

August 18, 2021

CITIZEN PETITION REGARDING REGULATORY STATUS OF NAC

The undersigned, on behalf of the Natural Products Association (“NPA”), submits this petition under 21 U.S.C. §321(ff) and 21 C.F.R. § 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs either determine, based on the facts provided herein, that N-acetyl-L-cysteine (“NAC”) is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3) or, in the alternative, to recommend and support to the Secretary of HHS, that they issued a regulation, after notice and comment, finding that NAC, would be lawful under the Food, Drug, and Cosmetic Act (the “Act”).¹

About the NPA

Founded in 1936, the Natural Products Association (“NPA”) is the nation’s largest and oldest nonprofit organization dedicated to the natural products industry. Natural products are represented by a wide array of consumer goods that grow in popularity each year. These products include natural and organic foods, dietary supplements, pet foods, health and beauty products, “green” cleaning supplies and more. Generally, natural products are considered those formulated without artificial ingredients and that are minimally processed. NPA advocates for the right of consumers to have access to products that will maintain and improve their health, and for the right of retailers and suppliers to sell these products. NPA represents over 1,400 members, accounting for more than 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, and health/beauty aids. NPA unites a

¹ 21 U.S.C. 301 *et seq.*

diverse membership, from the small health food stores to large dietary supplement manufacturers.

NPA played a key role in the passage of the Dietary Supplement Health and Education Act of 1994 (“DSHEA”), Pub. L. No. 103-417, 108 Stat. 4325. This important legislation struck a balance between the need for consumers to have access to and information about safe and effective dietary supplements while also preserving the government’s interest in protecting the public from unsafe products and false and misleading claims. Currently, NPA advocates before Congress, the Food and Drug Administration, the Federal Trade Commission, and other federal and state agencies, legislatures, state attorneys' general and the court.

I. ACTION REQUESTED

For the reasons that follow, NPA respectfully requests that the Commissioner of Food and Drugs either determine, based on the facts provided herein, that NAC is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B) or, in the alternative, to recommend and support to the Secretary of HHS, that, in their discretion, they issue a regulation, after notice and comment, finding that NAC would be lawful under the Act.

II. STATEMENT OF GROUNDS

A. Background

a. Exclusion from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B)

21 U.S.C. §321(ff)(3)(B), Section 201(ff)(3)(B) of the Act, prohibits from the definition of a dietary supplement any article:

- that is approved under 21 U.S.C. § 355 (section 505 of the Act); or
- 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.

There are two exceptions to 201(ff)(3)(B):

- verifiable, contemporaneous evidence documenting that article or any other compound containing the article as its active moiety was marketed as a dietary supplement or as a food prior to the article's authorization for investigation as a new drug under an IND;² or
- the Secretary, at the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under the Act.³

This Section of the Act has come to be known in the industry as creating a “race to market” between those interested in investigating an article as a drug and others interested in marketing the same article in a product labeled as dietary supplements. This Section of the Act purportedly is intended to preserve the financial incentives to both bring dietary ingredients to market and to conduct research on new drugs.

b. FDA's inequitable interpretation and application of 21 U.S.C. §321(ff)(3)

In passing the Act,⁴ Congress charged the FDA to “protect the public health” by ensuring that “foods are safe, wholesome, sanitary, and properly labeled.” 21 U.S.C. § 393(b)(2)(A). In 1994, the FDCA was further amended with the Dietary Supplement Health and Education Act (“DSHEA”).⁵ DSHEA established a new category of food products – dietary supplements – that have unique, comprehensive safety, labeling, manufacturing, and other related standards. DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of dietary supplements. *See, e.g.*, 103 CONG. REC. S17049 (daily ed. Nov. 23, 1993) (statement of Sen. Hatch).

i. “Old Dietary Ingredients”

² FDA Response to BioStratum Inc., Docket No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305). Page 14

³ 21 U.S.C. § 321(ff)(3)(B)(ii).

⁴ Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301 *et seq.* (1998).

⁵ Pub. L. No. 103-417, § 4, 108 Stat. 4325 (1994).

Among other things, DSHEA established the definition of a dietary supplement under Section 201(ff) of the Act.⁶ Under this definition, a dietary supplement must, among other things, contain at least one dietary ingredient, be swallowed, not intended to replace a meal, and not contain an ingredient found to be excluded under the race-to-market clause. DSHEA also established, under Section 413(d) of the Act, the definition of a “new dietary ingredient” (“NDI”) to mean a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994.⁷ Although there is no statutory or regulatory definition, the term “old dietary ingredients” has come to describe ingredient that were on the market prior to DSHEA and would retroactively satisfy the definition of a dietary ingredient under DSHEA.⁸ There is no authoritative list of dietary ingredients – old dietary ingredients, that were marketed in dietary supplements before October 15, 1994. Even more, the entire category of food we now call dietary supplements, nor any of the requirements for a food to be classified as one, including the race-to market clause, even existed prior to October 15, 1994. The statutory interplay between the race-to-market clause and the effective date of Sections of DSHEA results in a situation in which an ingredient, legally market pre-DSHEA (before October 15, 1994), could retroactively have become violative of the Act because of the race-to-market. Prior to DSHEA, there was no need for a responsible distributor to be concerned with the approval date of drug/biologic or when a new drug was authorized for investigation. Essentially, the distributor of what was legal ingredient, pre-DSHEA could be forced off the market because of losing a race-to-market that did not exist when they first placed the ingredient into commerce. To my knowledge, FDA has been silent on its position concerning how it would proceed if ever presented with a situation that

⁶ 21 U.S.C. § 321(ff).

⁷ 21 U.S.C. 350b(d).

⁸ 21 U.S.C. § 321(ff)(1).

led to such a confused and highly inequitable end result. The Congressional Record that accompanied the passage of DSHEA may, however, provide some insight. For example, the Senate Report published by the Committee on Labor and Human Resources, of which Senator Hatch was the chairman, stated:

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 foods, including carbonated beverages, and it has also been approved by FDA as a drug.⁹

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. What is telling is that the report establishes this with our any analysis under, or even reference to, the "race-to-market" paradigm of Section 201(ff)(3) of the Act as amended by DSHEA. This would indicate that congressional intent relative to articles that were marketed as both drugs and dietary

⁹ See: Section B – Senate Report 103–410 (to accompany S. 784) October 8, 1994

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 Act as amended by DHEA. It seems odd that FDA would now take a view counter to this with regards to NAC.

ii. Generally

As noted above, other than the date of approval for a new drug or biologic, the date an article is authorized for investigation as a new drug or biologic is necessary for a distributor or manufacturer of a dietary ingredient would be excluded from the definition of a dietary supplement under Section 201(ff)(3)(b) of the Act. According to the FDA's Draft Guidance *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* published in August 2016 (herein draft guidance), the FDA has taken a position that Congress, in DSHEA, intended the term "authorized for investigation" to mean an article that is subject of an IND that has gone into effect."¹⁰ This interpretation and application of the Act is troubling for at least two reasons; first, INDs are not authorized by FDA, and second, there is, to my knowledge, no public access to a list of current articles that are the subject of an IND. In short, there is no way for anyone, other than someone at FDA with access to the records, to know that an IND has become effective until either clinical studies begin under it, or there is a publication relating to it.

In this situation, it is perplexing that FDA has determined that Congress intended the phrase "authorized for investigation" to mean the date an IND became effective. Under 21 C.F.R. Part 312, the regulations pertaining to IND applications, it is clear that FDA can only respond to an IND application by either placing it on clinical hold or allowing it to become effect 30 days it

¹⁰ U.S. Food and Drug Administration. (August 2016). *Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance For Industry*, Draft Guidance. Washington DC. Page 44.

was submitted for review to the agency. Equally perplexing is FDA's determining that Congress would set up a regulatory race-to-market between those wishing to distribute/manufacture dietary supplements and those investigating articles as drugs and not intend for both sides to have access to the data that would be absolutely necessary to make any determination as to the marketing status of an ingredient. It is more likely that Congress intended something a bit more equitable. For example, although INDs are not approved by FDA – they simply become effective, the actual protocols conducted under an effective IND are approved, as required by regulations enforced by FDA, by an Institutional Review Board.¹¹ IRBs are required to register with FDA prior to reviewing and approving protocols. A likely solution would be for FDA to establish a registry of IRB approved clinical studies that would be accessible to stakeholder intending to distribute or manufacture dietary ingredients. In order to highlight the extent of just how inequitable this interpretation and application of the regulations can be, I'll offer the following scenario and how it would result under the current paradigm:

- October 15, 2021: The date an IND for the subject article becomes effective;
- October 16, 2021: The date, after ensuring that all applicable aspect of the Act and pertinent regulations are met, and after a diligent search of all publicly available records demonstrated that the subject article was NOT excluded from the definition of a dietary supplement under the race-to-market clause, the subject article is first distributed in a product labeled as a dietary supplement;
- October 17, 2024: The date a protocol to conduct a substantial clinical study of the subject article as a drug is approved, under the effective IND for the subject article, by an IRB; and

¹¹ 21 C.F.R. Part 56.

- October 18, 2026: The first date the existence of this investigations has been made public by a publication in a scientific or medical journal.

In this scenario, despite the fact that the subject article was legally marketed as a dietary ingredient for five (5) years, based on FDA's current interpretation and application of the race-to-market clause, the subject article would become a violative ingredient, in products marketed as dietary supplements, as of October 18, 2026. Considering that, as noted above, "DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of dietary supplements." It is difficult to understand how FDA has determined that this outcome meets the will of Congress in legislating DSHEA.

c. NAC

i. Ingredient Background

N-acetylcysteine (also known as N-acetyl-cysteine, NAC) is a precursor to the amino acid L-cysteine and consequently the endogenous metabolite antioxidant glutathione (GSH). Cysteine is a semi-essential amino acid. It's considered semi-essential as the human body produces it from two other amino acids, methionine and serine. It becomes essential only when the dietary intake of methionine and serine is suboptimal or deficient. Two other amino acids — glutamine and glycine are used with NAC to make and replenish GSH. NAC is most notably found in plants of the *Allium* species, especially in the onion (*Allium cepa*, 45 mg NAC/kg). The mercapturic acid (MA) pathway is a metabolic route for the processing of glutathione conjugates to MA (N-acetylcysteine conjugates). An N-acetyltransferase enzyme, NAT8, catalyzes the transfer of an acetyl group from acetyl-CoA to the cysteine amino group, producing a MA, which is excreted in the urine. N-terminal acetylation (NTA) is a prevalent protein modification in eukaryotes. The

majority of proteins are acetylated at their N-terminus in a co-translational manner by ribosome-associated N-terminal acetyltransferases (NATs). Thus, NAC is a naturally occurring endogenous metabolite, in addition to a component of food.

In a series of Warning Letters issued by FDA in 2020, FDA claimed NAC was previously approved as a drug by FDA prior to marketing as a supplement. The specific forms and indications that preceded the supplement were as an intravenous injectable for acetaminophen overdose and as an inhalational drug for bronchopulmonary disease. In 2010 FDA challenged an NDIN on NAC, sending the submitter an NDL letter. In July of 2020, as part of a warning letter initiative on “hangover” disease claims, FDA reiterated that position. At the time of those letters 1,170 products containing NAC were listed in the National Institutes of Health (NIH) Dietary Supplement Label Database (DSLDB). Further complicating the issue, in 2018, as part of a response to a petition for a qualified health claim (QHC) by Sevo Nutraceuticals, FDA affirmed that NAC was a lawful component of food or a dietary supplement. A response to a QHC petition is considered final agency action whereas a warning letter is generally not.

ii. Analysis under and application of 21 U.S.C. §321(ff)(3)

In a series of Warning Letters issued by the Agency in 2020, FDA stated its position that, under Section 201(ff)(3)(B)(i) of the Act, NAC is excluded from the definition of a dietary supplement. According to Section 201(ff)(3)(B)(i) of the Act, an article is excluded from the definition of a dietary supplement if it is approved as a new drug under Section 505 of the Act before it was first marketed as a dietary supplement or as a food. In the aforementioned Warning Letters, FDA purports to have evidence demonstrating that NAC was approved as a drug by FDA prior to marketing as a supplement. However, the specific forms and indications of this approved NAC

article, that supposedly preceded the marketing of NAC as a supplement, were as an intravenous injectable for acetaminophen overdose and as an inhalational drug for bronchopulmonary disease. It is clear under Section 201(ff)(2) of the Act that an article must be intended for ingestion for it to meet the definition of a dietary supplement. What remains unclear is if the language provided for in Section 201(ff)(3)(B)(i) of the Act calls for an article's exclusion from the definition of dietary supplement when the article has been approved as a drug not intended to be administered by ingestion. Furthermore, I am aware from first-hand experience while leading the Agency's dietary supplement program that documents of the type, FDA is relying on to determine that date NAC was first approved as a new drug are questionable at best, and oddly not posted at the time of the 2020 warning letters. Usually, 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. In addition, it must also be considered that there is a long history of NAC being safely marketed in products that, post DSHEA, are considered and regulated under the Act as dietary supplements. For example, the attached advertisement clearly indicated that NAC was marketed as such in October of 1993, - a full year prior to the effective date of DSHEA. In other words, the provision of the Act FDA now relies on to determine that NAC is excluded from the definition of a dietary supplement did not even exist at the time NAC was first marketed as a dietary supplement. It is difficult to understand how the Agency could assume such an unreasonable and inequitable interpretation of Section 201(ff)(3) of the Act.

B. Conclusion

FDA's sudden change of policy relative to the status of NAC as dietary ingredient, along with the unreasonable and inequitable interpretation of the Act it relies in making such policy change,

are a detriment to entire dietary supplement stakeholder community. The current situation with NAC is yet another example of the inconsistent and mercurial way in which FDA chooses to both interpret DSHEA and then determines how to best use resources under DSHEA to protect the public health. Despite repeated requests from multiple stakeholders, FDA has been unable to articulate any risk to the public health posed by NAC when marketed as a dietary ingredient or dietary supplement.

For the foregoing reasons, FDA must reverse its arbitrary or capricious position that NAC is excluded from the definition of a dietary supplement under Section 201(ff)(3)(B)(i) of the Act. NPA respectfully requests that the Commissioner of Food and Drugs either determine, based on the facts provided herein, that NAC is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B) or, in the alternative, to recommend and support to the Secretary of HHS, that, in their discretion, they issue a regulation, after notice and comment, finding that NAC would be lawful under the Act.

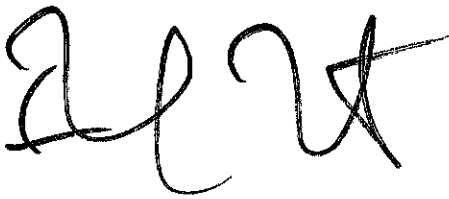
Additionally, considering that the agency will likely need to avail themselves of this process, to stabilize the consumer market for Cannabidiol (CBD). As the prior FDA Commissioner Dr..Hahn noted, it would be an “*fool’s errand*” to try to remove CBD from the marketplace, and that the agency will possibly issue a regulation to create a pathway to market for Cannabidiol (CBD) and possibly other Cannabinoids in dietary supplements and conventional foods in the immediate future. It would seem to be in the best interest of all stakeholders that FDA is actively using all tools at their disposal to meet their mandate of protecting and promoting public health.

III. ENVIRONMENTAL IMPACT

The Petitioners claims a categorical exclusion from the requirements for an Environmental Assessment under 21 CFR § 25.32 in light of the fact that, FDA granting NPA's request will not affect the environment.

IV. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations; NONE.: I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

A handwritten signature in black ink, appearing to read 'DF', is written over the signature line.

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