DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Rulemaking to Provide That N-acetyl-L-cysteine Is Not Excluded from the Dietary Supplement Definition

Docket No. FDA-2025-N-2699

Preliminary Regulatory Impact Analysis
Initial 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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I. Introduction and Summary

A. Introduction

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, Executive Order 14192, 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 benefits and costs of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits. The Office of Information and Regulatory Affairs (OIRA) has determined that this proposed rule is a significant regulatory action under section 3(f) of Executive Order 12866.

Executive Order 14192 requires that any new incremental costs associated with certain significant regulatory actions "shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least 10 prior regulations." This proposed rule, if finalized as proposed, is expected to be an Executive Order 14192 deregulatory action because it is an enabling regulatory action that may expand production options.

The Regulatory Flexibility Act requires us to consider the impact of regulatory proposals on small entities. While we do not anticipate that the proposed rule would significantly increase costs to manufacturers, we have prepared an Initial Regulatory Flexibility Analysis for the purpose of providing information and soliciting comment.

The Unfunded Mandates Reform Act of 1995 (Section 202(a)) requires us to prepare a written statement, which includes estimates of anticipated impacts, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted

annually for inflation) in any one year." The current threshold after adjustment for inflation is $187 million, using the most current (2024) 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. Overview of Benefits, Costs, and Transfers

To estimate benefits, costs, and transfers associated with the proposed rule, we assume that the appropriate baseline is the state of the world in which N-acetyl-L-cysteine (NAC) is excluded from the dietary supplement definition but FDA exercises enforcement discretion with respect to the sale and distribution of certain products that contain NAC and are labeled as dietary supplements. We then compare the likely impacts of the proposed rule against this baseline. We do not estimate benefits due to the proposed rule. It is possible that firms may react to the legal clarity of NAC dietary supplement products by introducing new products to market. To the extent that this occurs, consumers may benefit from expanding availability of products that may serve different purposes and uses than the FDA-approved NAC drug products. However, the likelihood and magnitude of such impacts are difficult to estimate.

The costs of the proposed rule are associated with costs to industry for reading and understanding the rule. Because there are few firms operating in the NAC market, these impacts are small. When annualized over a period of 10 years, we estimate these costs range from approximately $89 to $112 at a 3 percent discount rate. At a 7 percent rate of discount, these estimates range from $109 to $136. Our primary annualized estimates are approximately $99 and $121 at 3 and 7 percent rates of discount, respectively. The primary estimate of the present value of total costs resulting from any final rule that may be issued based on the proposed rule is

approximately $848. The annualized values are summarized in Table 1. Note that the values are scaled down to zero because they are so small.

Table 1. Summary of Benefits, Costs, and Distributional Effects of the Proposed Rule (millions of 2024 dollars)

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized $millions/year				2024	7%	10 years	
						3%	10 years	
	Annualized Quantified							
	Qualitative							
Costs	Annualized Monetized $millions/year	$0.00	$0.00	$0.00	2024	7%	10 years	
		$0.00	$0.00	$0.00		3%	10 years	
	Annualized Quantified							
	Qualitative							
Transfers	Federal Annualized Monetized $millions/year							
	From/To	From:			To:			
	Other Annualized Monetized $millions/year							
	From/To	From:			To:			
Effects	State, Local or Tribal Government: None							
	Small Business: None							
	Wages:							
	Growth:							

In line with Executive Order 14192, in Table 2 we estimate present and annualized values of costs, cost savings, and net costs over a perpetual time horizon. Note that the values are scaled down to zero because they are so small. This proposed rule may lead to new products, which could increase consumer choice and expand production options for industry. The impacts from these options are left unquantified in this analysis. Because the proposed rule is deregulatory in nature, any eventual final rule based on this proposed rule is expected to be an Executive Order 14192 deregulatory action despite these unquantified impacts.

Table 2. Executive Order 14192 Summary Table (millions of 2024 dollars, discounted over a perpetual time horizon relative to year 2024 at a 7 percent discount rate)

	Primary Estimate	Low Estimate	High Estimate
Present Value of Costs	$0.0		
Present Value of Cost Savings	Not quantified		
Present Value of Net Costs	N/A		
Annualized Costs	$0.0		
Annualized Cost Savings	Not quantified		
Annualized Net Costs	N/A		

Note: Values in parentheses denote net negative costs (i.e., net cost savings).

We request comment on our estimates of benefits, costs, and transfers of this proposed rule.

II. Preliminary Economic Analysis of Impacts

A. Background

The Federal Food, Drug, and Cosmetic Act (referred to hereafter as the FD&C Act) defines the term "dietary supplement" and establishes requirements for what dietary supplements must contain, how they must be used, and how they must be labeled. Section 201(ff)(3)(B) of the FD&C Act excludes certain articles from this definition, including an article that is approved as a new drug under section 505 of the FD&C Act that was not before such approval marketed as a dietary supplement or as a food. FDA, however, has the authority under section 201(ff)(3)(B) of the FD&C Act to provide an exception for an article by issuing a rule finding that the article may be lawfully marketed in or as a dietary supplement under the FD&C Act, provided that such product is not otherwise in violation of the FD&C Act.

This proposed rule, if finalized, would be the first use of this authority and the corresponding authority under section 301(ll)(2) of the FD&C Act "approving the use of the drug . . . in the food" (i.e., providing that the addition of the article to the food would not be a

prohibited act under section 301(ll) of the FD&C Act). NAC is excluded from the definition of dietary supplement. We currently exercise enforcement discretion with respect to the sale and distribution of certain products that contain NAC and are labeled as dietary supplements (2022 final guidance).[1] The enforcement discretion policy applies to products that would be lawfully marketed dietary supplements if NAC were not excluded from the dietary supplement definition and that are not otherwise in violation of the FD&C Act (id.). This proposed rule, if finalized, would codify an exception to bring NAC within the definition of dietary supplement (i.e., no longer excluded under section 201(ff)(3)(B) of the FD&C Act) and make it not a prohibited act under section 301(ll) of the FD&C Act to add NAC to dietary supplements, removing any uncertainty about the future status of NAC-containing products that are labeled as dietary supplements and currently on the market.

B. Potential Need for Federal Regulatory Action

The proposed rule does not directly address a market failure. It may, however, improve the overall well-being of society. If finalized, the proposed rule would remove uncertainty regarding the marketing status of NAC-containing products that are labeled as dietary supplements, and individual firms may choose to enter the NAC supplement market. Additionally, innovative NAC supplement products may be introduced to the market. These outcomes would boost competition and improve consumer choice and welfare.

C. Purpose of the Proposed Rule

[1] As described in final guidance entitled "Policy Regarding N-acetyl-L-cysteine: Guidance for Industry", published in the *Federal Register* of August 2, 2022 (87 FR 47220).

Currently, NAC is excluded from the dietary supplement definition, meaning NAC cannot be lawfully sold in or as a dietary supplement. However, FDA currently exercises enforcement discretion with respect to the sale and distribution of NAC-containing products that would be lawfully marketed dietary supplements if NAC were not excluded from the dietary supplement definition and that are not otherwise in violation of the FD&C Act. This means that FDA does not object to the sale and distribution of such NAC-containing products.

The proposed rule, if finalized, would provide that NAC is not excluded from the dietary supplement definition in the FD&C Act and that the addition of NAC to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act. Accordingly, if a product that is or contains NAC is labeled as a dietary supplement and otherwise meets the definition of a dietary supplement under section 201(ff) of the FD&C Act, FDA would regulate such a product as a dietary supplement. This means that NAC-containing products that are currently being sold or distributed under the enforcement discretion policy could remain on the market and would be regulated as dietary supplements. For example, the manufacture of an NAC-containing dietary supplement would have to comply with the applicable requirements in FDA's regulation for current good manufacturing practice in manufacturing, packaging, labeling or holding operations for dietary supplements (21 CFR part 111).

D. Baseline Conditions

OMB's Circular A-4 offers guidance to Federal agencies on the development of regulatory analysis. A first step in developing the analysis is to "[i]dentify a baseline. Benefits and costs are defined in comparison with a clearly stated alternative. This normally will be a 'no action' baseline: what the world will be like if the rule is not adopted." In our analysis, we adopt two baselines. The first is a baseline that incorporates the enforcement discretion policy. This

reflects the best forecast of the world without the rule. We also analyze the effects of the rule relative to a second baseline that excludes the enforcement discretion policy. This allows us to explore more of the effects of the policy than the first baseline. In this section, we describe the two baselines and also present an estimate of the difference in the economic impacts between the two analytic baselines.

a. First Baseline

We adopt, as our first baseline, current market conditions for the products covered under the scope of the proposed rule. This baseline accounts for the growth in sales following the 2022 final guidance announcing the enforcement discretion policy, to the extent we are able to measure the sales of these products. Thus, the estimated benefits and costs reported in our main analysis reflect the incremental impact of the proposed rule against the status quo, assuming the 2022 final guidance remains in effect without further sub-regulatory action.

We use scanner data to describe the current market for NAC-containing products that are labeled as dietary supplements. This data is point-of-sale from Circana and covers the entire calendar year of 2023.[2,3] Circana defines multi-outlet and convenience retailers as brick-and-mortar food, drug, mass-market (including Walmart), club (excluding Costco), dollar, military, and convenience stores. The Circana data do not cover all distribution channels for supplement products. Notably, the data do not include online sales and sales from specialty retailers. We request public comment on supplementary data sources that better cover the outstanding channels. We obtained annual data on dollar sales and unit sales from relevant products at the

[2] Data was accessed via Unify (https://advantage.iriworldwide.com/unify-client/index.html). More information about Circana can be found on https://www.circana.com/.
[3] Food and Drug Administration custom research definitions based on Circana, LLC (fka Information Resources Inc.) data 2023, dollar sales, unit sales, product name, and descriptive label variables, Total Multi Outlet with Convenience.

Universal Product Code (UPC) level. For 2023, we find there were 44 NAC-containing products labeled as dietary supplements with positive sales. These products were manufactured and sold by 15 firms. The market for NAC products labeled as dietary supplements accounted for over 115,000 units (bottles or containers) and over $1.5 million in total revenue in 2023. The average revenue per unit sold is over $13.50. Given the data limitations, this represents a lower bound of market size for these products. These products are currently marketed under the enforcement discretion policy.

The current market provides gains to both consumers and producers, compared to a scenario in which there is no enforcement discretion (that is, where baseline quantity exchanged in the market would be 0). These gains count as cost-savings in the form of the opportunity costs of previously foregone purchases. A portion of these cost savings is consumer surplus, or the difference between the price a consumer pays for NAC-containing products labeled as dietary supplements and the maximum price they are willing to pay.[4] To better illustrate consumer surplus in the market with enforcement discretion, we calculate the consumer surplus based on market revenue and the price elasticity of demand.[5] As reported above, market revenue is approximately $1.5 million annually. We assume an elasticity of -0.4, based on an existing estimate for the price elasticity of demand of vitamins (Chung, Lee, & Brown, 1998). Using these inputs, we estimate consumer surplus of approximately $1.9 million each year [0.5 x $1.5 million x (1 / 0.4) = $1.9 million]. Producers also gain surplus. We request comment on the

[4] Alternatively, consumer surplus is the monetary benefit consumers receive when they pay a price for a product that is less than the maximum price they are willing to pay for that product.

[5] Consumer surplus is the triangular area below the demand curve and above the price for NAC-containing products labeled as dietary supplements. If approximated with an assumption of linearity in the demand curve, the formula for this area is: Consumer Surplus = 0.5 x Market Revenue x (1 / Price Elasticity of Demand).

supply elasticity in the market, which would allow us to approximate the value of producer surplus with enforcement discretion.

b. Second Baseline

While we believe the first baseline described above reflects the best forecast of the world without the rule, we have identified a second baseline that allows us to explore more of the effects of the 2022 final guidance. For this second baseline, we omit the preceding sub-regulatory action, the enforcement discretion policy regarding the use of NAC in or as a dietary supplement (i.e., the baseline is the status quo in which NAC is excluded from the dietary supplement definition and, therefore, may not be lawfully marketed in or as a dietary supplement, and FDA does not exercise enforcement discretion with respect to such products). In addition to the benefits and costs measured against our first baseline that we report below, the additional incremental impacts under this second baseline include the welfare gains currently experienced by consumers and producers. Specifically, compared to the second baseline, the proposed rule is an enabling regulation that would generate the consumer and producer surplus reported above. Thus, the cost-savings include consumer surplus of approximately $1.9 million each year, and producer surplus, which is not quantified in this analysis.

Consumers who normally purchase NAC products labeled as dietary supplements would incur costs from FDA not exercising enforcement discretion. Costs would accrue to consumers because they would lose the ability to purchase these products. Therefore, in the event that FDA ceases to exercise enforcement discretion prior to the publication of a final rule, the rule would lead to cost-savings.

E. Benefits and Cost Savings of the Proposed Rule

There are potential public health benefits associated with the proposed rule that we do not quantify or monetize. These benefits are difficult to predict and any impacts on social welfare are highly uncertain. Firms may react to the rule by introducing new NAC supplement products to the market. Additional entry and competition in the NAC market may increase innovation and lead to products that more closely align with consumer preferences. However, the likelihood and magnitude of such impacts are difficult to quantify.

F. Costs of the Proposed Rule

1. Costs to industry to read and understand the proposed rule

Manufacturers incur a one-time cost to read and understand the proposed rule, if finalized. As recommended by guidance from the Department of Health and Human Services, we assume a reading speed of between 200 and 250 words per minute (Office of the Assistant Secretary for Planning and Evaluation, 2016). For simplicity, we take the midpoint of this range, 225 words per minute, as our primary estimate of reading time. The proposed rule consists of approximately 8,000 words. This implies that nearly 36 minutes, or 0.6 hours, are needed to read and understand the proposed rule (8,000 words / 225 words per minute = 36 minutes). Estimates of reading time based on a reading speed of 200 and 250 words per minute range from approximately 40 to 32 minutes, respectively.

We use these estimates to calculate the monetary costs associated with reading and understanding the proposed rule, if finalized. To do so, we use information on hourly wages. We assume that 1 compliance officer at each firm reads and interprets the proposed rule. The mean hourly wage for compliance officers in the pharmaceutical and medicine manufacturing industry, as reported by the US Bureau of Labor Statistics, is $47.69 (US Bureau of Labor Statistics,

2025). We double this wage to account for the value of benefits and other indirect costs. This fully loaded hourly wage is just over $95. Across all firms with positive NAC sales in the past year, the total cost is approximately $848 (15 firms x 36 minutes x $95 / 60 minutes = $848).[6] The high and low reading speed cost estimates are approximately $763 and $954. We assume that facilities incur this cost immediately after publication of the proposed rule, if finalized. These estimates are summarized in Table 3, below.

2. Summary of costs

We summarize annualized costs of the proposed rule, if finalized, in Table 3. Total annualized costs in the 10 years after rule publication range from approximately $89 to $112 at a 3 percent rate of discount. At a 7 percent rate of discount, these values range from $109 to $136. The primary annualized cost estimates are $99 at a 3 percent discount rate and $121 at a 7 percent discount rate.

There is the potential for this rule to generate additional costs, which we do not estimate in this analysis. Because the rule may result in product innovation and market entry, some consumers may use dietary supplements containing NAC rather than an FDA-approved NAC drug product; though, for the reasons discussed in the proposed rule, FDA expects this rule is unlikely to negatively impact NAC drug development. Any potential impacts from this behavior change for either industry or consumers are uncertain and difficult to predict.

Table 3. Costs to industry to read and understand the proposed rule

Discount Rate	Low	Primary	High
Costs incurred by industry	$763	$848	$954
3%	$89	$99	$112

[6] This operation, as shown in the parenthetical, yields a value of $855.00. The correct value is $847.82. The difference is due to rounding.

7%	$109	$121	$136

Note: Dollar values in 2024 dollars

G. Analysis of a Regulatory Alternative to the Proposed Rule

1. Delay effective date 1 year

The proposed rule, if finalized, becomes effective immediately upon publication in the *Federal Register*. An alternative is to delay the effective date to 1 year after publication. Under this scenario, firms will not have to fully read and understand the rule until the end of the 1-year period. These costs are no longer incurred immediately upon final rule publication, but after 1 year.

Table 4 shows total costs under this regulatory alternative. Overall, these costs are slightly smaller than in the main analysis. In the 10 years following any final rule that may be issued based on the proposed rule, the primary present values of costs are now approximately $823 at a 3 percent rate of discount and $792 at a 7 percent rate of discount. The primary annualized values under this alternative are roughly $97 at a 3 percent rate of discount and $113 at a 7 percent rate of discount.

Table 4. Total Costs if Effective Date is Delayed to 1-Year

	Discount Rate	**Low**	**Primary**	**High**
Present Value of Costs	3%	$741	$823	$926
	7%	$713	$792	$891
Annualized Value of Costs	3%	$87	$97	$109
	7%	$102	$113	$127

Note: Dollar values in 2024 dollars

H. Distributional Effects

We do not anticipate that the proposed rule, if finalized, would result in differential impacts across varying groups of individuals or entities. This is primarily because we only estimate impacts accruing to industry. However, consumers who purchase supplements may be affected by this rule. These impacts could come in the form of improved consumer choice and NAC product innovation. If access to supplements varies across groups of individuals or entities, then these impacts may not be evenly distributed.

III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to consider the impact of their regulatory proposals on small entities. While the costs and cost-savings imposed by the proposed rule on industry are small relative to firm revenue, we provide the Initial Regulatory Flexibility Analysis to provide information and solicit comment. This analysis, as well as other sections in this document and the Preamble of the proposed rule, serves as the Initial Regulatory Flexibility Analysis.

A. Description and Number of Affected Small Entities

We find that most entities affected by this rule are classified as small. The North American Industry Classification System (NAICS) code that best matches the affected industry is 325411.[7] For this code, the Small Business Administration (SBA) defines entities as small if they have 1,000 or fewer employees (US Small Business Administration, 2023). We compare this threshold with establishment data from the Economic Census (US Census Bureau, 2025). Based on these data, shown in Table 5, there were 754 establishments in NAICS code 325411 in

[7] This code corresponds to entities in the Medicinal and Botanical Manufacturing industry.

2022. All but 58 of these establishments were below the employee threshold defined by SBA. This implies that 696 establishments in 2022 were small under the SBA standard.

Table 5. Distribution of Firms under NAICS Code 325411 by Number of Employees

Number of Employees	Number of Establishments	Percent of Total Establishments	Total Revenues
Less than 5	254	33.69%	$222.15
5 to 9	116	15.38%	$209.97
10 to 19	93	12.33%	$356.13
20 to 99	136	18.04%	$1,882.39
100 to 999	97	12.86%	$6,439.39
Less than 1,000	696	92.31%	$9,110.03
Greater than 999	58	7.69%	$7,482.84
Total	754	100.00%	$16,592.87

Note: Dollar values in millions of 2024 dollars

B. Description of the Potential Impacts of the Rule on Small Entities

We anticipate the proposed rule, if finalized, will not have a significant impact on a substantial number of small entities.[8] Table 6 shows information on average establishment revenue. Based on data from the 2022 Economic Census, the average revenue per establishment under NAICS code 325411 is approximately $22 million in 2024 dollars (US Census Bureau, 2025). Using the total costs from the main analysis, the overall average cost per entity affected by the rule ranges from approximately $51 to $64, with a primary estimate of $57. As a percentage of average revenue per establishment, these average cost values do not exceed 1 percent. We do not estimate cost-savings accruing to industry and therefore do not incorporate estimates of cost-savings into this analysis.

[8] HHS guidelines suggest the threshold for "significant impact" is 3% of annual revenue and the threshold for "substantial number" is 5% of small entities. See https://aspe.hhs.gov/reports/proper-consideration-small-entities-rulemakings-us-dhhs.

Table 6. Comparison of Proposed Rule Costs with Firm Revenues

Number of Employees	Average Revenue per Entity*	Low: Avg. Cost per Covered Entity^	Low: Cost as % of Average Revenue	Primary: Avg. Cost per Covered Entity^	Primary: Cost as % of Average Revenue	High: Avg. Cost per Covered Entity^	High: Cost as % of Average Revenue
Less than 5	$0.87	$51	0.01%	$57	0.01%	$64	0.01%
5 to 9	$1.81	$51	0.00%	$57	0.00%	$64	0.00%
10 to 19	$3.83	$51	0.00%	$57	0.00%	$64	0.00%
20 to 99	$13.84	$51	0.00%	$57	0.00%	$64	0.00%
100 to 999	$66.39	$51	0.00%	$57	0.00%	$64	0.00%
Less than 1,000	$13.09	$51	0.00%	$57	0.00%	$64	0.00%
Greater than 999	$129.01	$51	0.00%	$57	0.00%	$64	0.00%
Total	$22.01	$51	0.00%	$57	0.00%	$64	0.00%

*Dollar values are in millions of 2024 dollars.

^Dollars values are in 2024 dollars.

C. Alternatives to Minimize Burden on Small Entities

This proposed rule, if finalized, is an enabling regulatory action that may expand production options. There are no additional provisions that are more deregulatory and still within the scope of this proposed rule.

IV. References

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