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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 190**

**[Docket No. FDA-2025-N-2699]**

**RIN 0910-AI91**

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

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA or we) is proposing to issue a regulation finding that N-acetyl-L-cysteine (NAC) is not excluded from the dietary supplement definition in the Federal Food, Drug, and Cosmetic Act (FD&C Act). This action, if finalized, would allow products containing NAC to be lawfully marketed as dietary supplements, provided that such products are not otherwise in violation of the FD&C Act. We also propose to provide that the addition of NAC to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act.

**DATES:** Either electronic or written comments on the proposed rule must be submitted by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**ADDRESSES:** You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

*Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

*Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions*: All submissions received must include the Docket No. FDA-2025-N-2699 for "Rulemaking to Provide by Regulation That N-acetyl-L-cysteine Is Not Excluded from the Dietary Supplement Definition." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential

Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

*Docket*: For access to the docket to read background documents, the plain language summary of the proposed rule of not more than 100 words as required by the "Providing Accountability Through Transparency Act," or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Gerie Voss, Office of Dietary Supplement Programs, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College

Park, MD 20740, 240-620-9744; or Alexandra Beliveau, Office of Regulations and International Programs, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-2378.

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## I. Executive Summary

### *A. Purpose of the Proposed Rule*

This proposed rule, if finalized, would provide by regulation that NAC is not excluded from the dietary supplement definition in the FD&C Act. This action would allow NAC-containing products to be lawfully marketed as dietary supplements, provided that such products are not otherwise in violation 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 (21 U.S.C. 321(ff)), FDA would regulate such product as a dietary supplement. The proposed rule also would provide that the addition of NAC to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act (21 U.S.C. 331(ll)).

### *B. Summary of the Proposed Rule*

We are proposing to establish a regulation entitled "Dietary Ingredients Not Excluded from the Dietary Supplement Definition" at 21 CFR 190.1 (§ 190.1) to provide for the lawful use in dietary supplements of certain ingredients that would otherwise be excluded from the dietary supplement definition. Specifically, this proposed rule would provide that ingredients listed under this regulation are not excluded for use in or as a dietary supplement under section 201(ff)(3)(B) of the FD&C Act and that the addition of such ingredients to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act. NAC would be the first ingredient listed under this new regulation.

### *C. Legal Authority*

We are issuing this proposed rule to establish a regulation to provide for the lawful use of certain ingredients in dietary supplements that would otherwise be excluded from the dietary supplement definition and to list NAC as the first ingredient under this new regulation, consistent with our authority in sections 201(ff)(3)(B), 301(ll)(2), and 701(a) of the FD&C Act (21 U.S.C. 321(ff)(3)(B), 331(ll)(2), and 371(a)).

### *D. Costs and Benefits*

This 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.

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 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.

## II. Background

### *A. Dietary Supplement Definition*

Section 201(ff) of the FD&C Act defines the term "dietary supplement" and establishes requirements for what dietary supplements must contain, what they must not contain, how they must be used, and how they must be labeled. A dietary supplement must be a product intended to supplement the diet that contains one or more dietary ingredients (section 201(ff)(1) of the FD&C Act). Under section 201(ff)(1) of the FD&C Act, a "dietary ingredient" is any one of the following: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any dietary ingredient from the preceding categories. In addition, under section 201(ff)(2) of the FD&C Act, a dietary supplement: must be intended for ingestion in tablet, capsule, powder, softgel, gelcap, or liquid form or comply with section 411(c)(1)(B)(ii) of the FD&C Act (21 U.S.C. 350(c)(1)(B)(ii)); must not be represented for use as a conventional food or as a sole item of a meal or the diet; and must be labeled as a dietary supplement.

Section 201(ff)(3)(A) of the FD&C Act provides that a product that otherwise meets the definition of a dietary supplement *does not* lose its status as a dietary supplement if it includes an article that is approved as a new drug under section 505 of the FD&C Act (21 U.S.C. 355) or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), provided that the article was marketed as either a dietary supplement or as a food before it was approved as a new drug or licensed as a biologic. Section 201(ff)(3)(A) of the FD&C Act provides an exception to this general rule, authorizing the Secretary of Health and Human Services (Secretary) to issue a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f) of the FD&C Act.

Section 201(ff)(3)(B) of the FD&C Act (the exclusion clause) provides that a product that would otherwise meet the definition of a dietary supplement *loses* its status as a dietary supplement if the product includes certain articles. Specifically, the general rule of section

201(ff)(3)(B)(i) of the FD&C Act is that a dietary supplement cannot include an article that was approved as a new drug under section 505 of the FD&C Act, certified as an antibiotic under section 507 of the FD&C Act, or licensed as a biologic under section 351 of the Public Health Service Act before the article was marketed as a dietary supplement or as a food. The general rule of section 201(ff)(3)(B)(ii) of the FD&C is that a dietary supplement cannot include an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless the article was marketed as a dietary supplement or as a food before such authorization. Section 201(ff)(3)(B) of the FD&C Act provides an exception to the general rules of sections 201(ff)(3)(B)(i) and (ii) of the FD&C Act. Under this exception, the article is not excluded if the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the FD&C Act.

This proposed rule is the first use of our rulemaking authority described in section 201(ff)(3)(B) of the FD&C Act.

*B. Regulatory Status of NAC*

The names for NAC include, but are not limited to, acetylcysteine; L-acetylcysteine; L-alpha-acetamido-beta-mercaptopropionic acid; N-acetyl cysteine; N-acetyl-3-mercaptoalanine; N-acetyl-L-cysteine; NAC; and mercapturic acid. These names all refer to the same article.

Because the elements of the dietary supplement definition in sections 201(ff)(1), (2), and (3) of the FD&C Act are phrased conjunctively (separated by "and"), a product qualifies as a dietary supplement only if it satisfies the criteria in all three paragraphs (see section II.A of this document for a detailed explanation). Thus, demonstrating that a product satisfies the requirement in section 201(ff)(1) of the FD&C Act to contain a dietary ingredient does not establish that the product meets the other criteria in sections 201(ff)(2) and (ff)(3) of the FD&C Act. NAC is a dietary ingredient under section 201(ff)(1)(E) of the

FD&C Act, but it also is excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act, as discussed below.

NAC is a dietary ingredient under section 201(ff)(1)(E) of the FD&C Act, i.e., a dietary substance for use by man to supplement the diet by increasing the total dietary intake. For example, a February 1995 advertisement in Vegetarian Times describes NAC as an ingredient in the advertised shake, a conventional food (Ref. 1).

NAC is not a "new dietary ingredient" under section 413(d) of the FD&C Act (21 U.S.C. 350b(d)). The term "new dietary ingredient" (NDI) means a dietary ingredient that was not marketed in the United States before October 15, 1994, and does not include any dietary ingredient which was marketed in the United States before October 15, 1994. We are aware of an August/September 1991 advertisement for an NAC-containing supplement (Ref. 2). Thus, NAC is not an NDI.

Although NAC is a dietary ingredient, NAC is excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act because NAC was approved as a new drug before it was marketed as a dietary supplement or as a food. NAC was approved as a new drug under section 505 of the FD&C Act on September 14, 1963, under New Drug Application (NDA) 013601, Mucomyst (acetylcysteine) (see 28 FR 13509, December 13, 1963). (In accordance with then-21 CFR 130.33, we provided notice of the new drug approval in the *Federal Register* in December 1963 (28 FR 13509, December 13, 1963).) We are not aware of any evidence that NAC was marketed as a dietary supplement or as a food before September 14, 1963, but request evidence to the contrary.

FDA stated NAC's regulatory status several times over the past 25 years. For example, we stated this position in July 2001 in response to a health claim petition for a claim about an NAC-containing product, when we allowed the petition to be denied by operation of law (Ref. 3). The petition did not meet the requirements for a health claim petition as established in 21 CFR 101.70, including the requirement that the petition contain a complete explanation of how

the substance that is the subject of the proposed claim conforms to the requirements of 21 CFR 101.14(b). Our response explained that the petition did not meet these requirements because, among other things, the petitioner did not demonstrate that use of NAC in a dietary supplement was lawful. In particular, after citing the exclusion clause, we noted that NAC was approved as a new drug under section 505 of the FD&C Act on September 14, 1963, under NDA No. 013601, Mucomyst (acetylcysteine), and the petition failed to document a history of NAC having been marketed as a dietary supplement before that date (Ref. 3). Because the health claim petition was denied by operation of law, our July 2001 response was not made available to the public when it was sent to the company that submitted the petition, per section 403(r)(4)(A)(i) of the FD&C Act (21 U.S.C. 343(r)(4)(A)(i)) (Ref. 3). Consequently, this historical response has remained non-public to protect proprietary commercial information; however, a redacted copy of our July 2001 response is being placed in the public docket for this rulemaking (id.) to allow for public review and comment on FDA's administrative precedent.

In 2010, in response to an NDI notification for NAC ethyl ester, we stated that, under the exclusion clause, NAC-containing products cannot be dietary supplements (Ref. 4). In July 2020, as part of warning letters sent to companies illegally selling unapproved products that claimed to cure, treat, mitigate, or prevent hangovers while also labeling their products as dietary supplements, we stated that NAC-containing products are excluded from the definition of dietary supplement under the exclusion clause (Refs. 5 through 8).

In 2021, we received two citizen petitions requesting that we conclude that NAC is not excluded from the definition of dietary supplement under section 201(ff)(3)(B) of the FD&C Act (https://www.regulations.gov; Docket Nos. FDA-2021-P-0523 and FDA-2021-P-0938). One citizen petition also asked that, if FDA did not change our position that products containing NAC are excluded from the definition of a dietary supplement under section 201(ff)(3)(B) of the FD&C Act, we recommend that the Secretary issue a regulation, after notice-and-comment rulemaking, finding that NAC would be lawful under the FD&C Act (see Docket No. FDA-

2021-P-0938). On March 31, 2022, we issued a joint final response to both petitions, denying one petition in its entirety and denying the other petition in part. We stated our conclusion that NAC is excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act, as described above. In addition, we explained that we had not yet reached a final decision on the request to initiate rulemaking and that we were considering initiating rulemaking under section 201(ff)(3)(B) of the FD&C Act to permit the use of NAC in or as a dietary supplement. We acknowledged that, although NAC-containing products labeled as dietary supplements have been sold in the United States for over 30 years, and consumers continue to seek access to such products, we needed additional time to complete our review, including a full safety review of NAC, before responding to the remaining request.

In the *Federal Register* of August 2, 2022 (87 FR 47220), we announced the availability of a final guidance for industry entitled "Policy Regarding N-acetyl-L-cysteine: Guidance for Industry" (enforcement discretion guidance), which announced our intent to exercise temporary enforcement discretion with respect to the sale and distribution of certain products that contain NAC and are labeled as dietary supplements until either of the following occurs: we complete notice-and-comment rulemaking to allow the use of NAC in or as a dietary supplement, or we deny the citizen petition's request for rulemaking. The enforcement discretion guidance explained our determination that NAC is excluded from the dietary supplement definition because NAC was approved as a new drug before it was marketed as a dietary supplement or as a food (Ref. 9). We stated that, while FDA's full safety review of NAC remained ongoing, our initial review did not reveal safety concerns with respect to the use of NAC in or as a dietary supplement (id.). 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.). If this proposed rule is finalized, FDA intends to withdraw this enforcement discretion guidance.

## III. Legal Authority

As discussed in section II.A of this document, section 201(ff)(3)(B) of the FD&C Act excludes certain articles from the definition of dietary supplement. Our discussion focuses primarily on the mention of new drug approval in section 201(ff)(3)(B) of the FD&C Act, as that is at issue for NAC; however, the same logic would apply to other articles described in clauses (i) and (ii) of section 201(ff)(3)(B) of the FD&C Act.

The general rule of section 201(ff)(3)(B) of the FD&C Act is if an article is approved as a new drug under section 505 of the FD&C Act, then that article is outside the dietary supplement definition unless the article was marketed as a dietary supplement or a food before such approval. However, there is an exception if FDA (under authority delegated by the Secretary) issues a regulation, after notice-and-comment rulemaking, "finding that the article would be lawful under this Act" (i.e., the FD&C Act). In this context (the dietary supplement definition), we interpret this phrase to mean a regulation providing that the article is not excluded from the dietary supplement definition. In other words, because the regulation provides that the article is not excluded from the dietary supplement definition, such 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.

Congress included section 201(ff)(3)(B) of the FD&C Act in the dietary supplement definition for two main reasons. The first reason is to prevent manufacturers from escaping appropriate safety and efficacy review and FDA oversight for drugs by classifying these products as dietary supplements. See, e.g., Statement of Sen. Kennedy ("There continue to be differences among us as to how to achieve these goals most effectively. For example, the Hatch legislation offers a definition of dietary supplements that many feel is too broad. It will allow certain products which are treated as prescription drugs in other countries, or as unapproved drugs in this country, to be treated as dietary supplements and therefore subjected to inadequate safeguards.") (Ref. 10); Statement of Sen. Harkin ("[T]he [Hatch-Harkin] compromise assures that prescription drugs cannot escape appropriate review and oversight by being classified as dietary

supplements. This concern was raised by a number of Senators and the legislation before us addresses it in a sensible manner.") (Ref. 11); Ref. 12, at V § 3 ("During consideration of S. 784, concerns were expressed that manufacturers or importers of drugs could avoid the drug approval process by marketing drug products as dietary supplements. Although current authorities should be adequate to deal with such potential problems, the committee is sensitive to those concerns. Accordingly, Senators Harkin and Hatch agreed to formulate additional language prior to consideration of S. 784 in the Senate."). The second reason is to protect the incentives for new drug development. Section 201(ff)(3)(B)(ii) of the FD&C Act provides that the term dietary supplement does not include an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, unless certain criteria are met. This clause extends the scope of the drug exclusion provision beyond approved new drugs, certified antibiotics, and licensed biologics, which are covered by sections 201(ff)(3)(A) and (B)(i) of the FD&C Act. Accordingly, Congress's inclusion of this provision in addition to sections 201(ff)(3)(A) and (B)(i) of the FD&C Act demonstrates that Congress sought to protect investigational new drugs, antibiotics, and biologics that are not yet approved, certified, or licensed. In other words, one of the overarching purposes of section 201(ff)(3)(B)(ii) of the FD&C Act is to protect the incentives for new drug development.

Congress chose to accomplish these goals by establishing a general framework under which a substance is excluded from the dietary supplement definition if its approval as a new drug (or its authorization for investigation as a new drug) preceded its marketing as a dietary supplement or a food. However, recognizing that applying this general framework would not always further these goals, Congress delegated authority to FDA to make exceptions in limited circumstances, through notice-and-comment rulemaking, so that a substance could be used in or as a dietary supplement even though it was approved as a new drug (or authorized for investigation as a new drug) before it was marketed as a dietary supplement or a food.

Accordingly, through the statutory structure, purpose, and legislative history of section 201(ff)(3)(B) of the FD&C Act, Congress limited FDA's authority to provide an exception for a substance that otherwise would be excluded from dietary supplements to situations where both of the following conditions are satisfied:

1. There would be adequate safeguards if the substance were regulated as a dietary supplement--i.e., regulation as a dietary supplement would provide appropriate review and oversight of the substance; and
2. Allowing use of the substance in or as a dietary supplement would be unlikely to impede new drug development.

Further, because Congress defined "dietary supplement" in section 201(ff) of the FD&C Act, this restricts FDA's rulemaking authority under section 201(ff)(3)(B) of the FD&C Act to articles that are capable of meeting the definition of dietary supplement. Thus, if an article is not a dietary ingredient as described in section 201(ff)(1) of the FD&C Act, that article itself is not capable of meeting the definition of dietary supplement, even if such article is not excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act. Accordingly, if an article is not a dietary ingredient, FDA cannot use its rulemaking authority under section 201(ff)(3)(B) of the FD&C Act to provide that such article may be a dietary supplement. Moreover, when FDA uses its rulemaking authority in section 201(ff)(3)(B) of the FD&C Act, the article that is the subject of the rule (e.g., NAC) becomes eligible to be used in or as a dietary supplement. In turn, a dietary supplement that is or contains such article would be deemed a food under section 201(ff) of the FD&C Act and subject to all applicable requirements for food as well as those requirements specific to dietary supplements under the FD&C Act and FDA regulations.

One consequence of a dietary supplement being deemed a food is that section 301(ll) of the FD&C Act, which applies to food, would apply to the dietary supplement. Section 301(ll) of the FD&C Act makes it a prohibited act to introduce or deliver for introduction into interstate

commerce any food to which has been added a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public unless an exception applies. One exception is if we have issued a regulation, after notice-and-comment rulemaking, approving the use of the drug or biological product in the food (section 301(ll)(2) of the FD&C Act).

Given the statutory language and structure of sections 201(ff) and 301(ll) of the FD&C Act, with respect to dietary supplements, the rulemaking authority provided by section 301(ll)(2) of the FD&C Act is inextricably linked with the rulemaking authority provided by section 201(ff)(3)(B) of the FD&C Act. That is, if we use our rulemaking authority under section 201(ff)(3)(B) of the FD&C Act to provide that an article is not excluded from the dietary supplement definition, that article would be eligible for use in or as a dietary supplement, and a dietary supplement that is or contains such article would be deemed a food under section 201(ff) of the FD&C Act and, thus, would be subject to section 301(ll) of the FD&C Act. However, if we do not simultaneously use our rulemaking authority under section 301(ll)(2) of the FD&C Act to provide that the addition of such article to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act, this would lead to an illogical result. Specifically, the rule would make the article eligible for use in or as a dietary supplement and also bring that product within the scope of section 301(ll) of the FD&C Act, thereby making it a prohibited act under section 301(ll) of the FD&C Act to add the article to a dietary supplement. Accordingly, if we exercise our rulemaking authority under section 201(ff)(3)(B) of the FD&C Act to provide that an article is not excluded from the definition of dietary supplement, we would necessarily exercise our rulemaking authority under section 301(ll)(2) of the FD&C Act to provide that the addition of such article to a dietary supplement is not a prohibited act under section 301(ll) of the FD&C Act. Thus, in addition to the authority specified in section 201(ff)(3)(B) of the FD&C

Act, section 301(ll)(2) of the FD&C Act provides authority to issue this proposed regulation.

In addition to the authority specified in sections 201(ff)(3)(B) and 301(ll)(2) of the FD&C Act to issue this proposed regulation, section 701(a) of the FD&C Act gives us the authority to promulgate regulations for the efficient enforcement of the FD&C Act.

## IV. Application of Rulemaking Authority to NAC

We are aware that, for more than 30 years, NAC has been available for sale in the United States both as FDA-approved drugs and as products improperly labeled as dietary supplements. As discussed above, FDA may use its rulemaking authority under section 201(ff)(3)(B) of the FD&C Act to remove an ingredient from the dietary supplement exclusion and regulate such ingredient as a dietary supplement when such ingredient can be appropriately regulated as a dietary supplement and such removal would be unlikely to negatively impact drug development. We are proposing to apply this rulemaking authority to NAC based on its safety profile and the minimal, if any, impact this rule is likely to have on NAC drug development.

### *A. Safety Assessment of NAC In or As a Dietary Supplement*

To help inform the decision of whether to exercise FDA's rulemaking authority for NAC, FDA reviewed published information on the use and safety of NAC. Safety determinations related to the FDA drug approval for NAC are not directly applicable to the safety assessment of NAC as a dietary supplement, because drug safety review relies on a risk/benefit paradigm, whereas a safety assessment for a dietary supplement generally considers only risk. Therefore, to support the safety assessment of NAC as a dietary supplement, we collected safety endpoints from published studies using NAC in a variety of clinical contexts, largely outside its approved drug use. Specifically, we conducted a systematic review of studies of orally administered (i.e., ingested) NAC to assess the adverse events (AEs) associated with NAC use in order to demonstrate an expectation of safety for NAC in or as a dietary supplement (Ref. 13). The protocol, results analysis, and conclusions underwent external peer review, as indicated on FDA's Peer Review of Scientific Information and Assessments webpage (id.).

The systematic review identified 41 studies of high confidence, which were used for conclusions on AEs and NAC exposure (id.). One study identified a significant increase in nausea among NAC-treated patients, but most other studies reported no AEs or AEs that were not significantly different from non-NAC-treated comparators (id.). Studies included high NAC doses (up to 9000 milligrams (mg) per day (d)) and long durations (up to 3 years), which did not demonstrate an increase in AE reporting (id.). Doses used in the NAC clinical studies were comparable to the recommended serving of available NAC-containing products labeled as dietary supplements, demonstrating similarity of NAC exposure and, therefore, a similar safety profile (id.).

This systematic review evaluated the NAC literature on studies of orally administered (i.e., ingested) NAC in healthy and patient populations to estimate a qualitative Level of Concern (LoC) for the known AEs related to NAC, then translated that LoC conclusion to an expectation of safety for NAC in or as a dietary supplement (id.). A "minimal" LoC was concluded based on the consistent reporting of no AEs or statistical conclusion that reported AEs were not attributed to NAC. The concern level was selected from the 5-point scale developed by the National Toxicology Program to provide a standardized summary of risk concern levels (Ref. 14). The reported AEs were found across disparate populations (e.g., from healthy individuals to patients with end-stage renal disease) and varied exposure conditions (e.g., 200 mg/d to 9000 mg/d, for durations 5 days to 3 years); the noted exception is a singular report of non-serious nausea, which would be expected with ingestion of a sulfurous compound (Ref. 13). The commonly reported AEs in the NAC clinical data set are gastrointestinal (GI) pain/discomfort, nausea, vomiting, and rash, and suggest that these non-serious GI-related symptoms may occur in relation to NAC exposure, although only statistically proven in one study reviewed (id.).

NAC exposure from commercially available products labeled as dietary supplements based on the labeled serving size was compared to the doses reported in the collective NAC clinical data. There was significant overlap of the recommended servings of NAC in products

labeled as dietary supplements with the doses of the NAC clinical studies. NAC-containing products labeled as dietary supplements recommend a serving of 600 mg/d, 1000 mg/d, or 1200 mg/d more frequently than other serving sizes, similar to the multiple studies that investigated a 1200 mg/d NAC dose. Based on the overlapping exposure to NAC, the conclusions of the systematic review derived from the study groups are relevant to the demonstration of an expectation of safety for NAC in or as a dietary supplement (id.).

Accordingly, we concluded a minimal LoC for the reports of GI-related AEs associated with NAC administration (id.). The studied doses were inclusive of the recommended servings of commercially available NAC-containing products labeled as dietary supplements (id.). As such, the minimal concern can be directly translated to a reasonable expectation of safety for the use of NAC in or as a dietary supplement based on the systematic review of clinical NAC studies (id.).

*B. Impact on Drug Development*

As stated previously, we first approved NAC as a new drug under NDA 013601 for oral inhalation under the brand name "Mucomyst" in 1963 (see 28 FR 13509, December 13, 1963). NDA 013601 was withdrawn in 2009 at the sponsor's request for reasons other than safety or effectiveness (see 78 FR 67365, November 12, 2013). In addition, Cumberland Pharmaceuticals Inc. received approval for acetylcysteine (injectable) under brand name Acetadote on January 23, 2004, under NDA 021539. Acetadote is an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in adults and pediatric patients who weigh 5 kilograms or greater with acute ingestion or from repeated supratherapeutic ingestion. We are aware of at least 19 Abbreviated New Drug Applications (ANDAs) for the active ingredient acetylcysteine (as of April 2, 2026, a search of the term "acetylcysteine" in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations identified 19 current ANDAs (see https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm). Most of these ANDAs received approval after 1991, the first-known marketing of NAC in or as a dietary supplement. For

example, Hospira Inc. received approval for ANDA 073664 and ANDA 074037 on August 30, 1994. Luitpold Pharmaceuticals Inc. (now American Regent, Inc.) also received approval for ANDA 072489 and ANDA 072547 on July 28, 1995. As a drug product, acetylcysteine is approved for the indication described above (i.e., prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen) as well as an adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in certain conditions, such as chronic bronchopulmonary disease. Thus, NAC is currently approved as a new drug under section 505 of the FD&C Act and has been continuously approved as a new drug under section 505 of the FD&C Act since September 14, 1963. Since at least August/September 1991, NAC has been available for sale in the United States both as FDA-approved drugs and as products labeled as dietary supplements.

Similarly, a search to identify the number of clinical trials for NAC, some of which correspond to Investigational New Drug applications (INDs), revealed 832 different trials regarding the use of NAC as a drug (see Ref. 15). This illustrates the fact that researchers continue to study NAC, including for use as a drug, even though NAC-containing products labeled as dietary supplements have been sold in the United States for more than 30 years.

NAC-containing products improperly labeled as dietary supplements have been sold in the United States since at least August/September 1991 (Ref. 2). When Congress defined the term "dietary supplement" in 1994, NAC became ineligible to be lawfully sold as a dietary supplement in the United States, but firms illegally continued to sell NAC-containing products labeled as dietary supplements in the United States. During a period of more than 30 years, the sale of NAC-containing products improperly labeled as dietary supplements in the United States does not appear to have negatively impacted NAC drug development.

Given the existence, study, and development of NAC-containing drug products for over 30 years despite the continued sale of NAC-containing products improperly labeled as dietary supplements, we have no reason to believe that removing the dietary supplement exclusion for

NAC-containing products and allowing for their sale and regulation as dietary supplements will have an impact on any current or future development of NAC-containing drug products. We invite comment on whether the sale of NAC-containing products labeled as dietary supplements in the United States has negatively impacted NAC drug development or is anticipated to in the future.

We also note that in the notice announcing the availability of the draft enforcement discretion guidance (see 87 FR 24170, April 22, 2022), we stated that we were considering initiating rulemaking under section 201(ff)(3)(B) of the FD&C Act to allow the use of NAC in or as a dietary supplement and, if, among other considerations, we did not identify safety-related concerns as we continued to review the available data and information, we were likely to propose a rule providing that NAC is not excluded from the dietary supplement definition (id. at 24171). We provided a 30-day comment period for the guidance; although, as is the case for all FDA guidance documents, parties may ask that we revise or withdraw an existing guidance document at any time (21 CFR 10.115(f)(4)). To date, we have not received any comments expressing concern or providing data to demonstrate that allowing the sale of NAC in or as a dietary supplement would impact drug development or identifying any other concerns.

## V. Description of the Proposed Rule

Section 201(ff)(3)(B) of the FD&C Act authorizes FDA to issue a regulation, after notice-and-comment rulemaking, finding that an article previously excluded from the dietary supplement definition would no longer be excluded and, therefore, would be lawful under the FD&C Act for sale as a dietary supplement, provided that such product is not otherwise in violation of the FD&C Act. This proposed rule, if finalized, would remove the exclusion of NAC from the dietary supplement definition.

We propose to provide that certain ingredients are not excluded for use in or as a dietary supplement under section 201(ff)(3)(B) of the FD&C Act and that the addition of such ingredients to a dietary supplement is not a prohibited act under section 301(ll) of the

FD&C Act (see proposed § 190.1). Specifically, proposed § 190.1 would list "N-acetyl-L-cysteine" as the sole ingredient under proposed § 190.1(a), and we would reserve a new paragraph (b) to allow for additional ingredients to be added in the future. Thus, under proposed § 190.1(a), NAC would be allowed in or as a dietary supplement, provided that the NAC-containing product otherwise meets the dietary supplement definition under section 201(ff) of the FD&C Act. Such NAC-containing products would, therefore, be subject to the requirements that apply to dietary supplements under the FD&C Act and FDA's implementing regulations. Any adulterated or misbranded dietary supplement product may be subject to compliance or enforcement action. For example, if a dietary supplement has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations (section 402(g)(1) of the FD&C Act (21 U.S.C. 342(g)(1)); 21 CFR part 111), it may be subject to compliance or enforcement action.

## VI. Proposed Effective Date

We propose that any final rule resulting from this rulemaking become effective immediately upon publication of the final rule. As this rule would relieve a restriction, it can take effect sooner than 30 days after publication in the *Federal Register* (see 5 U.S.C. 553(d)(1)). We request comment on this proposed effective date.

## VII. Preliminary Economic Analysis of Impacts

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.

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 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 estimates 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: |

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. Any potential impacts from this behavior change for either industry or consumers are uncertain and difficult to predict; though, for the reasons discussed elsewhere in this document, FDA expects this rule is unlikely to negatively impact NAC drug development.

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. The 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.

We have developed a full Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full preliminary analysis of economic impacts is available in the docket for this proposed rule (Ref. 16) and at https://www.fda.gov/about-fda/economics-

staff/regulatory-impact-analyses-ria.

## VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

## X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

## XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. FDA invites comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

## XII. References

The following references marked with an asterisk (*) are on display at the Dockets

Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. Oxy-Nectar, Advertisement, Vegetarian Times, February 1995.

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*7. Center for Food Safety and Applied Nutrition. Warning Letter from William A. Correll, Jr., Director, Office of Compliance, Center for Food Safety and Applied Nutrition, to John Heathco, CEO, LES Labs, July 23, 2020. Accessed January 23, 2025. Available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/les-labs-593764-07232020.

*8. Center for Food Safety and Applied Nutrition. Warning Letter from William A. Correll, Jr., Director, Office of Compliance, Center for Food Safety and Applied Nutrition, to Monir Elias, CEO, Purple Biosciences, LLC, July 23, 2020. Accessed January 23, 2025. Available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/purple-biosciences-llc-593772-07232020.

*9. U.S. Food and Drug Administration. “Guidance for Industry: Policy Regarding N-acetyl-L-cysteine, August 2022.” Accessed January 23, 2025. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-policy-regarding-n-acetyl-l-cysteine.

*10. U.S. Congress. Senate. Congressional Record, Proceedings and Debates of the 103rd Congress, Second Session. Vol 140, Part 16. 103rd Cong., 2nd sess., August 13, 1994. p. 22413. Accessed September 9, 2025. Available at: https://www.govinfo.gov/app/details/GPO-CRECB-1994-pt16/.

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*12. U.S. Congress. Senate. Committee on Labor and Human Resources. *Conference Report to accompany S. 784*. Senate Report No. 103-410, 103rd Cong., 2nd sess., October 8, 1994.

*13. U.S. Food and Drug Administration. Safety Assessment for Ingested N-acetylcysteine Exposure: A Systematic Review. November 2026. Available at: https://www.fda.gov/science-research/peer-review-scientific-information-and-assessments/completed-peer-reviews.

*14. Jahnke, G.D., A. Iannucci, A. Scialli, et al. "Center for the Evaluation of Risks to Human Reproduction—The First Five Years." Birth Defects Research (Part B): Developmental and Reproductive Toxicology 74: 1-8. Wiley-Liss, Inc., February 2005. Accessed January 23, 2025. Available at https://doi.org/10.1002/bdrb.20028.

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**List of Subjects in 21 CFR Part 190**

Food additives, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 190 be amended as follows:

**PART 190--DIETARY SUPPLEMENTS**

1. The authority citation for part 190 continues to read as follows:

Authority: Secs. 201(ff), 301, 402, 413, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(ff), 331, 342, 350b, 371).

2. Add subpart A, consisting of § 190.1, to read as follows:

**Subpart A--Dietary Supplement Ingredients**

**§ 190.1 Dietary ingredients not excluded from the dietary supplement definition.**

The following ingredients, which would otherwise be excluded from the dietary supplement definition, are not excluded for use in or as a dietary supplement under section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) and the addition of such ingredients to a dietary supplement is not a prohibited act under section 301(ll) of the Act:

(a) N-acetyl-L-cysteine.

(b) [Reserved]

Robert F. Kennedy, Jr.,

*Secretary,*

*Department of Health and Human Services*

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