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Re: Dockets Nos. FDA-2021-P-0523 & FDA-2021-P-0938

Dear Mr. Mister, Ms. Olsen, and Dr. Fabricant:

This letter responds to the above-referenced citizen petitions regarding N-acetyl-L-cysteine (NAC). As described below, the citizen petition from the Council for Responsible Nutrition (CRN) dated June 1, 2021 (CRN Petition), and the citizen petition from the Natural Products Association (NPA) dated August 18, 2021 (NPA Petition), both request that the Food and Drug Administration (FDA or we) change our position that products that contain NAC are excluded from the definition of dietary supplement under section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321(ff)(3)(B)) (the "exclusion clause"). In addition, the NPA Petition asks 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]." Given the subject matter overlap between the petitions, FDA has considered the petitions' requests together.

For the reasons stated below, FDA is denying the CRN Petition in its entirety and the NPA Petition's request that FDA reverse our position that products containing NAC are excluded from the definition of dietary supplement under the exclusion clause. FDA has not yet reached a decision on the NPA Petition's request that FDA undertake rulemaking to permit the use of NAC in or as a dietary supplement, but we are considering initiating rulemaking under section 201(ff)(3)(B) 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). Although FDA is still working to complete our review of the available data and information, our review thus far has not identified safety concerns with respect to the use of NAC in or as a dietary supplement. If, among other considerations, FDA does not identify such safety 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. Once we have completed our review and reached a decision, we intend to respond to the NPA Petition, in accordance with our regulations. In the interim, in light of the absence of safety concerns based on our review thus far, among other factors, we think it appropriate to consider exercising enforcement discretion

for products labeled as dietary supplements that contain NAC if such products would be lawfully marketed dietary supplements if NAC were not excluded from the definition of dietary supplement and are not otherwise in violation of the FD&C Act, and we intend to issue guidance on this topic.

I. Background

A. Legal Background

The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325, amended the FD&C Act to define the term "dietary supplement" and change the way dietary supplements are regulated. Under the exclusion clause, added by DSHEA, the term "dietary supplement" excludes:

> (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
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> (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,
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> 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.

As part of this new framework for dietary supplement regulation, DSHEA also amended the FD&C Act by adding section 413 (21 U.S.C. 350b), which defines the term "new dietary ingredient" (NDI) and requires the manufacturer or distributor of an NDI, or of the dietary supplement that contains the NDI, to submit a premarket notification to FDA (an NDI notification) unless the exception described in section 413(a)(1) of the FD&C Act applies. Under section 413(d) of the FD&C Act,[1] the term "new dietary ingredient" is defined as "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."

Unlike section 413 of the FD&C Act, the exclusion clause does not distinguish between dietary ingredients marketed before October 15, 1994, and those first marketed after October 15, 1994. Nor does the exclusion clause distinguish between drugs approved before October 15, 1994, and those approved after October 15, 1994.

[1] Current section 413(d) of the FD&C Act was added by DSHEA as section 413(c) of the FD&C Act. The FDA Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat. 3885, amended section 413 of the FD&C Act by redesignating subsection (c) as subsection (d) and inserting a new subsection (c).

Under case law interpreting section 201(ff)(3)(B) of the FD&C Act, either an entire product or a product component may be "an article that is approved as a new drug" or an article "authorized for investigation as a new drug" for purposes of the exclusion clause. *See Pharmanex v. Shalala*, 221 F.3d 1151, 1154-60 (10th Cir. 2000). *Pharmanex* involved a product called Cholestin that was marketed as a dietary supplement. The sole ingredient in Cholestin was red yeast rice, which is a dietary ingredient under section 201(ff)(1) of the FD&C Act. Unlike traditional red yeast rice, however, the red yeast rice in Cholestin had been manufactured to contain high levels of lovastatin, the active ingredient[2] of the prescription drug Mevacor, which FDA approved in 1987. In addition to manufacturing Cholestin to contain lovastatin, Pharmanex also marketed Cholestin for its lovastatin content.

In an administrative decision, FDA found, among other things, that: (1) lovastatin was an "article approved as a new drug" within the meaning of the exclusion clause because it was the active ingredient in Mevacor, and (2) by marketing Cholestin as a dietary supplement for its lovastatin content, Pharmanex was also marketing lovastatin, and therefore lovastatin was an "article . . . marketed as a dietary supplement" within the meaning of the exclusion clause. Based on these findings, FDA concluded that Cholestin was excluded from the dietary supplement definition under the exclusion clause because the approval of Mevacor as a new drug preceded Pharmanex's marketing of lovastatin as a dietary supplement.

Pharmanex challenged FDA's decision, and the district court ruled for Pharmanex, holding that only finished drug products, not individual active ingredients like lovastatin, can be considered "articles approved as new drugs" for purposes of the exclusion clause of the dietary supplement definition. The U.S. Court of Appeals for the Tenth Circuit reversed, upholding FDA's interpretation of the term "article" in the exclusion clause to include active ingredients as well as finished drug products. The Tenth Circuit, in examining the statutory text, found that "article" in section 201(ff)(3) of the FD&C Act was ambiguous based on, among other things, contrasting use of the narrower term "product" in other parts of the dietary supplement definition,[3] the use of "article" in the drug definition to refer to both finished drug products and their components,[4] and on provisions of the FD&C Act and FDA regulations indicating that active ingredients, as well as finished drug products, are the subject of clinical investigations and are approved in the new drug application process.[5] *Pharmanex,* 221 F.3d at 1155-56.

The court of appeals then held that FDA's interpretation of "article" in the exclusion clause to include active ingredients was entitled to deference under *Chevron, U.S.A. v. Natural Resources Defense Council,* 467 U.S. 837 (1984). The court found that FDA's interpretation "comport[ed] with common sense and the overall purposes of the [FD&C Act]" in that under a contrary interpretation limiting "article" to finished products, manufacturers would be able to market dietary supplements with components identical to the active ingredients in approved drugs. *Id.* at 1159-60. To adopt such an interpretation, the court concluded, would render the exclusion from

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[2] "Active ingredient" means "any component that is intended to furnish pharmacological activity or other direct effect . . . . The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." 21 CFR 210.3(b)(7). If two molecules are the same active ingredient, they are chemically identical.

[3] *See* FD&C Act 201(ff)(1), (ff)(2).

[4] *See* FD&C Act 201(g) (definition of "drug").

[5] *See, e.g.*, FD&C Act 505(c)(3)(E); 21 CFR 312.23(a)(7)(i).

the dietary supplement definition in section 201(ff)(3)(B) of the FD&C Act meaningless and contravene the fundamental purposes of the FD&C Act by allowing manufacturers to evade the safety and efficacy requirements for new drugs and undermining incentives for drug development. *Id.* at 1159.[6]

In concluding that the meaning of "article" in the exclusion clause was ambiguous, the court noted that the intended application of section 201(ff)(3)(B) of the FD&C Act "is not elucidated" by the legislative history, "but rather becomes less clear." *Pharmanex*, 221 F.3d at 1158. The chief sponsors of DSHEA expressly disclaimed as a source of legislative intent everything but a short Statement of Agreement. *See* Statement of Agreement, 140 Cong. Rec. H28668 (Oct. 6, 1994) ("It is the intent of the chief sponsors of the bill . . . that no other reports or statements be considered as legislative history for the bill."). The court commented that this disclaimer "certainly contributes to an overall sense of ambiguity as to the weight we should accord to the statements contained within the disclaimed legislative materials," but concluded that to the extent the disclaimed Senate Report (S. Rep. No. 103-410 (1994)) is evidence of legislative intent, "it favors the FDA's interpretation." *Pharmanex*, 221 F.3d at 1158.

The legislative history indicates that Congress believed that allowing an article to be marketed as a dietary supplement after it had been first approved or studied as a drug would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market; would serve as a disincentive to the significant investment needed to gain FDA approval of new drugs; and would enable manufacturers to escape appropriate safety and efficacy review and FDA oversight by being classified as dietary supplements. *See, e.g.*, 140 Cong. Rec. S12104 (Aug. 18, 1994), 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."); S. Rep. No. 103-410 (1994), 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.").

Senator Hatch explained the impetus for the Hatch-Harkin compromise language (the exclusion clause) as follows:

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[6] In *Pharmanex*, the active ingredient and active moiety of the "article . . . approved as a new drug" were the same, lovastatin. (Under 21 CFR 3l6.3(b)(2), "active moiety" means "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.") In 2009, FDA responded to a citizen petition requesting that FDA determine the regulatory status of all pyridoxamine products marketed as dietary supplements, which prompted FDA to consider whether the term "article" in the exclusion clause also includes active moieties. Consistent with the holding of *Pharmanex* and with the purposes of the exclusion clause, FDA concluded that it does. *See* Letter from Michael A. Chappell, Acting Associate Commissioner for Regulatory Affairs, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP, responding to Citizen Petition FDA-2005-P-0259 submitted on behalf of Biostratum, Inc. (Jan. 12, 2009), available at: https://www.regulations.gov/document/FDA-2005-P-0259-0004.

> Drafters of the legislation . . . were criticized for a definition of dietary supplement which some felt was overly broad. We have tried to tighten that up.
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> Some then believed that the language would allow drugs such as taxol to be marketed in the United States as dietary supplements. Senator Harkin and I worked for some time after the markup to resolve that issue, and the language we present today addresses that concern.

140 Cong. Rec. S22413 (Aug. 13, 1994), Statement of Sen. Hatch. Taxol, the drug that Senator Hatch mentioned as a reason for the exclusion clause, was approved in December 1992, prior to DSHEA's enactment, with an injection route of administration (i.e., a route of administration other than ingestion).[7]

The exclusion clause does, however, permit continued marketing of a dietary supplement that was first marketed as such or as a food, even if the article is subsequently studied or approved as a new drug. In such a case, the dietary supplement was on the market first and does not lose its status as a dietary supplement if a drug manufacturer later chooses to study or seek approval for the article as a new drug.

B. Regulatory History of NAC

FDA's longstanding position has been that, under the exclusion clause, NAC-containing products cannot be dietary supplements. FDA stated this position in a July 2001 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.[8] The petition did not meet the requirements for a health claim petition as stated 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). FDA's 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 to the exclusion clause, FDA noted that "NAC was approved as a new drug under section 505 of the [FD&C Act] on September 14, 1963" under New Drug Application (NDA) No. 013601, Mucomyst (acetylcysteine),[9] and the petition failed to document a history of NAC having been marketed as a dietary supplement before that date.

In 2010, in response to an NDI notification for NAC ethyl ester, FDA again stated that, under the exclusion clause, NAC-containing products cannot be dietary supplements. *See* Letter from Dan D. Levy, Ph.D., Microbiologist, Supervisor, New Dietary Ingredient Review Team, Division of

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[7] For information on the drug approval history of Taxol (paclitaxel), *see* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020262.

[8] Because the health claim petition was denied by operation of law, FDA's 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. A redacted version of the response is available in the dockets for the two petitions.

[9] NAC and acetylcysteine are the same article. The approval of acetylcysteine as a new drug was public knowledge. In accordance with then-21 CFR 130.33, FDA provided notice of the new drug approval in the Federal Register in December 1963 (28 FR 13509 (Dec. 13, 1963)).

Dietary Supplement Programs, Office of Nutrition, Labeling and Dietary Supplements, Center for Food Safety and Applied Nutrition, to Tiara Pharmaceuticals, dated October 21, 2010 (2010 Letter).[10]

NAC's regulatory status was mentioned again in a February 2017 application for a search warrant. In the affidavit supporting the search warrant application, an FDA special agent explained that an FDA investigation of a firm revealed, among other things, that the firm sold NAC-containing products labeled as dietary supplements and that NAC is excluded from the definition of dietary supplement under the exclusion clause because it was approved as a new drug before it was marketed as a dietary supplement or as a food. *See* Blackstone Labs Warrant, Agent Aff. at ¶¶ 106-107.

FDA reiterated its position on NAC in four warning letters[11] issued in July 2020 to companies illegally selling unapproved products that claimed to cure, treat, mitigate, or prevent hangovers, although they also claimed to be dietary supplements (the July 2020 Warning Letters).[12] The warning letters note that, even if the products were not distributed with therapeutic claims, these NAC-containing products are excluded from the definition of dietary supplement under the exclusion clause.[13]

C. Citizen Petitions

After FDA issued the July 2020 Warning Letters, CRN and NPA filed their citizen petitions asking the agency to reverse our position on the regulatory status of NAC. The CRN Petition asks FDA to reverse our "recently adopted position that the [FD&C Act] prohibits manufacturers from marketing products containing [NAC] as dietary supplements" (CRN Petition at 1). The NPA Petition asks FDA to "either determine, based on the facts provided [in the petition], that [NAC] is not excluded from the definition of dietary supplement under 21 U.S.C. § 321(ff)(3) or,

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[10] This letter may be found at www.regulations.gov/document/FDA-2010-S-0665-0004. The CRN Petition has mistakenly identified the author of the 2010 Letter as Dr. Fred Hines, a former consumer safety officer in the Division of Dietary Supplement Programs. Dr. Hines was the author of the memorandum attached to the 2010 Letter that asked FDA personnel to put the letter on public display in accordance with section 413(a) of the FD&C Act.

[11] FDA warning letters are "informal and advisory." They are intended to "communicate[] the agency's position on a matter, but [they] do[] not commit FDA to taking enforcement action" and are not final agency action. *See* FDA's Regulatory Procedures Manual, § 4-1-1, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual.

[12] Letter from William A. Correll, Jr., Director, Office of Compliance, Center for Food Safety and Applied Nutrition (CFSAN), to Jason Burke, MD, President, Vita Heaven, LLC dba Hangover Heaven (July 23, 2020); Letter from William A. Correll, Jr., Director, Office of Compliance, CFSAN, to Ben Shaw, Owner/President, Happy Hour Vitamins (July 23, 2020); Letter from William A. Correll, Jr., Director, Office of Compliance, CFSAN, to John Heathco, CEO, LES Labs (July 23, 2021); and Letter from William A. Correll, Jr., Director, Office of Compliance, CFSAN to Monir Elias, CEO, Purple Biosciences, LLC (July 23, 2020). All of the July 2020 Warning Letters may be accessed via the links at https://www.fda.gov/food/cfsan-constituent-updates/fda-sends-warning-letters-seven-companies-illegally-selling-hangover-products.

[13] FDA acknowledges that a response to a qualified health claim petition involving a product that contained NAC, dated December 12, 2018, erroneously described the product as "a dietary supplement that includes vitamins or other nutritional substances (i.e., N-acetyl cysteine . . .) . . . ." 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.

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]" (NPA Petition at 1).

In support of their requests, the CRN Petition and the NPA Petition assert:

- FDA's records do not reliably demonstrate that the exclusion clause applies to NAC (CRN Petition at 4; NPA Petition at 10). Each petition alleges that FDA's records are flawed and, hence, may be unreliable (CRN Petition at 4; NPA Petition at 10). In particular, the CRN Petition asserts that the September 14, 1963, approval date for acetylcysteine is unreliable because the date was handwritten at the top of FDA's letter to Mead Johnson & Company (Mead Johnson) approving the company's new drug application dated May 17, 1962, a copy of which is included in Attachment A of the CRN Petition. The CRN Petition states, "This is not the type of document that should be regarded as authentic" (CRN Petition at 4). The NPA Petition argues that "[u]sually, evidence from the period of time in question are hand-written notes and documents. There are often gaps in the record and the information available can be both unverifiable and unreliable" (NPA Petition at 10). In addition, the CRN Petition notes that in an NDI notification response, FDA stated a different date (1985) as the date NAC was first approved as a new drug (CRN Petition at 4).[14]

- When determining whether the exclusion clause is applicable, the delivery form/route of administration must be considered (CRN Petition at 5 through 6). More specifically, the CRN Petition argues that when FDA relied on the September 14, 1963, new drug approval of acetylcysteine as evidence that NAC products are excluded from the definition of dietary supplement under the exclusion clause, we "overlooked" that this approval was for an inhaled drug (CRN Petition at 5). The CRN Petition goes on to assert that "[a]n inhaled substance should not be treated as the same article as an orally consumed substance" and argues that 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"—and notes that a dietary supplement must be intended for ingestion (CRN Petition at 5). Furthermore, the CRN Petition argues that *Pharmanex v. Shalala* "is not dispositive of this matter either" (CRN Petition at 6). The NPA Petition also raises the issue of the drug's route of administration, noting that it "remains unclear" if the exclusion clause applies to an article that "has been approved as a drug not intended to be administered by ingestion" (NPA Petition at 10).

- NAC was marketed in or as a dietary supplement before DSHEA was enacted in October 1994, and thus the exclusion clause does not apply to NAC (CRN Petition at 6 through 7;

[14] The CRN Petition states that "[d]ocuments obtained through another [Freedom of Information Act] 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" (CRN Petition at 4 n.15).

NPA Petition at 3 through 6, and 10).[15] In support of its argument that the exclusion clause does not apply to ingredients that were marketed as dietary supplements pre-DSHEA, the NPA Petition quotes the following text from a Senate Report, S. Rep. No. 103-410 (1994) at V §3:

> On occasion, a substance that is properly included as a dietary ingredient in a dietary supplement (food) product may also function as an active ingredient in a drug product. There is nothing particularly surprising about this fact.
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> As an example, the dietary substance L-carnitine may properly be used as an ingredient in a dietary supplement (as FDA itself has acknowledged), although it is also the active ingredient in a drug product that has been approved by FDA for a particular prescription-only usage. Similarly, the substance caffeine is a natural component of food products such as coffee and tea; it is used as an added ingredient in other foods, including carbonated beverages, and it has also been approved by FDA as a drug (NPA Petition at 5).

The NPA Petition states:

> It is clear from the language in the [Senate] Report that both L-carnitine and caffeine were marketed as both dietary ingredients and approved drugs prior to the passage of DSHEA. It is also clear from the Report's language that Congress intended for these ingredients to continue to be marketed as both drugs and dietary ingredients after the effective date of DSHEA, October 15,1994 [sic]. What is telling is that the report establishes this with our [sic] any analysis under, or even reference to, the 'race-to-market' paradigm of Section 201(ff)(3) of the [FD&C] Act as amended by DSHEA. This would indicate that congressional intent relative to articles that were marketed as both drugs and dietary ingredients prior to the effective date of DSHEA to be able to continue such marketing regardless of an analysis under Section 201(ff)(3) of the [FD&C] Act as amended by D[S]HEA (NPA Petition at 5 through 6).

In addition, the CRN Petition argues that interpreting the exclusion clause to apply to articles that were approved as new drugs before DSHEA's enactment would have an impermissible retroactive effect not intended by Congress (CRN Petition at 6 through 7). Citing *Landgraf v. USI Film Products*, 511 U.S. 244, 270 (1994), the CRN Petition asserts that FDA's interpretation of the exclusion clause "violates the well-established presumption against statutory retroactivity" because the exclusion clause "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" (CRN Petition at 6 through 7) (emphasis in original).

[15] Furthermore, the NPA Petition asserts that NAC is a dietary ingredient under section 201(ff)(1) of the FD&C Act (NPA Petition at 4).

- FDA's current position on the regulatory status of NAC is a sudden policy change with widespread implications and is arbitrary and capricious under the Administrative Procedure Act (APA) (CRN Petition at 2 through 3, and 7 through 8; NPA Petition at 10 through 11). In support of its position that the July 2020 Warning Letters announced a sudden policy change, the CRN Petition claims that FDA has reviewed over 100 30-day notifications of structure/function claims for NAC and has never raised any issues with the exclusion clause (CRN Petition at 8). In addition, the two petitions both note that a few years before FDA issued the July 2020 Warning Letters, FDA reviewed a qualified health claim for a multi-ingredient product containing NAC and stated that NAC was a component of a dietary supplement (CRN Petition at 8; NPA Petition at 9).[16] Furthermore, the NPA Petition states that at the time of the issuance of the July 2020 Warning Letters, 1,170 products containing NAC were listed in the National Institutes of Health Dietary Supplement Label Database (NPA Petition at 9).

In support of its request, the CRN Petition also asserts that:

- "The equitable defense of laches prevents FDA from enforcing its new policy" (CRN Petition at 9). The CRN Petition argues that this defense is available against the government and that dietary supplement manufacturers can demonstrate the factors required to prevail in asserting it: (1) that the delay resulted from the plaintiff's own lack of diligence, and (2) that the defendant has suffered undue prejudice as a result of the plaintiff's delay (CRN Petition at 9). In particular, the CRN Petition argues that there is ample evidence that FDA has long been aware that NAC products have been marketed as dietary supplements and has "*actively* considered" yet failed to object to the marketing of such products (CRN Petition at 9) (emphasis in original). The CRN Petition also asserts that FDA's July 2020 Warning Letters have resulted in "extreme economic consequences" to dietary supplement manufacturers (CRN Petition at 9).

- It is not clear whether the approval date of discontinued drugs may be used to determine the date of preclusion for dietary supplement use (CRN Petition at 5).

In addition, the NPA Petition points out that there does not appear to be any risk to the public health when NAC is marketed as a dietary ingredient or dietary supplement (NPA Petition at 11).

On November 24, 2021, FDA issued tentative responses to the two petitions (collectively, the "November 2021 Tentative Response Letters").[17] In our letters, we advised that we were evaluating both petitions concurrently due to the overlap between them. Furthermore, to help us

[16] The CRN Petition quotes from FDA's 2018 response to a qualified health claim petition: "[T]he 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 . . .) . . ." (CRN Petition at 8 (citing 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)).

[17] Letter from Douglas W. Stearn, Deputy Director for Regulatory Affairs, CFSAN, to Steve Mister and Megan Olsen, CRN (Nov. 24, 2021) (in the docket for the CRN Petition) and Letter from Douglas W. Stearn, Deputy Director for Regulatory Affairs, CFSAN, to Dr. Daniel Fabricant, NPA (Nov. 24, 2021) (in the docket for the NPA Petition).

evaluate the petitions' requests, we requested additional information from you and interested parties by January 25, 2022. Specifically, FDA expressed interest in receiving data and information on the earliest date that NAC was marketed as a dietary supplement or as a food. In addition, to help us evaluate NPA's rulemaking request, should we reach that issue, we asked for data, research results, and other information related to the safe use of NAC in products marketed as dietary supplements, and any safety concerns.

FDA has received comments, data, and information in connection with your petitions from consumers, trade associations, and industry, and has considered this information when developing this response.

II. Discussion

A. The Exclusion Clause's Application to Pre-DSHEA Products

Under section 201(ff)(3)(B) of the FD&C Act, if an article has been approved as a new drug under section 505 of the FD&C Act or has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, 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 or authorization. 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.

The exclusion clause does not provide an exception for drugs that were approved prior to DSHEA, drugs that were authorized for investigation prior to DSHEA, or dietary supplements or foods that were marketed as such prior to DSHEA. Thus, if Substance A was approved as a new drug in 1987 and was first marketed as a dietary supplement or as a food in 1992, the exclusion clause precludes Substance A from being a dietary supplement any time *after* DSHEA's enactment (unless FDA issues a regulation providing otherwise).

FDA's interpretation of the exclusion clause does not give it retroactive effect. A statute has a retroactive effect if "it would impair rights a party possessed when he acted, increase a party's liability for past conduct, or impose new duties with respect to transactions already completed." *Landgraf v. USI Film Prods.*, 511 U.S. 244, 280 (1994). FDA's interpretation of the exclusion clause does none of these things. DSHEA was signed into law on October 25, 1994. The exclusion clause does not change the legality of acts committed before DSHEA's enactment. For example, it does not make it unlawful to have sold an NAC supplement prior to October 25, 1994. Rather, beginning on DSHEA's effective date, the exclusion clause impacted future conduct by providing that an article that is approved as a new drug cannot be a dietary supplement unless an exception applies (e.g., the article was marketed as a dietary supplement or as a food prior to its approval as a new drug). Your petitions cite no cases that support your contention that a statute that makes future conduct unlawful has a retroactive effect.

Your reliance on *Landgraf* and the fact that FDA approved NAC as a new drug prior to DSHEA's enactment is misplaced. As the Supreme Court noted in *Landgraf*, "a statute 'is not made retroactive merely because it draws upon antecedent facts for its operation.'" *Id.* at 269 n.24 (quoting *Cox v. Hart,* 260 U.S. 427, 435 (1922)). Likewise, even if a product that was marketed as a dietary supplement before DSHEA's enactment can no longer be lawfully marketed as such *after* the statute's enactment, this does not give the exclusion clause retroactive effect. *See, e.g., Nat. Res. Def. Council, Inc. v. U.S. Consumer Prod. Safety Comm'n*, 597 F. Supp. 2d 370, 380, 392-94 (S.D.N.Y. 2009) (holding that although the phthalate prohibition in section 108 of the Consumer Product Safety Improvement Act of 2008 (CPSIA) applied to inventory existing as of the prohibition's effective date (i.e., manufactured before the effective date), this does not attach new legal consequences to conduct that has already occurred and, therefore, does not give the prohibition retroactive effect).[18]

DSHEA created a new regime for the regulation of dietary supplements, including defining the term "dietary supplement" for the first time, thereby changing which products could be lawfully marketed as dietary supplements *going forward*. By their nature, new laws change parties' rights and obligations. "Even uncontroversially prospective statutes may unsettle expectations and impose burdens on past conduct: a new property tax or zoning regulation may upset the reasonable expectations that prompted those affected to acquire property; a new law banning gambling harms the person who had begun to construct a casino before the law's enactment or spent his life learning to count cards." *Landgraf*, 511 U.S. at 269 n.24*; see also Nat. Res. Def. Council, Inc.*, 597 F. Supp. 2d at 393 ("*Landgraf,* however, does not support the assertion that the phthalate prohibitions are retroactive because they change parties' expectations with respect to products that have already been manufactured.").

The exclusion clause is not ambiguous with respect to its application to pre-DSHEA products. FDA's interpretation is the only possible reading of the statutory text. The exclusion clause does not distinguish between products first marketed before DSHEA's enactment and those first marketed after it. Moreover, when Congress wanted DSHEA to set different requirements for products first marketed before DSHEA's enactment and those first marketed after it, it did so clearly in the statutory text. Section 413 of the FD&C Act, added by DSHEA, defines "new dietary ingredient" as "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," and requires a notification to FDA only for certain NDIs (and not for any dietary ingredient that was marketed in the United States before October 15, 1994). Likewise, in section 402(f) of the FD&C Act, Congress created a safety standard that applies to all dietary supplements (section 402(f)(1)(A) of the FD&C Act) and another, higher safety standard that applies only to NDIs (section 402(f)(1)(B) of the FD&C Act). The exclusion

[18] Section 108 of the CPSIA provides that "[b]eginning on the date that is 180 days after August 14, 2008 [i.e., February 10, 2009] . . . it shall be unlawful for any person to . . . offer for sale . . . or distribute in commerce . . . any children's toy or child care article that contains" the prohibited phthalates. The court concluded that "[t]he ordinary meaning of the words in the phthalate prohibitions is that beginning on February 10, 2009, it will be unlawful to sell or distribute *all* covered products containing the prohibited phthalates, regardless of when they were manufactured." *Id.* at 380 (emphasis in original). The court rejected the Commission's argument that this interpretation of the phthalate prohibition raised retroactivity concerns, noting that "[o]n their face, the phthalate prohibitions are not retroactive . . . [and] do not attach new legal consequences to conduct that has already occurred." *Id.* at 393.

clause, however, contains no language limiting its application to NDIs and other post-DSHEA products.

The legislative history does not support your interpretation of the exclusion clause. First, a statement by Senator Hatch (a chief sponsor of DSHEA) directly supports FDA's interpretation of the exclusion clause. As noted above, Senator Hatch explained the impetus for the Hatch-Harkin compromise language (the exclusion clause) as follows:

> Drafters of the legislation . . . were criticized for a definition of dietary supplement which some felt was overly broad. We have tried to tighten that up.
>
> Some then believed that the language would allow drugs such as taxol to be marketed in the United States as dietary supplements. Senator Harkin and I worked for some time after the markup to resolve that issue, and the language we present today addresses that concern.

140 Cong. Rec. S22413 (Aug. 13, 1994), Statement of Sen. Hatch. Taxol, the drug Senator Hatch mentioned as an example of the type of drug necessitating inclusion of the exclusion clause, was approved as a new drug in December 1992. Senator Hatch's statement shows that Congress intended the exclusion clause to cover drugs approved before DSHEA's enactment, consistent with the plain language of section 201(ff)(3)(B) of the FD&C Act.[19]

Other statements in the legislative history give no indication that Congress intended the exclusion clause to have the narrow scope you advocate. *See, e.g.*, 140 Cong. Rec. S12104 (Aug. 18, 1994), 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.").

NPA relies solely on a passage from the Senate Report as support for its contention that the exclusion clause is intended to apply only to post-DSHEA products.[20] The full passage in the Senate Report (S. Rep. No. 103-410 (1994), at V § 3) states:

> On occasion, a substance that is properly included as a dietary ingredient in a dietary supplement (food) product may also function as an active ingredient in a drug product. There is nothing particularly surprising about this fact.
>
> As an example, the dietary substance L-carnitine may properly be used as an ingredient in a dietary supplement (as FDA itself has acknowledged), although it is also the active ingredient in a drug product that has been approved by FDA for a particular prescription-only usage. Similarly, the substance caffeine is a natural component of food products such as coffee and tea; it is used as an added ingredient in other foods, including carbonated beverages, and it has also been approved by FDA as a drug ingredient.

[19] Based on available information, paclitaxel, the active ingredient in Taxol, was not marketed as a food or as a dietary supplement before it was approved as a new drug.
[20] See Section I.C.

> In general, it is the intended use of a particular finished product (as shown by representations made for it in promotional materials) that determines whether than [sic] product and its ingredients are subject to regulation as a food or as a drug. If a vitamin product or an herbal product, for example, is represented for use as a "dietary supplement," it is a food; if it is represented to cure, mitigate, treat, or prevent disease, it is a drug.
>
> 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.
>
> Under the substitute to S. 784 as approved by committee, a substance which has been marketed as a dietary ingredient in a dietary supplement, or otherwise as a food, does not lose its status as a food (assuming it is intended for use as a dietary supplement or other food purpose as shown by its promotional materials) just because FDA approves the substance for use as an active ingredient in a new drug, certifies a finished product containing the substance as an antibiotic, or licenses a finished product containing the substance as a biologic. Those types of products would be drugs because they would be promoted with drug claims. They would, and should, have no effect on the food status of a properly-labeled dietary supplement. For example, if ever FDA should eventually approve Vitamin C as a drug to treat cancer, Vitamin C properly would also continue to be available as a dietary supplement (food) product, so long as it is promoted as a dietary supplement without disease prevention claims.

This passage does not support NPA's interpretation of the exclusion clause. NPA points to the Senate Report's reference to the historical marketing of L-carnitine as a dietary supplement and of caffeine as a food, and claims this statement, which is ambiguous at best, demands that FDA interpret the exclusion clause to have a meaning inconsistent with the statute's plain language (NPA Petition at 5 through 6). But this passage does not support a conclusion that Congress intended the exclusion clause to apply only to drugs approved after DSHEA and that every product that was on the market pre-DSHEA could remain on the market. Moreover, the NPA Petition does not contend that caffeine and L-carnitine actually would be excluded from the dietary supplement definition under FDA's interpretation of the exclusion clause. Indeed, the NPA Petition ignores the crucial point that caffeine and L-carnitine would be excluded from the dietary supplement definition only if they were approved as new drugs or authorized for investigation as new drugs prior to being marketed as a dietary supplement or as a food (and, in the latter case, if the investigational new drug met the other requirements of section 201(ff)(3)(B)(ii) of the FD&C Act). The NPA Petition offers no evidence that caffeine and L-carnitine were not first marketed as a dietary supplement or as a food.[21] Indeed, both caffeine

[21] The NPA Petition says,

and L-carnitine have a long history of use as a food or as a dietary supplement, and these uses predate their approval as new drugs. Caffeine has been added to soft drinks since at least the 1910s,[22] before there was a federal drug approval system in the United States. Similarly, L-carnitine was marketed as a dietary supplement before it was approved as a new drug. For example, a January 25, 1984, ad in the Sarasota Herald-Tribune advertised an L-carnitine supplement; L-carnitine was first approved as a new drug on December 27, 1985.[23] Thus, the exclusion clause does not preclude the use of L-carnitine and caffeine in dietary supplements.[24]

> It is clear from the language in the Report that both L-carnitine and caffeine were marketed as both dietary ingredients and approved drugs prior to the passage of DSHEA. It is also clear from the Report's language that Congress intended for these ingredients to continue to be marketed as both drugs and dietary ingredients after the effective date of DSHEA, October 15,1994 [sic]. What is telling is that the report establishes this with our [sic] any analysis under, or even reference to, the 'race-to-market' paradigm of Section 201(ff)(3) of the [FD&C] Act as amended by DSHEA. This would indicate that congressional intent relative to articles that were marketed as both drugs and dietary ingredients prior to the effective date of DSHEA to be able to continue such marketing regardless of an analysis under Section 201(ff)(3) of the [FD&C] Act as amended by D[S]HEA.

(NPA Petition at 5 through 6). On the contrary, the fact that the Senate Report mentions caffeine and L-carnitine without any reference to the exclusion clause suggests that the two paragraphs that the NPA Petition relies on were not intended to pertain to the exclusion clause, are not relevant to its meaning, and thus should not be taken into consideration when interpreting it.

[22] *See, e.g.*, *United States v. Forty Barrels & Twenty Kegs of Coca Cola*, 241 U.S. 265, 272 (1916) (stating that caffeine is an ingredient in Coca-Cola). After this decision, Coca-Cola and the government settled, with Coca-Cola agreeing to cut the amount of caffeine in its soft drink by half. *See* Deborah Blum, *How a Lawsuit Against Coca-Cola Convinced Americans to Love Caffeine*, Time (Sept. 25, 2018), https://time.com/5405132/coca-cola-trial-caffeine-history/.

[23] The January 25, 1984, ad is available in the dockets for the two petitions. For information on the drug approval history of Carnitor (levocarnitine), *see* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018948.

[24] One comment on both petitions quotes the reference to vitamin C in the Senate Report ("if ever FDA should eventually approve Vitamin C as a drug to treat cancer, Vitamin C properly would also continue to be available as a dietary supplement (food) product, so long as it is promoted as a dietary supplement without disease prevention claims"). The comment asserts that vitamin C was first approved as a drug in 1947 and claims that Congress could not have reasonably expected that, upon DSHEA's enactment, all Vitamin C dietary supplements would be removed from the market absent evidence that they were marketed prior to the 1940s. The comment overlooks the fact that evidence of marketing of vitamin C as a food prior to 1947 also would demonstrate that vitamin C is not excluded from the dietary supplement definition. Vitamin C was marketed as a food prior to 1947, and thus is not excluded from the dietary supplement definition. *See, e.g.*, 4 FR 1549, 1570 (Apr. 11, 1939) ("The witness on cross-examination . . . stated in answer to a question that if he thought the only choice the consumer had was between tomato juice with the addition of water plus ascorbic acid (vitamin C) and juice in which there was no addition of water, not even an infinitesimal amount, but an impairment of the ascorbic acid, that the consumer would take the juice with the water and ascorbic acid, but that if the consumer were able to get a product of unimpaired vitamin C and without addition of water, the consumer preference would be for the one without manipulation."); 21 CFR 125.3(a)(1) (1941) ("If a food purports to be or is represented for special dietary use by man by reason of its vitamin property in respect of . . . Vitamin C (ascorbic acid) . . . the label [unless an exception applies] shall bear a statement of the proportion of the minimum daily requirement for such vitamin supplied by such food when consumed in a specified quantity during a period of one day. . . ."); 21 CFR 125.5 (1941) ("*Label statements relating to infant food*. . . . If such use of the food is by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk, the label shall also bear . . . a statement of the number of available calories and of U.S.P. units of vitamin A, vitamin B_1 (thiamine), vitamin C (ascorbic acid), and vitamin D supplied by a specified quantity of such food . . .").

The case law likewise does not support your reading of the exclusion clause. *Pharmanex*, 221 F.3d 1151, involved lovastatin, the active ingredient of the prescription drug Mevacor, which FDA approved in 1987. If your reading of the exclusion clause were correct, the exclusion clause would not have applied to lovastatin, and there would have been no need for the court to opine on the meaning of the term "article" in section 201(ff)(3)(B) of the FD&C Act.

Furthermore, your interpretation would open the possibility that any article approved as a new drug before DSHEA could be marketed as a dietary supplement at any time after DSHEA (assuming the product containing the article otherwise meets the definition of dietary supplement under section 201(ff) of the FD&C Act). Such a result, however, would raise safety and public health concerns. In 1993, half of the prescription drugs in the United States were derived from plants.[25] Your petitions, however, fail to acknowledge this fact and that these plant-derived drugs, like any drug, can have toxic effects. These risks do not disappear simply because the article is relabeled and sold as a dietary supplement. Moreover, if sold as a dietary supplement, such products would not be required to follow the requirements that apply to drugs under the FD&C Act and implementing regulations.[26] Nor would the product be prescribed by a physician who is familiar with the patient's medical history, prescribes the prescription drug in accordance with the physician's medical expertise, and then follows the patient.[27,28]

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[25] *Legislative Issues Related to the Regulation of Dietary Supplements: Hearing of the Committee on Labor and Human Resources*, 103d Cong. 1st Sess. at 21-22 (1993) (Testimony of Dr. Kessler, then-Commissioner of FDA).

[26] For example, unless an exception applies, new drugs may not be legally introduced or delivered for introduction into interstate commerce without prior approval from FDA, as described in sections 301(d) and 505(a) of the FD&C Act. FDA approves a new drug on the basis of scientific data and information demonstrating that the drug is safe and effective. There is no FDA-approval requirement for dietary supplements. Further, the Current Good Manufacturing Practice requirements that apply to drugs are more stringent than those that apply to dietary supplements (*compare* 21 CFR Parts 210-211, *with* 21 CFR Part 111).

[27] The CRN Petition argues that a "retroactive application of [the exclusion clause] 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. Congress's objective to preserve incentives for drug research would not be advanced by FDA's award of a monopoly to the drug industry for an ingredient that has co-existed in both drug and supplement forms for decades" (CRN Petition at 7).

We disagree. First, application of the exclusion clause to new drugs approved prior to DSHEA's enactment protects incentives for post-DSHEA development of generic versions of these drugs. A generic drug may be marketed only after a manufacturer has filed an abbreviated new drug application (ANDA) and received approval under section 505(j) of the FD&C Act. If the exclusion clause did not apply to new drugs approved before DSHEA's enactment, a company could formulate a product with the same active ingredient as such drug and market the product as a dietary supplement. To allow such marketing would serve as a disincentive to generic drug development because it would make generic drug companies less willing to submit ANDAs for products that could more easily be marketed as dietary supplements.

Second, protecting the incentives for new drug development was not the sole purpose of the exclusion clause. For example, another reason for the exclusion clause is that without it, DSHEA would have enabled manufacturers to escape appropriate safety and efficacy review and FDA oversight for prescription drugs by classifying them as dietary supplements. *See, e.g.*, 140 Cong. Rec. S12104 (Aug. 18, 1994), 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.").

[28] In its January 25, 2022, letter to the docket [FDA-2021-P-0938-0022], CRN argues that companies would have kept documentation of use only to demonstrate that an ingredient was not an NDI, not to demonstrate the inapplicability of the exclusion clause. CRN asserts that "This demonstrates another reason FDA's policy reversal on NAC is legally invalid – by trying to apply the drug preclusion provisions of DSHEA retroactively over 25 years

B. Route of Administration

Two products can contain the same "article" under section 201(ff)(3)(B) of the FD&C Act even if they have a different route of administration. Under case law interpreting section 201(ff)(3)(B) of the FD&C Act, either an entire product or a product component may be "an article that is approved as a new drug" or "an article authorized for investigation as a new drug" for purposes of the exclusion clause. *See Pharmanex*, 221 F.3d at 1154-60. Thus, under *Pharmanex*, if Substance A is the active ingredient in an approved drug product and is also an ingredient in a product labeled as a dietary supplement, the two products contain the same "article" for purposes of the exclusion clause, regardless of the drug product's route of administration.

Reading the exclusion clause as encompassing articles that are approved for any route of administration is fully consistent with the requirement that a dietary supplement must be intended for ingestion. It is the dietary supplement, not the drug product, that must be intended for ingestion under section 201(ff)(2)(A) of the FD&C Act.[29] Even if a drug product is approved for another route of administration, it is possible that a dietary supplement manufacturer would decide to add the product's active ingredient (which is "an article that is approved as a new drug" within the meaning of section 201(ff)(3)(B)(i) of the FD&C Act) to a product intended for ingestion. For example, Taxol was approved as a new drug by FDA for administration by injection. Although the drug was approved for another route of administration, Congress nonetheless was concerned that if the definition of dietary supplement did not include the exclusion clause, paclitaxel, the active ingredient in Taxol, would be added to a product that is intended for ingestion and sold as a dietary supplement. *See* 140 Cong. Rec. S22413 (Aug. 13, 1994), Statement of Sen. Hatch.

Further, while a drug's route of administration is relevant for purposes of drug approval under section 505 of the FD&C Act, this does not mean the route of administration must be considered to determine if ingredients are the same "article" for purposes of the exclusion clause. In *Pharmanex*, the Tenth Circuit upheld FDA's interpretation that "article" in the exclusion clause includes active ingredients, reasoning that "article" in section 201(ff)(3) of the FD&C Act was ambiguous because the Congressional drafters used it alternatively to refer to finished drug products and their components throughout the statute, and FDA's interpretation of that term in section 201(ff)(3) of the FD&C Act to include active ingredients was entitled to deference under *Chevron, U.S.A. v. Natural Resources Defense Council*, 467 U.S. 837 (1984). *Pharmanex*, 221 F.3d at 1155-60. Indeed, in rejecting the argument that the positions FDA took in cases involving other provisions of the FD&C Act required reading "article" in the exclusion clause to

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after DSHEA's passage, companies were never given the opportunity to preserve documentation that would counter FDA's current, legally invalid position on NAC." As discussed in this response, FDA has not made a policy reversal on NAC or on the scope of the exclusion clause. Further, while FDA appreciates that, for some products, there may be challenges to locating early evidence of marketing as a dietary supplement or as a food, this does not change the unambiguous statutory language of the exclusion clause.

[29] Section 201(ff)(2)(A) of the FD&C Act explicitly requires that a dietary supplement be a product "intended for ingestion," while section 201(ff)(3)(B) of the FD&C Act includes no such limiting language regarding the route of administration of an article "approved as a new drug," "licensed as a biologic," or "authorized for investigation as a new drug . . . or biological."

refer only to a finished drug product, the court recognized that even if two drug products would require separate applications for purposes of drug approval under section 505 of the FD&C Act or would be considered different drugs for purposes of market exclusivity pursuant to section 505(j)(5)(B)(iv) of the FD&C Act, the *active ingredient* in those products may nonetheless be considered the same "article" for purposes of the exclusion clause. *See id.* at 1157.[30,31]

In addition, the plain language of the exclusion clause supports FDA's interpretation. Section 201(ff)(3)(B) of the FD&C Act covers articles "licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262)" or "authorized for investigation as a . . . biological" as well as those approved as new drugs or authorized for investigation as new drugs. The inclusion of biologics in the exclusion clause would be illogical if products with different routes of administration could not be considered the same "article" under this provision, as biologics typically are not ingested.

To the extent that the legislative history speaks to the issue, it supports FDA's position that the exclusion clause includes non-ingested drugs. As noted above, Taxol, the drug Senator Hatch mentioned as an example of the type of drug necessitating inclusion of the exclusion clause,[32] was approved as a new drug in December 1992 with an injection route of administration.

FDA's reading of the exclusion clause also is consistent with the Congressional purpose that DSHEA not undermine incentives for the development and approval of new drugs, whether "pioneer" or generic, and the overall purposes of the FD&C Act. If a product with a different route of administration were considered to be a different "article" under section 201(ff)(3)(B) of the FD&C Act, a company could formulate a product with the same active ingredient as an approved new drug, change the route of administration to ingestion, and thereby create a new

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[30] The plaintiff in *Pharmanex* cited several cases in support of its position that the term "article" in the exclusion clause is limited to finished drug products, including *Pfizer, Inc. v. FDA,* 753 F. Supp. 171 (D. Md. 1990). In *Pfizer*, "FDA successfully argued that 'drug' in [sections 505(b)(1) and (c)(2) of the FD&C Act] means 'drug product,' thus requiring Pfizer to get a new NDA for its tablet version of its previously approved soft gelatin capsule version of nifedipine, on the grounds that although it contained the same active ingredient, it was nevertheless a different drug" because of the change in dosage form. *Pharmanex*, 221 F.3d at 1157. The plaintiff also cited *Apotex, Inc. v. Shalala,* 53 F.Supp.2d 454 (D.D.C.) *aff'd without comment,* No. 99–5231, 1999 WL 956686 (D.C. Cir. Oct. 8, 1999), in which "FDA successfully argued that the market exclusivity accorded to one drug product did not extend so as to preclude a generic product with the same active ingredient, (although of a differing strength), from receiving a 180-day period of market exclusivity pursuant to [section 505(j)(5)(B)(iv) of the FD&C Act]." *Pharmanex*, 221 F.3d at 1157. The *Pharmanex* court rejected the plaintiff's argument and interpretation of the exclusion clause, noting that "these cases are of limited relevance to the instant matter." *Id.*

[31] In its January 4, 2022, letter to the docket [FDA-2021-P-0523-0012], CRN argues for the first time that "FDA's position ignores the differences in . . . dosage levels of the products at issue." NPA's amended complaint in *NPA v. FDA*, case no. 8:21-cv-03112-TDC (D. Md.) makes a similar argument: "The [FD&C] Act makes it clear that when determining the similarity of drugs the FDA must include consideration of whether the route of administration is the same. For example, Section 505(j)(2)(A) of the [FD&C Act] contains the requirements that are used by FDA to determine whether an abbreviated new drug application's subject article is the same as the referenced new drug application article, stating that the abbreviated new drug application for the subject article must include 'information to show that the *route of administration*, the dosage for [sic], and the strength of the new drug' (emphasis added) that is the subject article are the same as those of the referenced article." NPA Amended Complaint at ¶ 43. This issue was addressed in *Pharmanex*, and as noted above, the court rejected the argument that FDA must consider factors such as the dosage form or strength of the substance when evaluating whether an article is excluded under the exclusion clause.

[32] 140 Cong. Rec. S22413 (Aug. 13, 1994), Statement of Sen. Hatch.

product that could be marketed as a dietary supplement. This could disadvantage a company that successfully pursued the drug approval process. Similarly, it could undermine the generic drug approval system because it would be easier to change the route of administration and market the product as a dietary supplement than to submit an abbreviated new drug application (ANDA) and receive approval under section 505(j) of the FD&C Act. Likewise, it would create a path for failed drugs (i.e., a substance that was investigated as a new drug but failed to gain FDA approval as a new drug) to be marketed as dietary supplements by changing the route of administration, which could potentially harm consumers.

Finally, FDA has taken the position that other articles that are approved as new drugs for a non-ingestion route of administration are excluded from the dietary supplement definition under the exclusion clause. For example, in a warning letter issued in January 2016, FDA stated that DMSA (an ingredient in the warning letter recipient's product) is the active ingredient in the FDA-approved drug DMSA Kit for the Preparation of Technetium TC-99M Succimer for Injection ("DMSA Kit"), approved on May 18, 1982, and that to FDA's knowledge, DMSA was not marketed as a dietary supplement or food prior to FDA's approval of DMSA Kit. Therefore, FDA explained, the firm's DMSA-containing product is excluded from the definition of a dietary supplement under section 201(ff)(3)(B) of the FD&C Act.[33]

C. Status of NAC Under Section 201(ff)(3) of the FD&C Act

FDA's longstanding position has been that NAC is excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act. FDA reaffirms that position here, but we note 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, as discussed below.

i. NAC Is Excluded from the Dietary Supplement Definition Under Section 201(ff)(3)(B)(i) of the FD&C Act

FDA has concluded that NAC products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the FD&C Act. NAC (acetylcysteine) was approved as a new drug under section 505 of the FD&C Act on September 14, 1963. Although this approval was for an acetylcysteine drug administered by inhalation, inhaled acetylcysteine and ingested acetylcysteine are the same "article" for purposes of the exclusion clause, for the reasons discussed above in Section II.B. FDA is not aware of any evidence that NAC was marketed as a dietary supplement or as a food prior to September 14, 1963. The earliest evidence that FDA has received or found of NAC being marketed as a dietary supplement or as a food is an August/September 1991 advertisement for an NAC-containing supplement.[34]

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[33] Letter from Michael Dutcher, DVM, Director, Minneapolis District, FDA to David S. Peterson, President and Co-owner, Nutri-Dyn Midwest, Inc. (Jan 15, 2016), available at https://wayback.archive-it.org/7993/20161022174029/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm482627.htm.

[34] On February 21, 2022, NPA filed an amended complaint in *NPA v. FDA*, case no. 8:21-cv-03112-TDC (D. Md.), asserting, among other things, that "L-Cysteine has been marketed as a dietary ingredient in dietary supplements prior to acetylcysteine's drug approval date in 1963." NPA Amended Complaint at ¶ 61. In addition, NPA argues that "NAC qualifies as [a] dietary ingredient under Section 201(ff)(1)(F), as a metabolite of L-cysteine (an amino

acid under Section 201(ff)(1)(D)). Because of this, NAC is [a] dietary ingredient under DSHEA that is not excluded from the definition of a dietary supplement by Section 201(ff)(3)(B)(i) because NAC was a metabolite of an amino acid that itself was marketed as a dietary supplement or a food prior to the date that acetylcysteine was approved as a drug." NPA Amended Complaint at ¶ 62. NPA also asserts that NAC qualifies as a dietary ingredient under section 201(ff)(1)(F) as a constituent of an herb or other botanical, such as onions and garlic, and that because foods like onions and garlic have been marketed long before acetylcysteine's approval as a drug, NAC is not excluded from the definition of dietary supplement by section 201(ff)(3)(B) of the FD&C Act. NPA Amended Complaint at ¶¶ 63-65.

As discussed below, although FDA agrees that NAC is a dietary ingredient under section 201(ff)(1) of the FD&C Act, we disagree with NPA's assertions regarding why NAC is a dietary ingredient. Further, NAC's status as a dietary ingredient is not relevant with respect to whether it is excluded from the dietary supplement definition pursuant to the exclusion clause. Finally, the examples NPA cites do not constitute evidence that NAC was marketed as a dietary supplement or as a food prior to the approval of acetylcysteine as a new drug on September 14, 1963.

NAC is not a metabolite of L-cysteine. A metabolite is a product of metabolism. In the dietary supplement context, a metabolite of a dietary ingredient is a molecular intermediate that incorporates structural elements of the ingested dietary ingredient and whose flux or net production in the human body increases on ingestion of the dietary ingredient. A metabolite can be part of (or an intermediate of) the catabolic or metabolic pathway of a dietary ingredient. FDA considers X to be a metabolite of Y if ingestion of Y by humans results in net production of/increased flux of X, incorporating structural elements of Y. *See, e.g.,* Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, at 97-98 (August 2016).

There is no published evidence indicating there is a metabolic process that produces NAC from L-cysteine. Put differently, there is no published evidence suggesting that ingestion of L-cysteine by humans results in net product or increased flux of NAC. Upon ingestion of L-cysteine, it is rapidly oxidized and exists primarily as L-cystine. The body then metabolizes the L-cystine to form cysteinesulfinate. Thus, L-cysteine's primary metabolite is cysteinesulfinate. *See* J. Yin, W. Ren, G. Yang, J. Duan, X. Huang, R. Fang, C. Li, T. Li, Y. Yin, Y. Hou, S.W. Kim, G. Wu. L-Cysteine metabolism and its nutritional implications. Molecular Nutrition and Food Research. (2016), 60(1), 134-146; N.C. Plaza, M.R. Garcia-Galbis, R.M. Martinez-Espinosa. Effects of the Usage of L-Cysteine (L-Cys) on Human Health. Molecules. (2018), 23(3), 575; and A.K. Elshorbagy, C. Church, M. Valdivia-Garcia, A.D. Smith, H. Refsum, R. Cox. Dietary cystine level affects metabolic rate and glycaemic control in adult mice. Journal of Nutritional Biochemistry. (2012), 23(4), 332-40.

L-cysteine and NAC are different compounds with different chemical structures and chemical properties. *See* B. Pedre, U. Barayeu, D. Ezerina, T.P. Dick. The mechanism of action of N-acetylcysteine (NAC): The emerging role of H_2S and sulfane sulfur species. Pharmacology and Therapeutics. (2021), 228(12), 1-22. NAC has an acetyl moiety covalently bonded to the amino group of L-cysteine. Studies have shown that NAC can act by freeing bound cysteine already present in the body. While NAC also undergoes enzymatic deacetylation in the body to produce L-cysteine, this process happens within the cell and not at the point of ingestion. This indicates that NAC is a precursor to L-cysteine, not a metabolite of L-cysteine. *See* J.E. Raftos, S. Bogdan, B.E. Chapman, P.W. Kuchel. Kinetics of uptake and deacetylation of *N*-acetylcysteine by human erythrocytes. The International Journal of Biochemistry & Cell Biology. (2007), 39(9), 1698-1706. This also demonstrates that NAC and L-cysteine do not have the same active moiety.

FDA is not aware of reliable scientific evidence that NAC is a constituent of a botanical. A few publications refer to NAC as a constituent of a botanical (e.g., garlic (*Allium sativum*)), but these publications do not provide reliable scientific support for this conclusion. For example, a publication from Souza et al. refers to NAC as "an organosulfur from Allium plant" and potentially responsible for the beneficial effects of onion and garlic, citing two publications in support of this position. *See* G.A. Souza, G.X. Ebaid, F.R.F. Seiva, K.H.R. Rocha, C.M. Galhardi, F. Mani, and E.L.B. Novelli. n-Acetylcysteine an *Allium* plant compound improves high-sucrose diet-induced obesity and related effects. Evidence-Based Complementary and Alternative Medicine. Volume 2011, Article ID 643269 (citing M.E. Anderson. Glutathione: an overview of biosynthesis and modulation. Chemico-Biological Interactions. (1998), 111–112, 1–14; and K.E. Campos, Y.S. Diniz, A.C. Cataneo, L.A. Faine, M.J.Q.F. Alves and E.L.B. Novelli. Hypoglycaemic and antioxidant effects of onion, *Allium cepa*: dietary onion addition, antioxidant activity and hypoglycaemic effects on diabetic rats. International Journal of Food Sciences and Nutrition. (2003), 54(3), 241-246). However, neither of the cited publications reported or even claimed that NAC was identified as a constituent of garlic (*Allium sativum*) or any other botanical. Similarly, a publication from

While the CRN Petition questions the reliability of the September 14, 1963, drug approval date because it is handwritten, it offers no explanation for why a partially handwritten date at the top of a letter sent from a federal agency in the 1960s—before word processors were commonly used in the office and made typing, editing, and printing letters easy and convenient—is unreliable.

Nishikawa-Ogawa et al. claims, without providing a supporting citation, that NAC is a constituent of water-soluble organosulfur compounds contained in garlic. *See* M. Nishikawa-Ogawa, H. Wanibuchi, K. Morimura, A. Kinoshita, T. Nishikawa, S. Hayashi, Y. Yano, and S. Fukushima. N-acetylcysteine and S-methylcysteine inhibit MeIQx rat hepatocarcinogenesis in the post-initiation stage. Carcinogenesis. (2005), 27(5), 982–988.

FDA has been unable to identify an original publication or data supporting the claim that NAC is a constituent of *Allium* species or any other botanical. We note that a publication by Demirkol et al. and a non-peer-reviewed presentation by Dewi et al. reported the presence of NAC in an asparagus extract and a garlic extract, respectively. *See* O. Demirkol, C. Adams, and N. Ercal. Biologically important thiols in various fruits and vegetables. Journal of Agricultural and Food Chemistry. (2004), 52, 8151-8154; and A.D.R. Dewi, J. Kusnadi, and W.L. Shih. Comparison of the main bioactive compounds and antioxidant activity from garlic water-soluble and garlic oil. Conference Paper. NRLS Conference Proceedings. International Conference on Natural Resources and Life Sciences. (2016) Volume 2017. The data presented were tentative identifications and are not sufficient to confirm the identity of a single compound in the complex botanical extracts. Additional data and characterization methods would be required to positively confirm the identity of the unknown compound. *See, e.g.,* R.J. Molyneux, J.J. Beck, S.M. Colegate, J.A. Edgar, W. Gaffield, J. Gilbert, T. Hoffman, L. McConnell, and P. Schieberle. Guidelines for the unequivocal identification of compounds with biological activity of significance in food chemistry (IUPAC Technical Report). Pure and Applied Chemistry. (2019), 91(8), 1417-1437. FDA's searches of the scientific literature did not find additional characterization data.

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. However, NAC's status as a dietary ingredient is not relevant with respect to whether it is excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act. Because the elements of the dietary supplement definition in section 201(ff)(1), (2), and (3) are phrased conjunctively (separated by "and"), a product qualifies as a dietary supplement only if it satisfies the criteria in all three of these paragraphs. Demonstrating that a product satisfies the requirement in section 201(ff)(1) to contain a dietary ingredient does not establish that the product meets the other criteria in sections 201(ff)(2) and (ff)(3).

Moreover, NPA has not provided evidence that NAC was marketed as a dietary supplement or as a food prior to the new drug approval of acetylcysteine on September 14, 1963. First, the marketing of L-cysteine as a dietary supplement is not relevant to whether NAC (i.e., acetylcysteine) is excluded under section 201(ff)(3)(B) of the FD&C Act. L-cysteine (i.e., cysteine) and NAC (i.e., acetylcysteine) are not the same "article" within the meaning of section 201(ff)(3)(B) of the FD&C Act. As discussed above, L-cysteine and NAC are different compounds with different chemical structures and chemical properties, and they do not have the same active moiety. Thus, even if NAC were a metabolite of L-cysteine, the marketing of L-cysteine as a dietary supplement or as a food would not constitute "marketing" of NAC as a dietary supplement or as a food within the meaning of the exclusion clause.

Second, even if NAC were a constituent of garlic, onion, or another food, the mere presence of NAC as a component in those foods would not constitute "marketing" of NAC as a food within the meaning of the exclusion clause. Merely showing that a substance was present as a component in a marketed dietary supplement or food is not enough to show that the substance was "marketed" within the meaning of the exclusion clause. *See Pharmanex v. Shalala*, 2001 WL 741419, at *4 & n.5 (D. Utah March 30, 2001). By contrast, the following would constitute evidence of "marketing" of NAC as a dietary supplement or as a food: (1) evidence that NAC was sold or offered for sale in the U.S. as a dietary supplement, dietary ingredient for use in dietary supplements, or conventional food; or (2) evidence that NAC was a component of a food or dietary supplement that was sold or offered for sale in the U.S., *and* that a manufacturer or distributor of the food or dietary supplement marketed it for the content of NAC by, for example, making claims about NAC or otherwise highlighting its presence in the product. NPA has provided no such evidence of marketing of NAC as a dietary supplement or as a food prior to September 14, 1963, and FDA is aware of no such evidence.

Likewise, while the NPA Petition claims that "[t]here are often gaps in the record [from this time] and the information available can be both unverifiable and unreliable," it does not assert that there are any gaps in the acetylcysteine drug approval records specifically. Your petitions provide no evidence to support your allegations that FDA's records for the September 14, 1963, approval of acetylcysteine are unreliable and unverifiable. Moreover, FDA's records reliably demonstrate that NAC was approved as a new drug on September 14, 1963. For example, in accordance with the requirements of 21 CFR 130.33 at the time, FDA announced the September 14, 1963, new drug approval of acetylcysteine in the *Federal Register* on December 13, 1963. *See* 28 FR 13509 (Dec. 13, 1963).[35]

While the CRN Petition correctly notes that FDA's response to the NDI notification for NAC ethyl ester mistakenly characterized the 1985 approval of NAC as the "first approv[al]" of NAC as a new drug, this does not change the conclusion stated in the NDI notification response—that NAC is excluded from the dietary supplement definition—or call into question the reliability of the September 14, 1963, drug approval date. As stated earlier, NAC was first approved as a new drug on September 14, 1963. On January 31, 1985, FDA approved an efficacy supplement for NAC.[36]

Finally, the CRN Petition's assertion that "[i]t is not clear . . . whether the approval date of discontinued drugs may be used to determine the date of preclusion for dietary supplement use" (CRN Petition at 5) does not call into question the status of NAC under the exclusion clause. As discussed above, either an entire product or a product component may be "an article that is approved as a new drug" or "an article authorized for investigation as a new drug" for purposes of the exclusion clause. The NDA or ANDA under which it was approved is not an "article." Thus, the issue here is whether the active ingredient NAC is approved as a new drug. 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, albeit under different applications.[37] Thus, NAC is "an article that is approved as a new drug under section 505" of the FD&C Act, and it has been such since September 14, 1963. A different reading would be contrary to the purposes of the exclusion clause, as it would permit manufacturers to market dietary supplements with a component that is the active ingredient in a currently approved drug and has continuously been the active ingredient in an approved drug

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[35] There are additional indicia of reliability of the handwritten September 14, 1963, date on the approval letter. For example, the typed letter notes that the new drug application was dated May 17, 1962, and that the sponsor submitted an additional communication dated August 23, 1963, amending the application, which FDA filed on August 27, 1963.

[36] CRN and NPA both appear to have questions about the publicly available information about NAC's drug approval history, including in the Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations (CRN Petition at 4 through 5, 7; NPA Petition at 10). The Orange Book was first published in 1980. Orange Book entries regarding NAC for the 1960s are not available. However, as noted earlier, FDA published notice of the September 14, 1963, approval of NAC (acetylcysteine) as a new drug in a December 1963 Federal Register notice. Further, entries for the new drug approval on September 14, 1963, and for its supplemental approval on January 31, 1985, are available on FDA's website (Drugs@FDA) at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=013601.

[37] For example, on August 30, 1994, NAC was approved as a new drug under ANDA 074037, *see* https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=074037, which was over a decade before NDA 013601 was withdrawn for reasons other than safety or effectiveness, *see* 74 FR 6896, 6897 (Feb. 11, 2009).

since well before the ingredient was marketed as a dietary supplement or as a food simply because the original NDA holder decided to discontinue distribution of its drug.

ii. FDA's Longstanding Position Has Been that NAC is Excluded from the Dietary Supplement Definition Under Section 201(ff)(3)(B) of the FD&C Act

FDA disagrees with your petitions' assertion that the July 2020 Warning Letters announced a "policy change" regarding whether NAC may be used as or in a dietary supplement. As described in Section I.B, FDA's position for over 20 years has been that NAC is excluded from the dietary supplement definition because of the exclusion clause. Thus, the July 2020 Warning Letters did not state a new position, were not a policy change, and were not arbitrary and capricious under the APA. Moreover, the APA provides for judicial review of "final agency action for which there is no other adequate remedy in a court," 5 U.S.C. 704, and the July 2020 Warning Letters do not constitute final agency action. *See, e.g.*, *Holistic Candlers & Consumers Ass'n v. FDA*, 664 F.3d 940 (D.C. Cir. 2012).

CRN's reliance on the fact that FDA "never raised any issues with the drug preclusion clause" when reviewing structure-function claim notifications for NAC-containing products (CRN Petition at 8) is misplaced. An FDA response, or lack thereof, to a structure-function claim notification is of limited relevance to our position on an ingredient's status under the exclusion clause. FDA's review of such notifications focuses on the criteria in section 403(r)(6) of the FD&C Act. This review generally does not include a review of the ingredients themselves. In fact, under 21 CFR 101.93(a)(2), the notification of a structure-function claim is not even required to list the ingredients in the product. Further, a response to a structure-function claim notification is not required or intended to be an all-inclusive statement of issues that may exist in connection with the product(s). Thus, FDA's silence on an ingredient's status under the exclusion clause in a response to a structure-function claim notification (or a lack of FDA response) should not be read as a statement that the ingredient is permitted in dietary supplements.[38,39]

iii. FDA Continues to Evaluate the NPA Petition's Request to Undertake Rulemaking to Permit the Use of NAC in or as a Dietary Supplement

As discussed above, in the November 2021 Tentative Response Letters, FDA asked for data, research results, and other information related to the safe use of NAC in products marketed as

[38] That said, FDA acknowledges that a response to a qualified health claim petition involving a product that contained NAC, dated December 12, 2018 (CRN Petition at 8 n.29), erroneously described the product as "a dietary supplement that includes vitamins or other nutritional substances (i.e., N-acetyl cysteine . . .) . . . ."

[39] The CRN Petition also contends that "the long-established structure-function claims" for NAC-containing products labeled as dietary supplements "(*e.g.*, maintain cellular health, boost cellular glutathione levels, antioxidant support) are vastly different than the disease claims made for the NAC products considered by the agency prior to 1994 to which FDA points for establishing NAC's pre-existing use as a drug (as a mucolytic)" (CRN Petition at 6). There is nothing in the statutory language of the exclusion clause, the legislative history, or the *Pharmanex v. Shalala* decision that provides that two products have to be marketed for similar intended uses to be considered the same "article" under section 201(ff)(3)(B) of the FD&C Act.

dietary supplements, and any safety concerns, to help us evaluate NPA's rulemaking request.[40] While we are continuing to review the data received, we note that we have received comments supporting NPA's rulemaking request and providing information on the safety of NAC in dietary supplements.

Although our review of the available data and information is still in progress, thus far we have not identified safety concerns with respect to the use of NAC in or as a dietary supplement. FDA has not yet reached a decision on the NPA Petition's request that FDA undertake rulemaking to permit the use of NAC in or as a dietary supplement. However, if, among other considerations, FDA does not identify such safety 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. Once we have completed our review and reached a decision, we intend to respond to the rulemaking request in the NPA Petition, in accordance with our regulations. In the interim, in light of the absence of safety concerns based on our review thus far, among other factors, we think it appropriate to consider exercising enforcement discretion for products labeled as dietary supplements that contain NAC if such products would be lawfully marketed dietary supplements if NAC were not excluded from the definition of dietary supplement and are not otherwise in violation of the FD&C Act, and we intend to issue guidance on this topic.

D. Other Issues Raised in the Petitions and Comments

FDA offers the below responses to the other issues raised in the petitions and comments.

i. The equitable defense of laches

Although the CRN Petition asserts that the equitable defense of laches prevents FDA from enforcing its position regarding the regulatory status of NAC (CRN Petition at 9), it does not explain how the doctrine of laches supports its request that FDA reverse its position that NAC is excluded from the definition of dietary supplement. Laches is an affirmative defense that a defendant may raise in litigation. The citizen petition process is not an enforcement action. Thus, the equitable defense of laches does not apply here. Moreover, you have not shown that this is one of the limited circumstances in which a defense of laches could be raised against the government. *See, e.g.*, *United States v. Beebe*, 127 U.S. 338, 344 (1888).

[40] CRN has stated in comments to the docket (FDA-2021-P-0523-0012 and FDA-2021-P-0938-0009) that it is "very concerned" with FDA's request in the November 2021 Letters for "extensive and irrelevant NAC marketing and safety information" (FDA-2021-P-0523-0012 & FDA-2021-P-0938-0009 at 3). On page 2 of another comment letter (FDA-2021-P-0938-0022), CRN also states that the "information on safety and current market evaluation…does not even appear to be relevant to the NPA request for rulemaking, given that the [FD&C Act] makes no reference to a safety evaluation when granting this rulemaking authority." As explained above, however, information on the earliest marketing of NAC as a dietary supplement or as a food is relevant to our analysis of the requests in the CRN Petition and the NPA Petition. Furthermore, we disagree with CRN's assertion as to the need for safety information, and we intend to address this further in our final response to NPA's request for rulemaking. Data and information in response to our request for safety information will facilitate our ability to efficiently respond to NPA's rulemaking request.

ii. Interpretation and application of the term "authorized for investigation" in section 201(ff)(3)(B)(ii) of the FD&C Act

The NPA Petition asserts that FDA's interpretation and application of the term "authorized for investigation" in section 201(ff)(3)(B)(ii) of the FD&C Act[41] "to mean an article that is subject of an [investigational new drug application (IND)] that has gone into effect" is "troubling" because "INDs are not authorized by FDA" and there is "no public access to a list of current articles that are the subject of an IND" (NPA Petition at 6). The NPA Petition also asserts that "it is perplexing that FDA has determined that Congress intended the phrase 'authorized for investigation' to mean the date an IND became effective" and claims this interpretation is inequitable (NPA Petition at 6 through 8). However, the NPA Petition does not explain how these assertions and the arguments made to support them are related to the requests made in the petitions or to NAC specifically, and they do not in fact appear to be related. In particular, the meaning of the phrase "authorized for investigation" in section 201(ff)(3)(B)(ii) of the FD&C Act has no bearing on whether NAC is excluded under section 201(ff)(3)(B)(i) of the FD&C Act, nor is it relevant to NPA's request for rulemaking. Therefore, FDA declines to address the assertions and arguments made pertaining to the interpretation or application of the term "authorized for investigation" in section 201(ff)(3)(B)(ii) of the FD&C Act.

iii. Scope of section 201(ff)(3)(B)(i) of the FD&C Act

One comment on the CRN Petition appears to take the position that section 201(ff)(3)(B)(i) of the FD&C Act requires, or should require, FDA to make an independent finding that use of the article as a dietary supplement would undermine the incentives for drug development or undermine an approved drug's market presence, and that FDA can only apply the exclusion if we have made this finding. We disagree. The statutory language plainly does not include such a requirement and the legislative history does not support reading this additional requirement into the statute. Although one of Congress's motivations for enacting the exclusion clause was addressing concerns about preventing DSHEA from undermining the drug development process, Congress chose to accomplish this goal by establishing the "race to market" framework under which a substance is excluded from the dietary supplement definition only if its approval as a new drug, or its authorization for investigation as a new drug (if there were substantial clinical investigations that were made public), preceded its marketing as a dietary supplement or as a food.

III. Conclusion

For the reasons discussed above, FDA is denying the CRN Petition in its entirety and the NPA Petition's request that we reverse our position that products containing NAC are excluded from the definition of dietary supplement under the exclusion clause. FDA has not yet reached a decision on the NPA Petition's request that FDA undertake rulemaking to permit the use of NAC

[41] As noted above, section 201(ff)(3)(B)(ii) of the FD&C Act provides that a dietary supplement does not include "an article has been authorized for investigation as a new drug … 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" or another exception applies.

in or as a dietary supplement. However, we are considering initiating rulemaking under section 201(ff)(3)(B) to permit the use of NAC in or as a dietary supplement and if, among other considerations, FDA does not identify safety 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. In the interim, while we work to complete our review, for the reasons stated above, we think it appropriate to consider exercising enforcement discretion with respect to products labeled as dietary supplements that contain NAC if such products would be lawfully marketed dietary supplements if NAC were not excluded from the definition of dietary supplement and are not otherwise in violation of the FD&C Act. As discussed above, we intend to issue guidance on this topic.

Sincerely,

Douglas W. Stearn -S

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