DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Amendments to the 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-2018-N-4845

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 have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. 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 we do not have enough information about the effect of the proposed rule on small entities, we find that the proposed 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 $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.

B. Summary of Costs and Benefits

We evaluated 31 bulk drug substances for this proposed rule. We propose to place five bulk drug substances on the 503A Bulks List and propose not to place 26 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 proposed rule, we also include a qualitative description of potential benefits and potential costs.

In Table 1, we summarize the impacts of the proposed rule. The estimated costs are derived from administrative costs related to reading the rule. The primary estimate of the present

value of the costs over 10 years is $1.03 million. The primary estimate of the annualized costs is $0.15 million at a 7 percent discount rate and $0.12 million at a 3 percent discount rate.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed 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)	$0.15	$0.10	$0.20	2017	7%	10 years	
		$0.12	$0.08	$0.16	2017	3%	10 years	
	Annualized Quantified							
	Qualitative	Costs to submit investigational new drug applications (INDs) for some compounded drug products.						
Transfers	Federal Annualized Monetized ($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							

In line with Executive Order 13771, in Table 2, we summarize the present and annualized values of costs and cost savings over an infinite time horizon. The present value of net costs equals $0.97 million. The annualized value of net costs equals $0.07 million at a 7 percent discount rate and $0.03 million at a 3 percent discount rate.

Table 2. EO 13771 Summary Table (in $ Millions 2016 Dollars, Over an Infinite Time Horizon)

	Primary Estimate (7%)	Lower Bound (7%)	Upper Bound (7%)	Primary Estimate (3%)	Lower Bound (3%)	Upper Bound (3%)
Present Value of Costs	$0.97	$0.65	$1.29	$0.97	$0.65	$1.29
Present Value of Cost Savings	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Present Value of Net Costs	$0.97	$0.65	$1.29	$0.97	$0.65	$1.29
Annualized Costs	$0.07	$0.05	$0.09	$0.03	$0.02	$0.04
Annualized Cost Savings	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Annualized Net Costs	$0.07	$0.05	$0.09	$0.03	$0.02	$0.04

II. Preliminary 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)[2] clarified that section 503A of the FD&C Act applies nationwide in the United States.

A bulk drug substance[3] 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 drug product approved by the Food and Drug Administration (FDA or Agency). Finally, if an applicable USP or NF monograph does not exist and the bulk

[1] "Pharmacy" or "pharmacies" refers to pharmacies compounding under section 503A of the FD&C Act.
[2] Public Law 113-54 (November 27, 2013)
[3] "Bulk drug substance" means active pharmaceutical ingredient as defined in 21 CFR 207.1.

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.[4]

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 that guidance, we stated our intent not to take regulatory action while we review bulk drug substances for the 503A Bulks List that have been nominated with adequate support, 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 proposed 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 incorrectly 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 FDA and the average consumer. With an information asymmetry, consumers may make choices they would not have made if they were better informed. Without this proposed 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 proposed rule, when finalized, will fulfill this statutory requirement.

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.

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

In 2018, FDA published a final rule establishing the criteria for evaluating substances for inclusion on the 503A Bulks List, placing six substances on the list, and identifying four other substances that were evaluated and not included on the 503A Bulks List (84 FR 4696). That final rule noted that additional substances were under evaluation, and that new substances may be added to the list through subsequent rulemaking.

Under 21 CFR 216.23, the following criteria are used to evaluate the nominated substances:

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 31 of the nominated bulk drug substances (Table 3) for this proposed rule. Based on our review and our consultation with the Pharmacy Compounding Advisory Committee (PCAC) and the USP, we propose to amend the 503A Bulks List by adding five additional substances. Under the proposed rule, drug products compounded by compounding pharmacies using these five bulk drug substances would qualify for the exemptions in section 503A, provided they meet the other conditions of section 503A. We also identify 26 other substances that FDA has evaluated and proposes not to include on the list. In general, under the proposed rule, compounding pharmacies would not be able to compound drug products with these 26 substances unless they are the subject of an investigational new drug (IND) application.

Table 3. Bulk Drug Substances Reviewed for this Proposed Rule

Bulk Drug Substance	**Proposed to Be Included on the 503A Bulks List**
7-keto DHEA	
Acetyl-L-carnitine (ALC)	
Alanyl L Glutamine	
Aloe Vera 200:1 Freeze Dried	
Artemisinin	
Astragalus Extract 10:1	
Boswellia serrata extract (BWSE)	
Cesium chloride	
Chondroitin Sulfate	
Chrysin	
Curcumin	
D-Ribose	
Deoxy-D-glucose	
Diindolylmethane	

Domperidone	
Epigallocatechin Gallate (EGCG)	
Germanium Sesquioxide	
Glutaraldehyde	X
Glycolic Acid	X
Glycyrrhizin	
Kojic Acid	
L-citrulline	X
Nettle	
Nicotinamide Adenine Dinucleotide (NAD)	
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)	
Pyruvic Acid	X
Rubidium Chloride	
Sodium Dichloroacetate	
Trichloroacetic Acid (TCA)	X
Vanadyl Sulfate	
Vasoactive Intestinal Peptide (VIP)	

An "X" indicates that we have proposed to include the substance on the 503A Bulks List. A blank entry indicates that we have evaluated and are not proposing to include the substance on the 503A Bulks List.

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 proposed rule may address market failures arising from information asymmetry, and provide public health benefits, in two ways. First, by taking regulatory action, we can prevent consumers from taking certain drugs compounded with bulk drug substances that we determine lack sufficient evidence to be used in compounded drugs. Second, this proposed rule will provide more information to consumers, reducing information asymmetry. Consumers with greater access to information may be less likely to believe that drugs compounded using substances not placed on the 503A Bulks List are safe and effective based solely on their availability. Thus, consumers may respond and substitute an FDA-approved drug or an OTC monograph product, potentially improving their health outcomes.

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 was not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product. However, in practice, before DQSA clarified that section 503A is applicable nationwide, compounders made drug products using bulk drug substances that were not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug product. Therefore, the baseline of this analysis is the world where compounders would have continued to use the 31 bulk drug substances identified in this proposed rule to compound drug products. The proposed rule will place five 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 proposed rule will affect, though we expect that the proposed 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.

We used internal FDA data to look at the reported value of bulk drug substance imports for human use from 2011 to 2015. We should note that not all substance imports will be used in compounded drug products, so these estimates serve as an upward bound of the amount of imported bulk drug substances used in compounding. Additionally, 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 4. Reported Value of Bulk Drug Substance Imports from 2011 to 2015

Bulk Substance	**2011**	**2012**	**2013**	**2014**	**2015**	**Total**
7-Keto DHEA	$57,869	$83,620	$19,788	$27,485	$47,457	$236,218
Acetyl-L-Carnitine	$0	$0	$0	$0	$0	$0
Alanyl-L-Glutamine	$0	$6,112	$0	$0	$0	$6,112
Aloe Vera Freeze Dried 200:1	$363	$356	$1,050	$0	$0	$1,770
Artemisinin	$0	$0	$0	$0	$0	$0
Astragalus Extract 10:1	$0	$0	$1	$0	$0	$1
Boswellia serrata extract (BWSE)	$0	$193	$0	$0	$0	$193
Cesium Chloride	$0	$1,163	$0	$0	$5,645	$6,808
Chondroitin Sulfate	$140,872	$2,369,224	$8,328	$1,572	$10,248	$2,530,244
Chrysin	$0	$0	$0	$0	$0	$0
Curcumin	$703	$2,953	$278,773	$2,963	$794	$286,187
D-Ribose	$4,548	$0	$8,324	$18,194	$2,147	$33,213
Deoxy-D-Glucose	$45,536	$54,694	$1,077	$0	$0	$101,306
Diindolylmethane	$839	$4,048	$0	$0	$22,540	$27,427
Domperidone	$41,291	$55,650	$194,970	$119,396	$72,313	$483,621
Epigallocatechin Gallate (EGCG)	$0	$0	$0	$0	$0	$0
Germanium Sesquioxide	$0	$0	$0	$0	$0	$0

Glutaraldehyde	$0	$0	$0	$0	$0	$0
Glycolic Acid	$1,031	$1,150	$66	$5,120	$7,598	$14,965
Glycyrrhizin	$12,484	$0	$0	$18,003	$24,724	$55,210
Kojic Acid	$7,902	$6,121	$4,855	$1,237	$1,928	$22,042
L-Citrulline	$19,324	$5,912	$871	$0	$0	$26,107
Nettle	$20,440	$0	$121	$781	$0	$21,341
Nicotinamide Adenine Dinucleotide (NAD)	$48,691	$0	$1,034	$416	$412	$50,554
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)	$6,370	$0	$0	$0	$721	$7,091
Pyruvic Acid	$1,685	$0	$39	$0	$0	$1,725
Rubidium Chloride	$0	$0	$0	$0	$0	$0
Sodium Dichloroacetate	$0	$1,061	$42	$0	$0	$1,104
Trichloroacetic Acid (TCA)	$9,687	$8,797	$4,303	$22,729	$9,569	$45,397
Vanadyl Sulfate	$0	$10,795	$0	$0	$0	$10,795
Vasoactive Intestinal Peptide (VIP)	$0	$0	$0	$0	$0	$0

Note: All reported values expressed in 2017 dollars.

Based on the information in Table 4, we can draw limited conclusions about the size of the markets for the 31 bulk drug substances considered in this proposed rule. Of the 31 bulk drug substances evaluated, 7-Keto DHEA, chondroitin sulfate, curcumin, and domperidone appear to be the most widely compounded. The total reported value of imports for each of these substances is above $200,000 (in one case over $2,000,000), and there are positive reported values for each year from 2011 to 2015. Additionally, there are 7 bulk drug substances that have no reported imports during this time period.

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

In Table 5, we describe the historical uses of the 26 substances not included on the 503A Bulks List based on information provided in the preamble of the proposed rule. These historical uses are not FDA-approved. Alternative treatments exist for the conditions that were proposed to be treated by many of the evaluated substances. These alternative treatments are FDA-approved, and are safe and effective under their approved conditions of use.

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

Bulk Drug Substance	Historical Uses
7-keto DHEA	Raynaud's phenomena; weight loss

Acetyl-L-carnitine (ALC)	Alzheimer's disease; chemotherapy-induced peripheral neuropathy; hepatic encephalopathy
Alanyl L Glutamine	Nutritional support in the critically ill; reducing the rate of infectious complications in surgically and critical ill patients
Aloe Vera 200:1 Freeze Dried	Burns; cuts; wounds
Artemisinin	Malaria; helminthic infections; protozoal (particularly toxoplasmosis) infections; stomach ulcers; cancer
Astragalus Extract 10:1	Diabetes mellitus; allergic rhinitis; wound healing; asthma; herpes simplex keratitis
Boswellia serrata extract (BWSE)	Rheumatoid arthritis; osteoarthritis
Cesium chloride	Cancer
Chondroitin Sulfate	Joint pain associated with osteoarthritis
Chrysin	Aromatase inhibitor
Curcumin	Familial adenomatous polyposis; gastric metaplasia; oral leukoplakia
D-Ribose	Heart disease; chronic fatigue syndrome
Deoxy-D-glucose	Cancer; herpes simplex virus
Diindolylmethane	Cancer
Domperidone	Gastroparesis; nausea and vomiting; lactation enhancement
Epigallocatechin Gallate (EGCG)	Obesity; type 1 and type 2 diabetes; cardiac hypertrophy; corneal neovascularization; non-alcoholic fatty liver disease; Parkinson's disease; wound healing
Germanium Sesquioxide	Cancer
Glycyrrhizin	Hepatitis C by intravenous administration
Kojic Acid	Melasma; an iron chelator in wound healing and photodamage prevention
Nettle	Glycemic control
Nicotinamide Adenine Dinucleotide (NAD)	Fatigue in patients with multiple sclerosis
Nicotinamide Adenine Dinucleotide Disodium Reduced (NADH)	Chronic fatigue syndrome
Rubidium Chloride	Cancer
Sodium Dichloroacetate	Cancer
Vanadyl Sulfate	Diabetes; hyperlipidemia; heart disease; cancer prevention
Vasoactive Intestinal Peptide (VIP)	Chronic inflammatory response syndrome

E. Benefits of the Rule

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

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

Consumers may choose compounded drug products in consultation with their prescribers 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 proposed rule will indirectly provide consumers and prescribers 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 in consultation with their prescribers 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 proposed 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 proposed rule as "second-best" to the compounded drug product. Therefore, they will experience some loss in utility from the proposed 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, may not be safe or effective. If the health benefits are larger than the loss in utility, then these consumers will benefit from the proposed rule. If the loss in utility is greater than the health benefits, then these consumers will incur negative benefits from the proposed rule.

F. Costs of the Rule

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

We lack sufficient data to quantify many of the potential costs of the proposed rule. For those costs that we cannot 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. Administrative Costs

We estimate that each firm affected by the proposed rule would spend between 1 and 2 hours on administrative costs related to reading and understanding the proposed rule. Based on Bureau of Labor Statistics (BLS) wage data, the mean hourly wage for pharmacists is $61.88 (Ref. 4). The fully loaded mean hourly wage for pharmacists, including 100% overhead, is $123.76. Therefore, each affected firm will incur administrative costs that range from $123.76 (1 hour × $123.76 per hour) to $247.52 (2 hours × $123.76 per hour).

The proposed rule includes the list of substances evaluated for inclusion on the 503A Bulks List. We expect that this information will be of interest to compounding pharmacies. Therefore, we assume that, as an upper bound, all compounding pharmacies will incur one-time administrative costs to read and understand the proposed rule. We estimate that there are 5,563 compounding pharmacies in the United States (Ref. 5). The total administrative cost to compounding pharmacies will range from $688,477 ($123.76 per firm × 5,563 compounding pharmacies) to $1,376,954 ($247.52 per firm × 5,563 compounding pharmacies).

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 proposed rule. However, we do not have enough data about the size of these markets to estimate the administrative costs to these types of firms.

2. Cost of an IND

It may be possible for consumers to access drug products compounded with a bulk drug substance that we propose not to 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.

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 BLS wage data, the mean hourly wage for physicians and surgeons is $101.64 (Ref. 4). The fully loaded mean hourly wage for physicians and surgeons, including 100% overhead, is $203.28. Therefore, we estimate that the cost to submit Form FDA 3926 is $252.46 (0.75 hours × $203.28 per hour). We do not have enough data to estimate the other costs of submitting an expanded access IND. Because we do not have complete data on the IND related costs and we assume that these requests would rarely occur, we do not include this cost in our total costs estimates.

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. We invite comment and data on these assumptions.

3. Summary of Costs of the Proposed Rule

In Table 6, we summarize the total quantified costs of the proposed rule over 10 years. The annualized cost of the proposed rule will range from $0.08 million to $0.16 million at a 3 percent discount rate and from $0.10 million to $0.20 million at a 7 percent discount rate.

Table 6. Total Quantified Costs of the Proposed Rule ($ millions)

Cost	Low Estimate	Primary Estimate	High Estimate
Reading and Understanding the Rule	$0.69	$1.03	$1.38
Present Value of Cost (3%)	$0.69	$1.03	$1.38
Present Value of Cost (7%)	$0.69	$1.03	$1.38
Annualized Value of Cost (3%)	$0.08	$0.12	$0.16
Annualized Value of Cost (7%)	$0.10	$0.15	$0.20

Note: Values are shown using 2017 dollars.

G. Distributional Effects

1. Loss or Transferred Profits

For each of the 26 substances we have evaluated and propose not to 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.

3. Payers

Some private and public payers may currently reimburse consumers for the cost of drug products compounded using bulk drug substances we propose not to include on the 503A Bulks List. For example, if consumers switch from the compounded drug to an alternative treatment, then the proposed rule will create transfers from payers to pharmacies or consumers or vice versa. If consumers choose to forego treatment and suffer no ill effects, then the proposed 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 proposed rule. We also find little evidence of widespread use of the 26 bulk drug substances that we propose not to include on the 503A Bulks List. Therefore, we expect that the proposed 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. 6). 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. We request comment on this and all aspects of the analysis.

J. Analysis of Regulatory Alternatives to the Rule

FDA considered alternatives to proposing to include five substances on the 503A Bulks List. One alternative for the proposed rule was to not propose the inclusion of any additional bulk drug substances on the list. Another alternative was to propose the inclusion of certain substances without any restrictions on their use. For example, we might have opted to propose including glutaraldehyde on the 503A Bulks List without restriction on its route of administration or concentration, or alternatively, to exclude this drug substance from the list in light of the concerns that led to the proposal to limit the route of administration and concentration.

FDA also considered alternatives to proposing not to include 26 substances on the 503A Bulks List. One alternative was to propose the inclusion of additional substances on the list without restrictions on their use. Another alternative was to propose the inclusion of additional substances with restrictions on their use.

However, in the case of each of the substances addressed in the proposed rule, balancing information regarding the physiochemical characteristics, safety of the substance when used in compounded drug products, effectiveness of the substance when used in compounded drug products for the proposed use, and historical use of compounded drug products that include the particular substance weigh in favor of the proposals for inclusion, or exclusion, as discussed in the preamble.

III. Small Entity Effects

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 proposed rule on small manufacturers, wholesalers, and compounding pharmacies, we find that the proposed 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 Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

A. Description and Number of Affected Small Entities

In Table 7, we describe the Small Business Administration's size standards for the industries affected by the proposed 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 7. Small Business Administration Size Standards for Industries Affected by the Proposed Rule

NAICS 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 proposed rule on small entities in these industries. Therefore, we cannot certify that the proposed rule will not have a significant impact on a

substantial number of small entities. To the extent that the affected firms are small businesses, the alternatives listed in the section above may mitigate impact on small entities. We request comment on the impact of this rule on small entities.

IV. References

1. **U.S. Food and Drug Administration.** Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act: Guidance for Industry. [Online] 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf

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4. **Bureau of Labor Statistics.** May 2017 National Industry-Specific Occupational Employment and Wage Estimates. [Online] 2017. https://www.bls.gov/oes/2017/may/oessrci.htm

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