



Council for Responsible Nutrition

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December 4, 2020

Mr. Steven Tave, Director
Office of Dietary Supplement Programs
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
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Mr. Tave,

On behalf of the Council for Responsible Nutrition (CRN),¹ we urge FDA to reverse its recently adopted position that the Federal Food, Drug, and Cosmetic Act (FDCA) prohibits manufacturers from marketing products containing N-acetyl-L-cysteine (NAC) as dietary supplements. This policy—which represents a sudden and drastic departure from past Agency practice—is legally invalid. As such, FDA should revert to its longstanding policy of allowing manufacturers to market products containing NAC as dietary supplements.

For decades, manufacturers have safely marketed products containing NAC as dietary supplements in the United States. There are currently hundreds of dietary supplements containing NAC on the market,² and thousands of consumers have come to rely on these products as a crucial source of nutrients. And, until recently, FDA has consistently and affirmatively permitted manufacturers to market these products. In fact, FDA has considered over 100 structure-function claim notifications regarding NAC and at least one qualified health claim petition for a dietary supplement containing NAC, and has not objected to the presence of NAC in any of these products.³

But, in July 2020, FDA enacted a sudden policy change by issuing multiple warning letters asserting that products containing NAC cannot be marketed as dietary supplements under section 201(ff)(3)(B)(i) of the FDCA.⁴ Section 201(ff)(3)(B)(i) prohibits manufacturers from marketing

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control, and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

² See NIH, *Dietary Supplement Label Database*, <https://dslid.od.nih.gov/dslid/lstIngredients.jsp?item=N-acetyl-L-cysteine>.

³ See Josh Long, *FDA Warning Letters on NAC Cause Stir in Supplement Sector*, Natural Products Insider (Aug. 11, 2020), <https://www.naturalproductsinsider.com/regulatory/fda-warning-letters-nac-cause-stir-supplement-sector>.

⁴ See, e.g., FDA, *Warning Letter to LES Labs, MARCS-CMS 593764* (July 23, 2020), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning->

products as dietary supplements if they contain an article that FDA has approved as a new drug under section 505 of the Act, unless that article was marketed in dietary supplements or food before it was approved as a drug (often called the “drug preclusion clause”). FDA’s warning letters assert that NAC was approved as a new drug in 1963 and, to FDA’s knowledge, was not marketed as a dietary supplement prior to that date. As such, FDA claims that products containing NAC cannot be marketed as dietary supplements. FDA has failed to provide any rationale for this policy change other than the basic assertions made in these warning letters.

FDA’s sudden policy change is legally invalid on multiple grounds. First, it is not even clear, from FDA records, whether section 201(ff)(3)(B)(i) applies to NAC as a dietary supplement. The decades-old records for NAC drug approval contain unreliable information, such as handwritten dates, and unverifiable information. Second, NAC drugs approved prior to 2016 appear to be comprised of different forms of NAC from that which is found in a dietary supplement. Third, interpreting FDCA section 201(ff)(3)(B)(i) to prohibit the marketing of dietary supplements containing NAC violates the well-established presumption against statutory retroactivity. CRN’s review of the drug approval records for NAC, and subsequent discovery of unreliable and conflicting information, demonstrates one of the significant dangers of statutory retroactivity. FDA’s policy change also is an arbitrary and capricious agency action that is invalid under the Administrative Procedure Act (APA). And finally, the equitable defense of laches prevents FDA from enforcing its new policy. For these reasons, we urge FDA to reverse this policy change and revert to its longstanding policy of allowing manufacturers to market dietary supplements containing NAC.

I. FDA’s records do not reliably demonstrate that section 201(ff)(3)(B)(i) applies to NAC.

CRN reviewed numerous FDA records on NAC to determine whether section 201(ff)(3)(B)(i) would even apply, absent other concerns with FDA’s retroactive application of this section and inconsistent policy in applying this section to NAC. The records contain a number of flaws that CRN believes make them unreliable to support an argument that NAC was approved as a new drug prior to NAC being marketed as a dietary supplement.

In the 2020 warning letters, FDA asserted that “NAC was approved as a new drug under section 505 of the Act [21 U.S.C. § 355] on September 14, 1963.”⁵ In the only other document, prior to the 2020 warning letters, that CRN could find alleging NAC was approved as a drug before it was used as a dietary supplement, FDA states that the agency “first approved N-Acetylcysteine (NAC) as a new drug in 1985.”⁶ In fact, neither date appears to be reliable.

[letters/les-labs-593764-07232020#:~:text=FDA%20is%20not%20aware%20of,in%20connection%20with%20your%20products.](https://www.fda.gov/oc/letters/les-labs-593764-07232020#:~:text=FDA%20is%20not%20aware%20of,in%20connection%20with%20your%20products.)

⁵ See *supra* n. 4.

⁶ See Feb. 2, 2011 Letter from F. Hines, FDA Consumer Safety Officer, Division of Dietary Supplement Programs to Tira Pharmaceuticals regarding N-acetylcysteine (NAC) ethyl ester 75 Day Premarket Notification of New Dietary Ingredient.

For the drug purportedly approved in 1963, CRN obtained the attached letter through a Freedom of Information Act (FOIA) request.⁷ The letter contains what appears to be a handwritten approval date of “1963”. This handwritten notation raises a number of questions about the reliability of this record, not the least of which is whether the approval date was actually 1963 or sometime later, why was the approval date handwritten, when was the notation made, and who made it. This is not the type of document that should be regarded as authentic. The unreliability of a handwritten date is exactly the type of issue that FDA likely would raise for a dietary supplement company providing similar evidence that an ingredient was marketed as a supplement before being approved as a drug. CRN has been unable to verify whether an NAC drug was approved in 1985, as there appear to be no drugs with NAC as an active ingredient listed in FDA’s Orange Book with a 1985 approval date.⁸

Another, even larger issue, appears to have been overlooked in the 2020 warning letters when FDA cited the 1963 approval as evidence that NAC is precluded from being a dietary supplement due to section 201(ff)(3)(B)(i). The 1963 approval, according to the document obtained by CRN, was for an inhaled drug.⁹ For section 201(ff)(3)(B)(i) to apply, the dietary supplement ingredient must be the same “article” as the approved drug. An inhaled substance should not be treated as the same article as an orally consumed substance. To do so would go against FDA’s own significant precedent and guidance. For example, for drug approval FDA would not consider an inhaled drug to be “the same” as an orally ingested drug, as the route of administration and dosage form, among other requirements, are considered by the agency.¹⁰ Further, a dietary supplement, by definition, must be “a product that . . . is intended for ingestion.”¹¹ Because of this limitation, a dietary supplement would, by its very nature, differ significantly in the route of administration and dosage form from an inhaled drug. Such significant differences, which will affect a substance’s impact on the human body, must preclude an inhaled ingredient from being considered the same “article” as an orally ingested ingredient.

The NAC drug approval record indicates that no NAC drug was approved for oral use only until 2016 – well after dietary supplement companies had been marketing NAC as a supplement. The Orange Book shows that NAC drugs were approved for “inhalation, oral” as early as 1982, however, the earliest that an NAC drug was approved for “inhalation, oral” form and route of administration and that has not been discontinued is August 1994. It is not clear (1) whether these inhaled/oral drugs could even be considered the same “article” as NAC used in a dietary supplement due to their dual route of exposure; and (2) whether the approval date of discontinued drugs should be used to determine the date of preclusion for dietary supplement use. With regard to discontinued drugs, section 201(ff)(3)(B) does include a clause precluding supplement use where a drug is approved for investigation, substantial clinical investigations are actually

⁷ See Attachment A.

⁸ Documents obtained through another FOIA search suggest that the 1985 date may be related to an approval for oral/intubation use for NAC as an additional indication for the drug purportedly approved in 1963, but the approval date is not included in the Orange Book as 1985. Even if this date is correct, CRN has concerns that the record does not reliably show that the NAC form of the drug approved prior to 1994 is the same “article” as NAC used in supplements, as described in more detail in this section.

⁹ See Attachment A, pg. 4 (the approved drug is a “mucolytic agent” intended to be taken “via face mask or mouthpiece (aerosolized) or . . . into a tent or croupette . . .”).

¹⁰ FDCA § 505(2)(A)(iii).

¹¹ FDCA § 201(ff)(2)(A).

conducted, and those clinical investigations made public. But, to invoke such a clause, to determine a specific preclusion date pre-1994 would require a record that those criteria were all met before NAC was marketed as a dietary supplement (in addition to the drug and dietary supplement being the same article) – likely a difficult task for FDA to demonstrate on records that are over 25 years old. As discussed in Section II below, NAC was being marketed as a dietary supplement well before October 1994. The conflicting nature of information in FDA documents and the difficulty in obtaining accurate information as to when NAC was in fact approved as a drug that could be considered the same “article” as an NAC supplement also underscores CRN’s significant concern that section 201(ff)(3)(B)(i) was never intended to be applied retroactively.

II. FDA’s interpretation of section 201(ff)(3)(B)(i) violates the well-established presumption against statutory retroactivity.

Even if FDA records reliably demonstrated drug approval before 201(ff)(3)(B)(i) was enacted, it is a well-established canon of statutory interpretation that legislation shall not be read to have a retroactive effect on private rights unless Congress expresses a clear, unambiguous intent to the contrary.¹² This “presumption against statutory retroactivity” ensures that Congress has “affirmatively considered the potential unfairness of retroactive application and determined that it is an acceptable price to pay for the countervailing benefits.”¹³ Courts have long held that this presumption is particularly important in the context of property rights, for which “predictability and stability are of prime importance.”¹⁴

FDA’s interpretation of section 201(ff)(3)(B)(i) is wholly inconsistent with the presumption against statutory retroactivity. Congress enacted section 201(ff)(3)(B)(i) as part of the Dietary Supplement Health and Education Act of 1994 (DSHEA),¹⁵ which took effect on October 25, 1994. Thus, the definitional exclusion established by section 201(ff)(3)(B)(i) should be read to have *proactively* prohibited products containing articles that were approved as new drugs *after* October 25, 1994 from being marketed as dietary substances, unless such articles were marketed in dietary supplements prior to approval. By contrast, section 201(ff)(3)(B)(i) should only be read to *retroactively* apply to products containing articles that were approved as new drugs *before* October 25, 1994 if Congress expressed a clear, unambiguous intent for this provision to have a retroactive effect. A thorough review of both the text of DSHEA and the legislative history of this provision indicates that Congress expressed no clear intent for this provision to have a retroactive effect. Thus, this provision should not be applied in a retroactive manner.

¹² See *Landgraf v. USI Film Products*, 511 U.S. 244, 270 (1994) (“Since the early days of this Court, we have declined to give retroactive effect to statutes burdening private rights unless Congress had made clear its intent.”); see also *United States v. Heth*, 7 U.S. (3 Cranch) 399, 413 (1806) (opinion of Paterson, J.) (“Words in a statute ought not to have a retrospective operation, *unless they are so clear, strong, and imperative, that no other meaning can be annexed to them*, or unless the intention of the legislature cannot be otherwise satisfied.”) (emphasis added).

¹³ *Landgraf*, 511 U.S. at 271.

¹⁴ *Id.* at 272–73.

¹⁵ Pub L. No. 103-417, 108 Stat. 4325 (1994).

Further, Congress created section 201(ff)(3)(B)(i) to protect commercial interests necessary to incentivize new drug development in the wake of DSHEA's enactment.¹⁶ A retroactive application of this section does nothing to incentivize new drug development because drugs and supplements that were both on the market prior to DSHEA's passage already co-existed and drug companies developed these products with no expectation of DSHEA's protections. Finally, as described above, CRN's review of the NAC drug approval records demonstrates another danger of statutory retroactivity – that decades-old records are often unreliable.

Here, even if NAC was approved as a new drug *before* October 25, 1994 in a form that can be considered the same “article” as NAC found in dietary supplements, dietary supplements containing NAC were also marketed during the intervening years between NAC's approval as a drug and the enactment of DSHEA.¹⁷ So, FDA's application of section 201(ff)(3)(B)(i) to products containing NAC qualifies as a retroactive application of the statute. FDA may argue that companies could easily have reviewed drug approvals at DSHEA's passage and determined whether to continue to market an ingredient, but the industry had no reason to do so given that Congress expressed no clear retroactive intent for section 201(ff)(3)(B). Further, as discussed in Section I of this letter, a search of FDA's drug approvals published in the Orange Book would have returned unreliable and incomplete information. Because there is no evidence that Congress intended for this provision to have a retroactive effect, FDA's actions directly violate the presumption against statutory retroactivity, and will likely be struck down by any reasonable court.

III. FDA's policy change is an arbitrary and capricious agency action that is invalid under the Administrative Procedure Act.

It is a well-established principle of administrative law that an agency must provide a reasoned explanation when changing its policies.¹⁸ It is particularly important that agencies provide such an explanation when the agency's prior position has “engendered serious reliance interests” among those whom it affects.¹⁹ Policy changes that are not accompanied by an adequate

¹⁶ See, e.g., S. Rep. 103-410, Part V, § 3 (1994); 140 Cong. Rec. S11,709 (daily ed. Aug. 13, 1994).

¹⁷ The dietary supplement industry considers NAC to be a “grandfathered” ingredient (i.e., marketed prior to DSHEA's passage on October 25, 1994). FDA has never questioned this status. For example, nowhere in FDA's record has FDA challenged the numerous companies who sell NAC as marketing this product without submitting a new dietary ingredient notification (NDIN) – a requirement of ingredients that were not marketed as dietary supplements prior to DSHEA's passage.

¹⁸ See *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2125 (2016) (“One of the basic procedural requirements of administrative rulemaking is that an agency must give adequate reasons for its decisions.”); *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (stating that, when adopting policy changes, agencies “must examine the relevant data and articulate a satisfactory explanation for its action including a ‘rational connection between the facts found and the choice made.’”) (citations omitted).

¹⁹ See *F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 515–16 (2009); see also *Smiley v. Citibank (South Dakota), N.A.*, 517 U.S. 735, 742 (1996) (“Sudden and unexplained change . . . or change that does not take account of legitimate reliance on prior interpretation . . . may be ‘arbitrary, capricious [or] an abuse of discretion’ [under 5 U.S.C. § 706(2)(A)].”) (citations omitted).

explanation are deemed “arbitrary and capricious,” and are invalid under section 706(2)(A) of the Administrative Procedure Act (APA).²⁰

Here, FDA has implemented a sudden policy change without providing a well-reasoned explanation, and has done so in a manner that will affect thousands of industry and consumer stakeholders in whom the Agency has “engendered serious reliance interests.” As noted above, prior to July 2020, it was FDA’s longstanding policy to permit the marketing of dietary supplements containing NAC. FDA had reviewed over 100 30-day notifications of structure/function claims for NAC and never raised any issues with the drug preclusion clause. FDA also had reviewed a qualified health claim for NAC and failed to raise the drug preclusion clause. As part of the qualified health claim review process, FDA specifically assesses whether the substance that is the subject of the qualified health claim qualifies as a food or dietary ingredient in dietary supplements. In response to the qualified health claim petition involving NAC, FDA states that NAC is a dietary supplement.²¹ This record demonstrates that FDA continued to treat NAC as a dietary supplement, even after the FDA 2011 letter in which FDA purportedly determined that NAC was subject to drug preclusion due to a 1985 drug approval.²²

In response to the extensive history of NAC being treated by FDA as a dietary supplement, manufacturers have invested substantial resources to develop hundreds of such products, and thousands of consumers have come to rely on such products to meet their daily nutritional needs. Now, FDA has decided to not only change its decades-long policy, but to do so through the issuance of warning letters that fail to provide any reasonable explanation for this consequential policy shift. Given the widespread implications of FDA’s policy change—and the immense reliance interests of those whom it will effect—FDA’s failure to provide an adequate explanation for this change renders it an invalid, arbitrary and capricious agency action.

IV. The equitable defense of laches prevents FDA from enforcing its new policy.

The equitable defense of laches prohibits defendants from bringing unreasonably delayed legal claims.²³ To prevail in asserting this defense, defendants must establish (1) that the delay resulted from the plaintiff’s own lack of diligence, and (2) that the defendant has suffered undue prejudice

²⁰ See 5 U.S.C. § 706(2)(A).

²¹ Letter to T. Shea, Sevo Nutraceuticals, Inc., Re: Petition for a Qualified Health Claim for a Nutraceutical Formulation and Management of Behavior and Cognitive Difficulties that Can Accompany Dementia (Docket No. FDA-2016-Q-1523), p. 7 (“the agency concludes that the six individual substances in the petitioner’s dietary supplement are either components of food . . . or a dietary supplement that includes vitamins or other nutritional substances (i.e., N-Acetyl cysteine . . .)”) (available at <https://www.fda.gov/media/119441/download>).

²² See *supra*, n. 6.

²³ See *Gardner v. Pan. R.R. Co.*, 342 U.S. 29, 30 (1951). While the defense of laches is more commonly raised against private party plaintiffs, multiple courts have affirmed that this defense is available in response to suits brought by the government. See, e.g., *NLRB v. P*I*E Nationwide*, 894 F.2d 887, 894 (7th Cir. 1990) (“[L]aches is generally and we think correctly assumed to be applicable to suits by government agencies as well as by private parties.”); *Hickey v. Ill. Cent. R.R. Co.*, 220 N.E.2d 415, 426 (Ill. 1966) (“[T]he reluctance to apply equitable principles against the State does not amount to absolute immunity of the State from laches and estoppel under all circumstances.”).

as a result of the plaintiff's delay.²⁴ Here, manufacturers of dietary supplements containing NAC can demonstrate both.

First, FDA's decades-long delay in bringing enforcement action against manufacturers of dietary supplements containing NAC indisputably resulted from a lack of diligence by FDA, rather than an unawareness that these products were on the market. In fact, there is ample evidence that FDA has long been aware that these products are on the market, and that FDA has *actively* considered—and failed to object to—structure/function and qualified health claim petitions regarding products containing NAC. Thus, FDA's long-delayed enforcement against these products resulted from the Agency's own lack of diligence.

Second, FDA's long-delayed enforcement actions would severely prejudice manufacturers. Defendants can demonstrate prejudice by showing that a plaintiff's delayed action has caused economic losses that “could have otherwise [been] avoided had the suit been filed earlier.”²⁵ Here, manufacturers will suffer extreme economic consequences as a result of FDA's delayed enforcement. For decades, manufacturers have invested in developing and producing dietary supplements containing NAC, largely based on FDA's longstanding policy of allowing manufacturers to market these products. These expectation-backed investments have led to the development of hundreds of products that will be affected by FDA's new policy—products that manufacturers would not have developed had FDA taken prompt enforcement action. This large-scale economic prejudice, coupled with FDA's lack of diligence, will allow manufacturers to successfully invoke a laches defense in response to any attempt by FDA to take legal action against the marketing of dietary supplements containing NAC.

V. Conclusion

FDA's decision to deviate from its decades-long policy regarding the regulation of dietary supplements containing NAC is invalid on multiple legal grounds. Accordingly, we urge FDA to reverse this policy change and revert to its longstanding policy of allowing manufacturers to market dietary supplements containing NAC.

²⁴ See *Costello v. United States*, 365 U.S. 265, 282 (1961).

²⁵ See, e.g., *A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1033 (Fed. Cir. 1992) (“Economic prejudice may arise where a defendant and possibly others will suffer the loss of monetary investments or incur damages which likely would have been prevented by earlier suit.”); *Dennis Joslin Co., LLC v. Johnson*, 138 S.W.3d 197, 201 (Tenn. Ct. App. 2003).

Mr. Steven Tave
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Thank you for your consideration of this matter.

Sincerely,

A handwritten signature in black ink that reads "Steve Mister". The signature is cursive and somewhat stylized.

Steve Mister
President & CEO

A handwritten signature in blue ink that reads "M Olsen". The signature is cursive and includes a long horizontal line extending to the right.

Megan Olsen
Vice President & Associate General Counsel

Cc: Douglas Stearn, Deputy Director, Center for Food Safety and Applied Nutrition, FDA