Policy Regarding N-acetyl-L-cysteine: Guidance for Industry

Draft Guidance

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Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that FDA considers your comment on this draft guidance before we begin work on the final version of the guidance, submit either electronic or written comments on the draft guidance within 30 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2022-D-0490 listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Center for Food Safety and Applied Nutrition (CFSAN), Office of Dietary Supplement Programs at 855-543-3784 or 240-402-2375.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

April 2022

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Policy Regarding N-acetyl-L-cysteine: Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

The purpose of this guidance is to advise dietary supplement manufacturers, distributors, and other stakeholders of our intent to exercise enforcement discretion with respect to the sale and distribution of certain products that contain N-acetyl-L-cysteine (NAC) [2] and are labeled as dietary supplements. As described below, the enforcement discretion policy would apply to products that would be lawfully marketed dietary supplements if NAC were not excluded from the definition of "dietary supplement" and that are not otherwise in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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II. Background

Section 201(ff)(3)(B) of the FD&C Act (21 U.S.C. 321(ff)(3)(B)) defines the term "dietary supplement" to exclude:

> (i) an article that is 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 (42 U.S.C. 262), or

[1] This guidance has been prepared by the Office of Dietary Supplement Programs and the Office of Regulations and Policy, both in the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration.
[2] 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 active ingredient.

> (ii) 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,
>
> which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act.

Thus, if an article has been approved as a new drug under section 505 of the FD&C Act (21 U.S.C. 355), products containing that article are outside the definition of a dietary supplement unless either of two exceptions applies. First, there is an exception if the article was marketed as a dietary supplement or as a food before such approval. Second, there is an exception if FDA (under authority delegated by the Secretary of Health and Human Services) issues a regulation, after notice and comment, finding that the article would be lawful under the FD&C Act.

FDA has determined that 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. Specifically, NAC (i.e., acetylcysteine) was approved as a new drug under section 505 of the FD&C Act on September 14, 1963 (see 28 FR 13509 (Dec. 13, 1963) (announcing the approval)). FDA is not aware of any evidence that NAC was marketed as a dietary supplement or as a food prior to September 14, 1963. As discussed below in Section III, FDA recently confirmed NAC's exclusion from the dietary supplement definition in response to two citizen petitions.[3] However, we are 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 (i.e., to provide by regulation that NAC is not excluded from the definition of dietary supplement), and, if, among other considerations, FDA does not identify safety-related concerns as we continue our review of the available data and information, we are likely to propose a rule providing that NAC is not excluded from the definition of dietary supplement.

III. Discussion

FDA received two citizen petitions, one from the Council for Responsible Nutrition (CRN) dated June 1, 2021, and one from the Natural Products Association (NPA) dated August 18, 2021, 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. In addition, the citizen petition from NPA asked FDA "in the alternative, to recommend and support to the Secretary of HHS, that they issued [*sic*] a regulation, after notice and comment, finding that NAC, would be lawful under the [FD&C Act]."

FDA issued tentative responses to these petitions on November 24, 2021, stating that we had not reached a decision on the petitions because of the complex nature of the requests and ongoing research we are working to complete. In addition, to help us evaluate NPA's request to initiate

[3] Docket Nos. FDA-2021-P-0523 & FDA-2021-P-0938.

rulemaking, we asked that interested parties submit information to the NPA docket (FDA-2021-P-0938) regarding the safe use of NAC as or in dietary supplements and data regarding potential safety concerns.

FDA issued a joint final response to both petitions on March 31, 2022, denying the CRN petition in its entirety and denying the NPA petition's first request. In this response, FDA stated that NAC products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act. In addition, we explained that we had not yet reached a final decision on the NPA petition's request to initiate rulemaking and that we are 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. While FDA's full safety review of NAC remains ongoing, our initial review has not revealed safety concerns with respect to the use of this ingredient in or as a dietary supplement. In addition, NAC-containing products represented as dietary supplements have been sold in the U.S. for over 30 years, and consumers continue to seek access to such products.

Accordingly, as described below, we intend to exercise enforcement discretion with respect to the sale and distribution of certain products that contain NAC and are labeled as dietary supplements. The enforcement discretion policy would apply to products that would be lawfully marketed dietary supplements if NAC were not excluded from the definition of "dietary supplement" and that are not otherwise in violation of the FD&C Act. For example, with respect to the sale of an NAC-containing product that is labeled as a dietary supplement, FDA does not intend to object solely because the product is intended to affect the structure or any function of the body of man and, therefore, is a drug under section 201(g)(1)(C) of the FD&C Act (21 U.S.C. 321(g)(1)(C)).[4] However, this enforcement discretion policy would not apply to an NAC-containing product that is labeled as a dietary supplement but is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and, therefore, is a drug under section 201(g)(1)(B) of the FD&C Act. Likewise, for example, the enforcement discretion policy would not apply to NAC-containing products that are adulterated or misbranded under the FD&C Act (other than those misbranded only because they contain NAC and are labeled as dietary supplements).

Unless we identify safety-related concerns during our ongoing review, FDA intends to exercise enforcement discretion until either of the following occurs: we complete notice-and-comment rulemaking to allow the use of NAC in or as a dietary supplement (should we move forward with such proceedings) or we deny the NPA citizen petition's request for rulemaking. Should we determine that this enforcement discretion policy is no longer appropriate, we will notify stakeholders by withdrawing or revising this guidance in accordance with 21 CFR 10.115.

[4] Under section 201(g)(1)(C) of the FD&C Act, the term "drug" includes "articles (other than food) intended to affect the structure or any function of the body of man or other animals." However, section 201(g)(1) of the FD&C Act provides that a dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) of the FD&C Act (e.g., a statement that describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans or characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function) is not a drug under section 201(g)(1)(C) of the FD&C Act solely because the label or the labeling contains such a statement. This exception does not apply to a product that is or contains an article that is excluded from the definition of dietary supplement, even if such product is labeled as a dietary supplement.