this additional information, consumers may prefer alternative treatments to the compounded drug product. If consumers and their prescribers opt for alternative treatments, these alternative treatments may be safer or more effective than drug products compounded using the bulk drug substances. These consumers may experience better health outcomes than they currently experience with the compounded drug product. Such consumers will benefit from the final rule.

For consumers who prefer the compounded drug product to alternative treatments, we expect that they, in consultation with their prescribers, will choose between alternative treatments or foregoing treatment. These consumers perceive their options under the final rule as "second-best" to the compounded drug product. Therefore, they will experience some loss in utility from the final rule. However, we expect that consumers who choose an alternative treatment will benefit from using treatments that may be safer or more effective. These consumers will also benefit by not using a treatment that, based on the evidence considered, is not safe or effective. If the health benefits are larger than the loss in utility, then these consumers will benefit from the final rule. If the loss in utility is greater than the health benefits, then these consumers will incur negative benefits from the final rule.

F. Costs of the Rule

We lack sufficient data to quantify many of the potential costs of the final rule. For those costs that we can't quantify, we qualitatively describe the costs of including a bulk drug substance on the 503A Bulks List and the costs of not including a bulk drug substance on the 503A Bulks List.

1. Costs to Submit Nominations

In 2014, we received nominations for over 2,000 substances in response to our initial request for nominations. We found that many of the substances that were the subject of those nominations were not eligible for the 503A Bulks List or were not an active pharmaceutical ingredient, or that the nominations did not include sufficient information for evaluation. We therefore requested new nominations and included a detailed description of the information we need to evaluate bulk drug substances. In response to this second solicitation, we received approximately 1,500 nominations for 740 unique substances.

We received comments in response to the proposed rule suggesting that, in response to the second solicitation for nominations, nominators spent 6 hours preparing and submitting each nomination for the 503A Bulks List; we did not receive data about the costs of the first round of nominations. The mean hourly wage for pharmacists is $56.16 (Ref. 7). The fully loaded mean hourly wage for pharmacists, including 100% overhead, is $116.32. Therefore, the cost of

[5] The final rule indirectly provides consumers with additional information by placing bulk substances on the 503A Bulks List. It does not directly provide information to consumers.

submitting nominations for the 503A Bulks List in response to the second solicitation for nominations is $697.92 per nomination (6 hours per nomination × $116.32 per hour). The total cost of nominations in response to the second solicitation for nominations is $1.05 million (1,500 nominations × $697.92 per nomination).

The nominations we received in response to the first solicitation for nominations varied significantly in size and substance. Therefore, we expect that firms spent less time preparing and submitting nominations in response to the first solicitation for nominations. We assume that, in response to the first solicitation for nominations, nominators spent between 0.5 and 6 hours on each nomination for the 503A Bulks List. Therefore, the cost of submitting nominations for the 503A Bulks List in response to the first solicitation for nominations ranges from $58.16 per nomination (0.5 hours per nomination × $116.32 per hour) to $697.92 per nomination (6 hours per nomination × $116.32 per hour). The total cost of nominations in response to the first solicitation for nominations ranges from $0.12 million (2,000 nominations × $58.16 per nomination) to $1.40 million (2,000 nominations × $697.92 per nomination).

Because the nominators incurred these costs in 2014, we calculate the present value of these costs in year 0. In Table 7, we show the one-time nomination costs. Combining the costs to submit nominations in response to the first and second solicitations for nominations, we estimate that nominators incurred nominal costs that ranged from $1.16 million to $2.44 million. The present value of these costs in year 0 ranges from $1.31 million to $2.75 million at a 3 percent discount rate and from $1.52 million to $3.20 million at a 7 percent discount rate. Over 10 years, the annualized value of the nomination costs of the final rule will range from $0.14 million to $0.29 million at a 3 percent discount rate and from $0.19 million to $0.40 million at a 7 percent discount rate.

Table 6. Nomination Costs of the Final Rule ($ millions)

Cost	Low Estimate	Primary Estimate	High Estimate
One-Time Nomination Costs in 2014	$1.16	$1.80	$2.44
Present Value of the One-Time Costs in Year 1 (3%)[1]	$1.31	$2.03	$2.75
Present Value of the One-Time Costs in Year 1 (7%)[1]	$1.52	$2.36	$3.20
Annualized Value Over 10 Years (3%)	$0.14	$0.21	$0.29
Annualized Value Over 10 Years (7%)	$0.19	$0.29	$0.40

[1] To calculate the present value, we assume the costs occur in year -4.

2. Administrative Costs

We estimate that each firm affected by the final rule would spend between 1 and 2 hours on administrative costs related to reading and understanding the final rule. Using a fully loaded mean hourly wage for pharmacists of $116.32, each affected firm will incur administrative costs that range from $116.32 (1 hour × $116.32 per hour) to $232.64 (2 hours × $116.32 per hour).

The final rule includes the criteria we will use to review bulk drug substances for inclusion on the 503A Bulks List. We expect that the criteria are of interest to all compounding pharmacies. Therefore, we assume that all compounding pharmacies will incur administrative costs to read and understand the final rule. We estimate that there are 5,563 compounding

pharmacies in the United States (Ref. 8). The total administrative cost to compounding pharmacies will range from $647,088.16 ($116.32 per firm × 5,563 compounding pharmacies) to $1,294,176.32 ($232.63 per firm × 5,563 compounding pharmacies). We assume that firms will incur administrative costs in year 0.

We expect that manufacturers of bulk drug substances, wholesalers who distribute bulk drug substances, and repackagers of bulk drug substances who supply compounding pharmacies will also incur administrative costs from the final rule. However, we do not have enough data about the size of these markets to estimate the administrative costs to these types of firms.

3. Cost of an IND

Under the final rule, it may be possible for consumers to access drug products compounded with a bulk drug substance that we do not put on the 503A Bulks List. For example, sponsor-investigators may submit an expanded access IND for a compounded drug product that uses the bulk drug substance not on the 503A Bulks List. For expanded access INDs, sponsor-investigators must show that the drug product will treat a serious or immediately life-threatening disease or condition when no satisfactory alternative therapy exists. A sponsor-investigator must identify a facility willing to supply the bulk drug substance or compound drug product. The sponsor-investigator then submits an IND application to us, and we determine whether the study (or studies) under the IND is safe to proceed. If we determine the IND is safe to proceed, the sponsor-investigator is responsible for monitoring the consumer for adverse events and submitting reports to the FDA.

In the preliminary regulatory impact analysis, we requested data about the costs of submitting an expanded access IND. While we received some qualitative comments in response to the proposed rule suggesting that submitting an expanded access IND may be burdensome in the context of drug products compounded using bulk drug substances, we did not receive specific data about the cost of submitting an expanded access IND. By contrast, based on their experience, our Center for Drug Evaluation and Research expects that the expanded access IND process would not typically be burdensome or time-consuming (Ref. 9). Therefore, we are uncertain of the burden related to expanded access INDs in the context of compounded drug products.

The cost of preparing an expanded access IND includes the costs for the sponsor-investigator to obtain informed consent, develop a written protocol, obtain approval from an Institutional Review Board, and submit the expanded access IND to us. If a sponsor-investigator uses Form FDA 3926, we estimate that completing the Form FDA 3926 would take a physician 45 minutes, provided the physician can reference chemical, manufacturing, and control (CMC) information in an existing IND. Based on Bureau of Labor Statistics (BLS) wage data, the mean hourly wage for physicians and surgeons is $110.76 (Ref. 7). The fully loaded mean hourly wage for physicians and surgeons, including 100% overhead, is $221.52. Therefore, we estimate that the cost to submit Form FDA 3926 is $166.14 (0.75 hours × $221.52 per hour). We do not have enough data to estimate the other costs of submitting an expanded access IND.

The cost of an expanded access IND also includes the costs of identifying a facility willing to supply the compounded drug product. Obtaining a compounded drug product may have upfront and ongoing costs, and these costs may affect the prices that patients pay for

compounded drug products. Finally, the cost of an expanded access IND includes the costs of monitoring the consumer for adverse events and submitting reports to the FDA. We do not have enough data to estimate the total cost of an expanded access IND.

4. Summary of Costs of the Final Rule

In Table 8, we summarize the total quantified costs of the final rule over 10 years. The annualized cost of the final rule will range from $0.21 million to $0.42 million at a 3 percent discount rate and from $0.27 million to $0.56 million at a 7 percent discount rate.

Table 7. Total Quantified Costs of the Final Rule ($ millions)[1]

Year	Low Estimate	Primary Estimate	High Estimate
Year -4 (Nominations)	$1.16	$1.80	$2.44
Year 0 (Administrative Costs)	$0.65	$0.97	$1.29
Present Value of Cost (3%)	$1.96	$3.00	$4.04
Present Value of Cost (7%)	$2.17	$3.33	$4.50
Annualized Value of Cost (3%)	$0.21	$0.31	$0.42
Annualized Value of Cost (7%)	$0.27	$0.42	$0.56

[1] All costs are one-time costs occurring in year -4 or year 0.

G. Distributional Effects

1. Loss or Transferred Profits

For each of the four substances we will not include on the 503A Bulks List, there may be a private cost to some producers. Manufacturers, wholesalers, repackagers, and compounding pharmacies will lose profits they earn from selling these bulk drug substances or drug products compounded from these bulk drug substances. The total private cost to these producers will depend on the profits these producers can earn by selling other bulk drug substances or other compounded drug products.

If consumers switch from the compounded drug product to an alternative treatment, the profits of producers of alternative treatments will increase. Therefore, some of the lost profits from the market for bulk drug substances will transfer to the producers of alternative treatments.

2. Payers

Some private and public payers may currently reimburse consumers for the cost of drug products compounded using bulk drug substances we will not include on the 503A Bulks List. For example, if consumers switch from the compounded drug to a costlier alternative treatment, then the final rule will create transfers from payers to pharmacies or consumers. If consumers choose to forego treatment and suffer no ill effects, then the final rule will create transfers from pharmacies to consumers and payers.

H. International Effects

We lack data on the number and size of foreign manufacturers and wholesalers affected by the final rule. We also find little evidence of widespread use of the four bulk drug substances

that we will not include on the 503A Bulks List. Therefore, we expect that the final rule will have no significant international effects.

I. Uncertainty and Sensitivity Analysis

The market for compounded drug products is dynamic. Market forces may change the amount of these substances used in compounding and their profitability. For example, in 2014, Express Scripts announced that it would stop coverage of drug products compounded from about 1,000 bulk drug substances (Ref. 10). We lack information about how such an action by a major payer might impact the market for compounded drugs in the future.

In the absence of specific data, we are uncertain about the current level of use of these bulk drug substances in compounded drug products, the wholesale market for the bulk drug substances, and the size of the markets for drug products compounded from these bulk drug substances. We lack information that would allow us to predict whether pharmacies and wholesalers will transition to producing alternative products, and information about the costs associated with such a transition. We do not know how many consumers take drug products compounded using these bulk drug substances, which alternative therapies they will choose in the absence of products compounded using those bulk drug substances, or how using alternative therapies will affect their well-being.

J. Analysis of Regulatory Alternatives to the Rule

One alternative we considered for the final rule was to include tranilast on the 503A Bulks List for use only in topical, and not oral, compounded drugs. With no FDA-approved drug products indicated for the treatment of keloids and hypertrophic scars, a topical dosage form of compounded tranilast could provide a treatment option for consumers with these conditions.[6] Under this alternative, compounding pharmacies could continue marketing drug products compounded using tranilast. Providers would not need to seek market approval to provide drug products compounded using tranilast to their patients.

However, we lack information available about the safety and effectiveness of a topical form of tranilast, and it is possible that absorption of topical tranilast could cause liver damage. Therefore, we do not know if this alternative would have higher net positive benefits than the final rule.

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. Because we lack data on the impact of the final rule on small manufacturers, wholesalers, and compounding pharmacies, we find that the final rule will 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.

[6] There are, however, other alternative therapies, including silicone gel sheeting, silicone gel, pressure garments, intralesional corticosteroid injections, bleomycin injections, surgery, 5-fluoruracil intralesional injections, and radiotherapy.

A. Description and Number of Affected Small Entities

In Table 9, we describe the Small Business Administration's size standards for the industries affected by the final rule. We lack data on the size of the affected firms. However, based on US Census data, we find that the Small Business Administration considers 97.5% of the firms in these industries as small.

Table 8. Small Business Administration Size Standards for Industries Affected by the Final Rule

NAICS[7] Code	Industry Description	Small Business Threshold
325412	Pharmaceutical Preparations Manufacturing	Fewer than 1,250 employees
424210	Drug and Druggists' Sundries Merchant Wholesalers	Fewer than 250 employees
446110	Pharmacies and Drug Stores	Less than $27.5m in revenue

We do not know the impact of the final rule on small entities in these industries. Therefore, we cannot certify that the final rule will not have a significant impact on a significant number of small entities.

IV. References

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[7] NAICS refers to the "North American Industry Classification System".

6. **U.S. Food and Drug Administration.** Transcript for the June 17, 2015 (PM Session) Meeting of the Pharmacy Compounding Advisory Committee. [Online] 2015. https://wayback.archive-it.org/7993/20170403224128/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM458513.pdf
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