UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

NATURAL PRODUCTS ASSOCIATION, Plaintiff, v. FOOD AND DRUG ADMINISTRATION; DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, in his official capacity as Secretary of the Department of Health and Human Services; and ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, Defendants.	Case No. 8:21-cv-3112-TDC

FIRST AMENDED COMPLAINT
FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff, Natural Products Association ("NPA"), for its First Amended Complaint against the defendants, Food and Drug Administration ("FDA"), Department of Health And Human Services ("HHS"), Xavier Becerra, in his official capacity as Secretary of the Department of Health and Human Services, and Robert M. Califf, M.D., in his official capacity as Commissioner of the FDA (collectively referred to as "Defendants"), alleges as follows.

INTRODUCTION

1. NPA brings this action against Defendants for declaratory and injunctive relief. Defendants have concluded that a product called N-acetyl-L-cysteine ("NAC") is excluded from the definition of a dietary supplement under a provision of the Food, Drug, and Cosmetic Act ("FDCA"), as amended by the Dietary Supplement Health and Education Act ("DSHEA"), 21 U.S.C. § 321(ff)(3)(B)(i). Defendants have taken final agency action in their determination that

NAC is excluded from the definition of a dietary supplement set forth in DSHEA. NAC could only be excluded from DSHEA's definition of a dietary supplement through Defendants' improper retroactive application of DSHEA or misapplication of the law. There is nothing in the relevant statute that allows for its retroactive application and all proper interpretations of DSHEA mandate that NAC is a lawful dietary ingredient that is not excluded from the definition of a dietary supplement.

2. NPA respectfully requests that the Court enter a declaratory judgment and a preliminary and permanent injunction under the Administrative Procedure Act and hold unlawful and set aside FDA's final agency actions with respect to NAC that are arbitrary, capricious, an abuse of discretion, and contrary to law. NPA requests that this Court order that Defendants cease the unlawful retroactive application of the FDCA, as amended by DSHEA, and declare that the drug exclusion provision (21 U.S.C. § 321(ff)(3)(B)) does not retroactively apply to NAC.

PARTIES

3. NPA is a Delaware non-profit corporation that does business as Natural Products Association. It has a principal place of business in Washington, DC.

4. FDA is an agency of the United States government tasked with administering and enforcing, among other things, the FDCA, as amended.

5. HHS is an executive department of the United States government and oversees the FDA.

6. Secretary Becerra is the Secretary of HHS. He oversees, among other things, the FDA. He is sued in his official capacity.

7. Dr. Califf is the Commissioner of Food and Drugs. He oversees the activities of FDA. He is sued in his official capacity.

JURISDICTION

8. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1346, and 5 U.S.C. §§ 701-06. An actual controversy exists between the parties within the meaning of 28 U.S.C. § 2201(a) and this Court may grant declaratory relief, injunctive relief, and other relief pursuant to 28 U.S.C. §§ 2201-02 and 5 U.S.C. §§ 705-06.

9. More particularly, jurisdiction under 5 U.S.C. §§ 701-06 exists as set forth further herein, based upon FDA's conclusive and final categorization that the drug exclusion clause applies retroactively and that, as such, NAC is a drug that is excluded from the definition of a dietary supplement under DSHEA.

10. Personal jurisdiction over Defendants exists in the State of Maryland because they are engaged in substantial activity here and the FDA is headquartered in the state.

11. Venue in this District is proper under 28 U.S.C. § 1391(e) because the action seeks relief against federal agencies located in this district and a substantial part of the events or omissions giving rise to the claim occurred in this district.

FACTS

I. NPA/STANDING

12. Founded in 1936, 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.

13. NPA advocates for the rights of consumers to have access to safe products that will maintain and improve their health, and for the rights of retailers and suppliers to sell these products.

NPA represents over 700 member organizations, 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 diverse membership, from the smallest health food store to the largest dietary supplement manufacturer.

14. NPA has standing to bring this action on behalf of itself and its members.

15. NPA advocates before Congress, FDA, HHS, the Federal Trade Commission, and other federal and state agencies, legislatures, state attorneys' general and courts. Additional information about NPA and its work is available at https://www.npanational.org/.

16. Further, NPA is an industry leader in promoting quality standards and has developed proactive certification programs for that purpose. NPA was the first organization to offer a third-party good manufacturing practices ("GMP") certification program for the manufacturing of dietary supplements. NPA's GMP standard includes all of the FDA GMP requirements of 21 C.F.R. Part 111 as well as certain requirements that exceed Part 111 or reflect best industry practices. NPA's GMP certification is only awarded to companies that meet a high level of compliance with NPA's standard. NPA's certification not only meets, but exceeds, FDA's GMP requirements. NPA's certification is awarded only after companies' satisfaction of NPA's rigorous requirements have been verified through comprehensive third-party inspections of the company's facilities and GMP-related documentation.[1] NPA also has a "Natural Seal" Standard and Certification programs that dictate whether cosmetic, personal-care-products, and certain home care products can be deemed truly "natural."[2]

[1] *See* https://www.npanational.org/certifications/npa-gmp-certification-program/.

[2] *See* https://www.npanational.org/certifications/natural-seal/.

17. In addition, NPA's "TruLabel" program is a dietary supplement label registration and random-testing program adopted by NPA in 1990 and subsequently made a requirement for supplier membership in NPA since 1995. This internal oversight program has created a high level of confidence with retailers and consumers that products sold in the marketplace under NPA's TruLabel program are accurately labeled; establish an ongoing self-regulatory process within the industry; demonstrate industry maturity to legislators; and provide a comprehensive industry product database. Under the TruLabel program, products are periodically selected for laboratory analysis to confirm the label; in other words, to verify that what is on the label is what is in the product.[3]

18. Another example of industry self-regulation effectuated by NPA's oversight is the Supplement Safety and Compliance Initiative ("SSCI"). SSCI is an industry-driven initiative led by the nation's leading retailers to provide a harmonized benchmark to recognize various safety standards throughout the entire dietary supplement supply chain. SSCI provides enhanced quality assurance for products on retailer shelves. Dietary supplements must meet or exceed the SSCI benchmark to be accepted in participating major retailers, all with the goal of providing quality products and increasing consumer confidence that the products they are consuming are safe.[4]

19. NPA also organized the Natural Products Foundation, a 501(c)(3) entity, to stimulate and support research, education and knowledge regarding dietary supplements, nutritional foods, and related products, with the overall objective of advancing the knowledge of the public, and thereby, improving the public health.

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[3] *See* https://www.npanational.org/certifications/trulabel-program/.

[4] *See* http://www.ssciglobal.org/.

20. NPA played a key role in the passage of the DSHEA. This important legislation, discussed further below, 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.

21. The dietary supplement industry is large. In the United States, the market currently exceeds $40 billion and includes thousands of companies – including manufacturers, retailers, and formulators that create and distribute a vast array of products aimed at improving consumer health. While estimates vary, the now former Commissioner of the FDA stated that: "What was once a $4 billion industry comprised of about 4,000 unique products, is now an industry worth more than $40 billion, with more than 50,000 – and possibly as many as 80,000 or even more – different products available to consumers."[5] "The use of dietary supplements, which include ingredients such as vitamins, minerals, amino acids, or herbs, has become a routine part of the American lifestyle. Three out of every four American consumers take a dietary supplement on a regular basis. For older Americans, the rate rises to four in five. And one in three children take supplements, either given to them by their parents or, commonly in teens, taking them on their own."[6] Indeed, physicians frequently recommend a supplement regimen in addition to medical intervention.

22. As the natural product industry has grown and become more sophisticated in increased compliance requirements and internal oversight as well as innovation of new products and methods of use, consistent and applicable legal and regulatory guidance and enforcement has been lacking. In some instances, FDA has taken illogical enforcement actions to preclude products

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[5] *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight* (Feb. 11, 2019), available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-new-efforts-strengthen-regulation-dietary.

[6] *Id.*

from the market without justification on the one hand, or simply refused to enforce its own statutes and regulations on the other hand. For example, under the FDCA, under most situations, FDA is required to review a distributor's basis for concluding that "new dietary ingredient" ("NDI") is reasonably expected to be safe prior to that distributor putting that NDI into commerce. *See* 21 U.S.C. § 350b. Although it has been conservatively estimated that there have been tens of thousands of new dietary ingredients introduced into the market since the passage of DSHEA, FDA has reviewed the basis for safety of less than 900 unique ingredients. FDA's enforcement of its enabling statutes and regulations promulgated under it has been slipshod at best, despite organizations like NPA striving to advocate for and provide oversight and compliance programs for safe dietary supplements and other products for consumers.

23. With specific reference to NAC, the actions by FDA impair NPA's ability to carry out its mission and commitment to consumer safety and access to natural health ingredients. NPA and its members have spent significant time and money in response to FDA's sudden and new position, discussed below, that the exclusion provision of DSHEA known as the "drug preclusion" or "race to market clause" is to be given *retroactive* effect (relative to October 15, 1994, the effective date of DSHEA), and that NAC is barred from the supplement market. Were FDA properly interpreting and applying DSHEA, NPA would not have been forced to take action in response, including: discussions and written communications with regulators and third parties, preparation and submission of a Citizen Petition, submission of numerous Freedom of Information Act requests, responses to media inquiries and the preparation and filing of this action. NPA and its members have suffered harm as a direct and proximate result of FDA's recent final agency actions concluding that the drug exclusion provision of DSHEA applies retroactively to NAC. NPA members who have been selling NAC for years, if not decades, have seen their sales dry up

as result of having to preemptively pull products from the shelves by virtue of FDA's unlawful decisions.

24. As discussed further below, in 2021, Amazon.com implemented a take-down policy requiring sellers on its platform to remove NAC-containing products that would violate FDA's recent final agency actions determining that NAC could not be included in products marketed as dietary supplements. In many instances, companies that are NPA members were forced to remove their products from Amazon, which was a direct result of FDA's final agency decisions and statements aimed at removing NAC from the dietary supplement market. NPA's members have lost and will continue to lose significant revenue because Amazon, among other retailers, will no longer allow companies to sell NAC-containing products. Those NPA members have been irreparably harmed as the result of FDA's interpretation and retroactive application of DSHEA with respect to NAC-containing dietary supplement products.

25. Further, FDA has recently denied issuing export certificates sought by one or more NPA members for dietary supplement products that contain NAC. Such certificates issued by FDA are required by many foreign countries as a condition of allowing the importation of dietary supplement products. By denying export certificates, FDA has taken another final agency action that works to preclude U.S. distributors from selling NAC-containing dietary supplement products in overseas markets due to the agency's misplaced position on the retroactive application of DSHEA's drug exclusion provision. FDA's denial of such certificates has irreparably harmed those NPA members.

II. REGULATION OF DIETARY SUPPLEMENTS

26. Asserting that "improving the health status of United States citizens ranks at the top of the national priorities of the Federal Government" and that "the importance of nutrition and the

benefits of dietary supplements to health promotion and disease prevention have been documented increasingly in scientific studies," DSHEA became law on October 25, 1994 as an amendment to the Food, Drug, and Cosmetic Act. DSHEA represented a victory for the millions of consumers of dietary supplements who felt that FDA advocated unreasonable regulatory guidelines prior to the passage of DSHEA. The language of DSHEA addressed the aforementioned consumer concern by stating that "the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products and accurate information to consumers" and that "dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare." DSHEA § 2. DSHEA further established that "consumers should be empowered to make choices about preventive health care programs based on data from scientific studies of health benefits related to particular dietary supplements." *Id.* § 2(8).

27. DSHEA was introduced to counteract "unnecessarily stringent" federal intervention into the manufacturing, sale, and labelling of dietary supplements and government overregulation. 103 CONG. REC. S4577 (daily ed. Apr. 7, 1993) (statement of Sen. Hatch); 103 CONG. REC. S17049 (daily ed. Nov. 23, 1993) (statement of Sen. Hatch). The legislation concluded that consumer well-being is improved when there is greater access to dietary supplements. 103 CONG. REC. S4577 (daily ed. Apr. 7, 1993) (statement of Sen. Hatch). Supplement producers and related companies should be free from intervention as long as "the labelling and advertising are truthful, non-misleading, and there exists a reasonable scientific basis for products claims." *Id.*

28. Section 201(ff) of the Food, Drug, and Cosmetic Act, as amended by DSHEA, specifically defined what it means to be a "dietary supplement." In relevant part, the term is defined as:

> a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following ingredients:
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> > (A) a vitamin;
> > (B) a mineral;
> > (C) an herb or other botanical;
> > (D) an amino acid;
> > (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
> > (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E).

21 U.S.C. § 321(ff)(1). Section 201(ff)(3)(B) of DSHEA goes on to exclude from the definition of dietary supplement:

> (i) an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, 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,
>
> 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.

21 U.S.C. § 321(ff)(3)(B). The first exception, known as the "drug exclusion" clause, the one most relevant to this case, means that companies may not market in products labeled as dietary supplements an article that has been approved as a new drug unless the article was marketed as a dietary supplement or as a food before it obtained approval as a drug. Significantly, DSHEA did not include any provision indicating that any of its regulations, including the drug exclusion provision, was intended to operate retroactively from the effective date of DSHEA.

29. Particularly, the legislative history of DSHEA actually contradicts any notion that the drug provision has retroactive effect:

> 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 offered in 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.

Sen. Rept. 103-410 (Oct. 8, 1994).

30. The near-ubiquitous ingredient L-carnitine is an oft-referenced example of an ingredient that would be excluded from dietary supplements under FDA's interpretation of the drug exclusion clause of DSHEA that it has applied to NAC. L-carnitine was marketed as both a dietary ingredient and an approved drug prior to the passage of DSHEA. L-carnitine continues to be marketed as a dietary ingredient in dietary supplement without impediment. This is an example of exactly why Congress logically intended for supplements and food ingredients that were in the relevant markets prior to DSHEA to continue to be marketed as dietary ingredients (even if those ingredients could simultaneously be marketed as drugs under DSHEA's rubric) after the effective date of DSHEA, October 15, 1994.

31. Under DSHEA, dietary supplement labels cannot claim to treat, cure, prevent, or mitigate a disease, but may include statements or claims of nutritional support, in which "the statement claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States, describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans, characterizes the documented mechanism

by which a nutrient or dietary ingredient acts to maintain such structure or function, or describes general well-being from consumption of a nutrient or dietary ingredient . . . .” 21 U.S.C. § 343(r)(6)(A). An example of a structure/function claim is the popular dietary supplement St. John’s Wort, which a seller may claim to be a “mood-brightener” but not a cure for depression, which is a specific disease. *See, e.g.*, J. Beisler, DIETARY SUPPLEMENTS AND THEIR DISCONTENTS: FDA REGULATION AND THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994, 31 Rutgers L.J. 511, 517 n.29 (2000).

32. DSHEA also requires that a statement of nutritional support must have “substantiation that such statement is truthful and not misleading” and contain a disclaimer that the “statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” 21 U.S.C. § 343(r)(6)(B)-(C).

33. The FDA has recognized that “DSHEA’s purpose [is] to broaden the scope of labeling claims that may be made for dietary supplements without subjecting them to regulation as drugs.” 65 Fed. Reg. 1000-01, 2000 WL 4559, *1024. Consistent with that purpose, substantiation of structure/function claims under DSHEA requires that manufacturers have “competent and reliable scientific evidence,” which has been defined by the FDA and the Federal Trade Commission to include “tests, analyses, research, studies, or other evidence . . . .” Guidance for Industry: Structure/Function Claims, Small Entity Compliance Guide (Criterion 8). Under DSHEA, dietary supplement manufacturers are not required to conduct clinical trials or efficacy testing. *See* FDA Comment Request, *Substantiation for Dietary Supplement Claims Made Under the Federal Food, Drug, and Cosmetic Act*, 76 Fed. Reg. 51988-01, 2011 WL 3624830 (2011).

III. NAC

34. The scientific name for NAC is N-acetylcysteine (also known as N-acetyl-cysteine or N-acetyl-l-cysteine), which can also be referred to simply as acetylcysteine. The naturally occurring amino acid L-cysteine is a precursor to NAC, wherein L-cysteine is naturally metabolized into NAC in the body. NAC is then naturally metabolized to the antioxidant glutathione. L-cysteine is a semi-essential amino acid. It is considered semi-essential because 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 glutathione.

35. NAC is most notably found naturally in plants of the *Allium* species, especially in the onion *(Allium cepa,* 45 mg NAC/kg) along with animal tissue, including chicken skin. The mercapturic acid pathway is a metabolic route for the processing of glutathione conjugates to mercapturic acid (N-acetylcysteine conjugates).

36. NAC satisfies the definition of dietary ingredient under Section 201(ff)(1)(F) of the FDCA in that it is a metabolite and constituent of other articles (as noted above) that themselves satisfy the definition of a dietary ingredient under Sections 201(ff)(1)(C), 201(ff)(1)(D), and 201(ff)(1)(E) of the FDCA.

A. Acetylcysteine's 1963 approval as an inhalant cannot form the basis of exclusion of orally ingested acetylcysteine supplements.

37. The FDA has asserted that acetylcysteine was allegedly approved as a mucolytic drug in 1963 called "Mucomyst."

38. Mucomyst was initially approved solely for use as an inhalant.

39. An inhalation drug is inhaled as compared to a dietary supplement, which is ingested by humans. Among other things, the term dietary supplement means a product that is intended for ingestion. *See* FDCA § 201(ff)(2).

40. On information and belief, NAC was marketed as a dietary supplement or as a food prior to its approval as an inhalant in 1963. Thus, the drug exclusion of Section 201(ff)(3)(B)(i) does not apply to NAC because NAC was marketed as a dietary supplement or as a food prior to acetylcysteine's alleged drug approval in 1963.

41. Further, acetylcysteine's approval as an inhalant cannot form the basis for exclusion of an orally ingested NAC dietary supplement because these are two entirely different routes of administration.

42. The "article" FDA is relying upon (an inhaled form of acetylcysteine) for its application of Section 201(ff)(3)(B)(i) is not the same as the article of the NAC form (an orally ingested form) that is a dietary ingredient used in dietary supplements.

43. The 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 FDCA 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, and the strength of the new drug" (emphasis added) that is the subject article are the same as those of the referenced article.

44. Here, applying the rubric of Section 505(j)(2)(A) to NAC and the 1963-approved acetylcysteine shows that the dosage and route of administration are the not the same, and the two articles are not the same "article" as the defined by the Act.

45. Therefore the 1963 approval date has no bearing on NAC's characterization as a lawful dietary ingredient for inclusion in dietary supplements because the drug exclusion clause cannot apply, even if DSHEA could be applied retroactively.

B. Acetylcysteine's alleged approval as an oral formulation does not establish the criteria necessary to conclude that the dietary ingredient NAC should be excluded from DSHEA's definition of a dietary supplement.

46. FDA's Orange Book records indicate subsequent approvals for Mucomyst listing the Route of Administration as "Solution; Inhalation, Oral" and the earliest such approval has an approval date no earlier than January 1, 1982, as NDA 013601.

47. Documents released via a Freedom of Information Act request to FDA included an approval for oral/intubation use of Mucomyst that was allegedly approved in 1985.

48. Purportedly, the 1985 approval was strictly limited to a use of the article as an antidote for acetaminophen poisoning (*i.e.*, as a drug to counteract overdoses of drugs like Tylenol®).

49. The specious and unspecified conditions of the records and their contents concerning the oral approval of acetylcysteine relied upon by FDA are insufficient to establish a drug approval that should be used to exclude the dietary ingredient NAC from the definition of a dietary supplement under DSHEA.

50. On information and belief, NAC was marketed and sold as a dietary ingredient and a dietary supplement for human ingestion before its approval as an orally-ingested drug. Thus, the

drug exclusion of Section 201(ff)(3)(B) does not apply to NAC because NAC was marketed as a dietary supplement or as a food prior to acetylcysteine's drug approval as an oral formulation.

C. NAC was sold as a dietary supplement prior to the enactment of DSHEA in 1994.

51. Despite NAC's limited applications for which it was approved as a drug, NAC was marketed and sold as a dietary ingredient and a dietary supplement for human ingestion before October 1994. Ex. 1 reflects true and correct copies of evidence that NAC was being marketed and sold as a dietary ingredient and a dietary supplement for ingestion before October 1994. Defendants' own documentation proves that NAC was marketed and sold as a dietary ingredient and a dietary supplement before July 1993. *See* Ex. 2, Department of Health and Human Services, Public Health Service, Food and Drug Administration, *Unsubstantiated Claims and Documented Health Hazards in the Dietary Supplement Marketplace*, July 1993, at page 85 (excerpt referencing a Cell Defense Formula X11 product that contained NAC). Thus, NAC was continuously sold for many years as a food ingredient, dietary ingredient, or dietary supplement after NAC delivery forms were approved as a drug (*e.g.*, as an inhalation product) and before the passage of DSHEA in 1994. In fact, those sales of NAC as a dietary supplement proceeded unabated until FDA's very recent objection.

52. Hundreds of popular dietary supplement products containing the dietary ingredient NAC have been on sale in the United States to consumers who have come to rely on them.

53. Dietary supplements containing NAC are safe to use. There is no evidence in the public record that NAC is harmful or injurious to consumers when the dietary supplement comprised of it is used as directed. Certainly, the FDA has never suggested that NAC, as a dietary ingredient used in dietary supplements, is an unsafe product. In fact, the National Institute of

Health has noted that NAC has been sold as a drug and supplement and that NAC is safe. *See* Ex. 3.

54. Not only was NAC marketed as a dietary supplement prior to 1994, the FDA's Orange Book records indicate that acetylcysteine was not approved as an oral tablet until 2016.

55. NDA 207916 lists acetylcysteine as the active ingredient, with a route of administration listed as "Tablet, effervescent; oral," with an approval date of January 29, 2016.

56. Thus, NAC was marketed as a dietary supplement prior to the passage of DSHEA and before the date on which acetylcysteine was approved as a drug having a route of administration listed as a tablet administered orally. Thus, the drug exclusion of Section 201(ff)(3)(B) does not apply to the dietary ingredient NAC because NAC was marketed as a dietary supplement or as a food prior to DSHEA's passage.

57. Further, the FDA was well aware of such sales. Over this period of time noted above, the FDA regularly provided dietary supplement companies, including one or more NPA members, with export certificates allowing NAC-containing dietary supplements to be exported from the U.S. to foreign countries. The industry, including NPA members, relied on the issuance of such certificates by FDA for NAC.

IV. NAC FALLS UNDER THE DEFINITION OF A DIETARY SUPPLEMENT AS A DIETARY INGREDIENT UNDER SECTION 201(ff)(1)(F).

58. Section 201(ff)(1)(F) of the FDCA states that a dietary supplement can include a dietary ingredient that is "a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

59. NAC is a metabolite of cysteine because the human body metabolizes L-cysteine to NAC after L-cysteine has been ingested.

60. L-cysteine has been in the human diet for as long as humans have been consuming meat. L-cysteine is a semiessential amino acid.

61. L-Cysteine has been marketed as a dietary ingredient in dietary supplements prior to acetylcysteine's drug approval date in 1963. Attached as Ex. 4 is a true and correct copy of advertisements of L-cysteine-containing dietary supplements predating acetylcysteine's drug approval date in 1963.

62. As noted above, NAC qualifies as 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 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.

63. Similarly, NAC occurs naturally in herbs or other botanicals, such as onions and garlic.

64. Section 201(ff)(3)(F) of the FDCA establishes that NAC falls under the definition of a dietary supplement as a dietary ingredient because it is a constituent of an herb or other botanical (Section 201(ff)(1)(C)) because it occurs naturally in foods, such as onions and garlic.

65. Foods like onions and garlic have been marketed for many years, and long before acetylcysteine's approval as a drug, therefore demonstrating that NAC was a constituent of an herb or another botanical present in the food supply long before that approval. Thus, NAC is a dietary ingredient under DSHEA that is not excluded from the definition of a dietary supplement by Section 201(ff)(3)(B) of the Act because NAC was a constituent of an herb or other botanical that

itself was marketed as a dietary supplement or as a food prior to the date that acetylcysteine was approved as a drug.

V. THE FDA HAS IMPROPERLY DECIDED THAT DSHEA'S DRUG EXCLUSION PROVISION MUST BE RETROACTIVELY APPLIED WITH RESPECT TO THE DIETARY INGREDIENT NAC.

66. The FDA has represented to the public—and a member of Congress—that it has not made any final determination on the regulatory status of NAC. *See, e.g.*, Exs. 5-9. That statement—made to a member of Congress—was knowingly false. FDA has definitively interpreted DSHEA to mean and require that, among other things, the drug exclusion provision has retroactive effect, and that interpretation and application by the FDA is final agency action on the issue as it applies to NAC.

A. *Blackstone* Case

67. FDA and the Department of Justice have previously interpreted DSHEA and its drug provision to apply retroactively to NAC in a criminal action in the U.S. District Court for the Southern District of Florida, captioned *United States v. Braun, et al.*, Case No. 19-80030-CR. The docket in that case is available on Pacer.gov and is incorporated by reference in its entirety.

68. On February 3, 2017, the government applied for search warrants for Blackstone Labs, LLC and VBS Laboratories, LLC, supported by an affidavit of Kelly McCoy, a Special Agent with FDA's Office of Criminal Investigations. Agent McCoy swore under oath that products containing NAC are excluded from the definition of dietary supplements:

> The Blackstone website also lists for sale other products that violate the FDCA, including products named "Gear Support" and "PCTV." The website includes images of each product and their labels. According to the products' labels, Gear Support and PCTV contain N-Acetyl-Cysteine ("NAC") and are described as dietary supplements.
>
> Products that contain NAC are excluded from the definition of dietary supplement under 21 U.S.C. § 321(ff)(3)(B)(i) because FDA approved NAC as a "new drug"

> in 1985 and FDA does not have any information that indicates that NAC was marketed as a dietary supplement or as a food prior to its approval as a "new drug."

Ex. 10 ¶¶ 106-07. Agent McCoy concluded that there was probable cause to believe that Blackstone introduced unapproved "new drug" products into interstate commerce in violation of 21 U.S.C. § 331(d). *Id.* ¶ 111. The search warrants were approved and executed.

69. On March 7, 2019, Blackstone and others were indicted for, among other things, violating § 331(d) based on sales of products containing the "new drug" NAC. *See* Ex. 11 (counts 1 and 2). On September 19, 2021, the defendants moved to suppress evidence obtained during the execution of the search warrants. The motion specifically challenged the allegations in Special Agent McCoy's affidavit. *See* Ex. 12. The government's opposition to the motion argued that the affidavit was not misleading in describing NAC as a drug. *See* Ex. 13 at 13. Defendants filed a reply that contested the government's arguments. *See* Ex. 14 at 9-10. The Court denied the motion to suppress on October 21, 2021.

70. Should the FDA seek to assert that it has not reached a final agency action in its determination as to NAC's categorization as dietary ingredient that is excluded from the definition of a dietary supplement because it was marketed as a drug before it was marketed in a food or in a dietary supplement, this is belied by FDA's actions and determinations in the *Blackstone* case. If FDA attempts to assert that it has not yet reached any final agency actions or determination as to whether NAC is a lawful ingredient in dietary supplements and what potential regulatory action FDA might take regarding NAC-containing products, these representations or assertions would be contradicted by the statements made to the Court in the pending criminal case cited above. The FDA has repeatedly taken the position that NAC is a new drug and cannot fall within the definition of a dietary supplement, most recently in the opposition to the defendant's motion to suppress filed October 4, 2021. The FDA cannot continue to claim that it has not yet formulated a determination

of NAC's regulatory status – and taken final agency actions based on it, when NPA's members have sought clarity on this issue. In fact, the FDA has taken final agency action as evidenced by its unambiguous representations to the Court in the *Blackstone* case, thereby establishing FDA's final agency action ripe for review under the Administrative Procedure Act.

71. For the avoidance of doubt, this pleading is not asking the Court for any declaratory, injunctive, or other relief in the *Blackstone* criminal case. NPA is not a party to that litigation. NPA relies on the record in *Blackstone* as evidence that the government has taken final action to interpret the drug exclusion clause of DSHEA retroactively and that the clause applies to NAC.

B. FDA Warning Letters

72. On or about July 23, 2020, FDA sent warning letters to four companies regarding their sale of certain products that included NAC as a dietary ingredients. Exs. 15-18.

73. The warning letters concluded that:

> [Y]our product could not be a dietary supplement, because it does not meet the definition of dietary supplement under section 201(ff) of the Act [21 U.S.C. § 321(ff)]. FDA has concluded that NAC products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(i) of the Act [21 U.S.C. § 321(ff)(3)(B)(i)]. Under this provision, if an article (such as NAC) has been approved as a new drug under section 505 of the Act [21 U.S.C. § 355], then products containing that article are outside the definition of a dietary supplement, unless before such approval that article was marketed as a dietary supplement or as a food. NAC was approved as a new drug under section 505 of the Act [21 U.S.C. § 355] on September 14, 1963. FDA is not aware of any evidence that NAC was marketed as a dietary supplement or as a food prior to that date.

Id.

74. These four warning letters all concluded that the drug exclusion provision of DSHEA was applicable to NAC and subject to retroactive effect.

C. Amazon

75. Members of NPA and other companies have been selling their dietary supplement products, including those containing NAC, through Amazon and other outlets for many years

without consumer harm or interference from FDA. For many of these companies, sales through Amazon alone represent all or a substantial part of their supplement business.

76. On information and belief, after issuing four warning letters in July 2020 as discussed above asserting NAC was a drug and not a lawful ingredient in dietary supplements, one or more FDA employees contacted Amazon. FDA alerted Amazon to the recent warning letters.

77. On information and belief, when informing Amazon about the July 2020 NAC warning letters, FDA also explained its position that the DSHEA drug exclusion provision applied retroactively to NAC. FDA also indicated that there was no evidence of pre-1963 marketing of NAC as a dietary supplement or food and that NAC could not legally be sold in products marketed as dietary supplements.

78. By at least May 2021, Amazon began acting on FDA's verbal communication and assertions and began removing NAC-containing dietary supplement products sold on its website.[7]

79. Amazon has informed retailers of NAC-containing dietary supplement products, including members of NPA, that such products can no longer be sold through Amazon. As a direct and proximate result, NPA members and other retailers have lost and continue to lose substantial revenue.

D. Congressional Letters And Citizen Petitions

80. As set forth above, the FDA has taken final agency action that is ripe for review. As further background for the Court, on July 27, 2021, Sen. Mike Lee sent a letter to FDA's Acting Commissioner, Dr. Janet Woodcock, regarding NAC and requested that the FDA hold a hearing on the matter pursuant to 21 C.F.R. Part 15. Ex. 5. FDA responded to Sen. Lee in two letters dated

[7] Josh Long, *Amazon confirms plans on removing NAC supplements*, Natural Products Insider (May 6, 2021), available at https://www.naturalproductsinsider.com/regulatory/amazon-confirms-plans-removing-nac-supplements.

August 19, 2021 and September 29, 2021. Exs. 6, 7. In denying Sen. Lee's request for a hearing, both responses made clear FDA's determination that DSHEA's drug exclusion provision was to be applied to NAC retroactively. The only open issue for FDA was whether there was evidence that NAC was marketed as a dietary supplement or food before September 1963, the date of the alleged new drug approval.

81. On August 18, 2021, NPA submitted a Citizen Petition to FDA on NAC. Ex. 8. The Citizen Petition argued that FDA's position on NAC was legally erroneous because, among other things, the drug exclusion provision of DSHEA was not entitled to be applied retroactively. As further alleged below, it is canonical that statutes are not to be applied retroactively unless the statute or, in limited circumstances, the legislative history unambiguously dictates such a result. There is no provision in DSHEA or any indication in its legislative history to overcome the presumption against statutory retroactivity. Here, the legislative history shows that the drug exclusion provision was not intended to apply retroactively.

82. NPA is not alone in its understanding that DSHEA does not apply retroactively. Another trade association, American Herbal Products Association, submitted comments to FDA on NPA's Citizen Petition on NAC and agreed that the drug exclusion provision should not be given retroactive effect. Ex. 19.

83. On November 24, 2021, FDA issued what it called a "tentative response" to NPA's Citizen Petition. Ex. 9. FDA again reiterated its decision that DSHEA's drug exclusion provision was retroactively effective as to NAC. There is no indication that FDA's decision on retroactivity as a matter of law, or any factual conclusions, were being reconsidered or that FDA would overturn its prior final determinations. FDA only sought additional information as to whether NAC was marketed as a drug or food before the alleged 1963 new drug application approval.

84. FDA cannot try to use informal action or discretion to try to avoid NPA's allegations that the agency has used a legally erroneous and arbitrary and capricious interpretation and application of DSHEA. Enforcement discretion cannot be used to sidestep FDA's violation of the relevant statute and to cause adverse action to be taken against NPA and its members relating to NAC, including without limitation the denial of export certificates and communications with Amazon that led the electric retailer, a critical sales outlet for many supplement companies, to pull NAC products from the market. These adverse actions must also be addressed.

E. Export Certificate

85. One or more members of NPA recently requested that FDA issue an export certificate covering a NAC-containing product marketed as a dietary supplement. FDA denied NPA's request in November 2021 on the ground that because of the drug exclusion provision of DSHEA, the product did not meet the statutory definition of a dietary supplement in 21 U.S.C. § 321(ff) and thus cannot be marketed as a dietary supplement. FDA concluded that § 321(ff)(B)(i) applied retroactively.

86. Accordingly, FDA's determination that the drug provision of DSHEA applies retroactively is shown in the *Blackstone* criminal case, the July 2020 warning letters, communications with Amazon, responses to Sen. Lee's letter, response to NPA's Citizen Petition, and its denial of export certificates.

87. Documents referenced or referred to herein are incorporated by reference.

CLAIM I
(Declaratory/Injunctive Relief – 5 U.S.C. § 706)

88. The foregoing allegations are incorporated here by reference.

89. As a federal agency, FDA has no power to act unless and until Congress confers that power. Actions that are unauthorized by Congress or inconsistent with Congressional direction are *ultra vires* and must be strictly established by statute.

90. FDA has taken final agency action to determination that the drug provision of DSHEA is to be applied retroactively.

91. FDA's determination is legally erroneous, contrary to DSHEA and exceeds FDA's statutory authority.

92. FDA's position on NAC was legally erroneous because, among other things, the drug provision of DSHEA was not entitled to be applied retroactively.

93. Statutes are not to be applied retroactively unless the statute or, in limited circumstances, the legislative history, unambiguously dictates such a result. See, e.g., *Landgraf v. USI Film Products*, 511 U.S. 244, 270 (1994) ("Since the early days of this Court, we have declined to give retroactive effect to statutes burdening private rights unless Congress had made clear its intent."); *United States v. Heth*, 7 U.S. (3 Cranch) 399, 413 (1806) ("Words in a statute ought not to have a retrospective operation, unless they are so clear, strong, and imperative, that no other meaning can be annexed to them, or unless the intention of the legislature cannot be otherwise satisfied.").

94. There was no provision in DSHEA or its legislative history to overcome the presumption against statutory retroactivity. Congress expressed no clear intent in the text of DSHEA or its legislative history to support FDA's erroneous legal determination. The legislative history shows that the drug provision was not intended to apply retroactively.

95. Further, the purpose of that provision was to incentivize the development of new drugs after DSHEA's enactment. Drug development would not be incentivized by precluding the sale of an ingredient that has been sold both as a drug and as a dietary supplement for many years before DSHEA was enacted.

96. Section 201(ff)(3)(B)(i) only applies to articles that were approved as new drugs by FDA after October 26, 1994.

97. FDA's actions with respect to applying the drug exclusion provision of DSHEA retroactively is not in accordance with law, exceeds its statutory authority and limitations, and is arbitrary and capricious under 5 U.S.C. § 706(2). As such, the FDA's determination as to the exclusion from the definition of a dietary supplement the dietary ingredient NAC should be vacated and set aside.

CLAIM II
(Declaratory Judgment – 5 U.S.C. § 706)

98. The foregoing allegations are incorporated here by reference.

99. The FDCA defines the term dietary supplement to mean a product that is intended for ingestion. *See* Section 201(ff)(2). Section 201(ff)(3)(B)(i) of the Act only excludes from the definition of dietary supplement "an article that is approved as a new drug under section 505".

100. The FDA has taken final agency action to determine that the drug provision of DSHEA applies retroactively and operates to exclude the dietary ingredient NAC from the definition of a "dietary supplement" that may be lawfully sold.

101. NAC was allegedly approved as a drug as an oral formulation in 1985.

102. Upon information and belief, NAC was marketed and sold as a dietary ingredient and dietary supplement for human ingestion before 1985.

103. Because NAC was marketed as a dietary supplement or food before it obtained approval as a drug, FDA's determination is legally erroneous, arbitrary, and capricious under 5 U.S.C. § 706(2) and should be vacated and set aside.

CLAIM III
(Declaratory Judgment – 5 U.S.C. § 706)

104. The foregoing allegations are incorporated here by reference.

105. NAC is a metabolite of cysteine because the human body metabolizes L-cysteine to NAC after L-cysteine has been ingested.

106. L-cysteine has been in the human diet for at least as long as humans have been consuming meat, given L-cysteine's status as a semiessential amino acid.

107. L-Cysteine has been marketed as a dietary supplement prior to acetylcysteine's drug approval date in 1963.

108. NAC qualifies as 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 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.

109. Similarly, NAC occurs naturally in herbs or other botanicals, such as onions and garlic.

110. Section 201(ff)(3)(F) establishes that NAC falls under the definition of a dietary supplement as a constituent of an herb or other botanicals (Section 201(ff)(1)(C)) because it occurs naturally in foods, such as onions and garlic.

111. NAC is dietary supplement under DSHEA that is not excluded by Section 201(ff)(3)(B)(i) because NAC was a constituent of an herb or other botanical that itself was

marketed as a dietary supplement or a food prior to the date that acetylcysteine was approved as a drug.

112. Because NAC was a metabolite or a constituent of one or more articles that were marketed as a dietary supplement or food before it obtained approval as a drug, FDA's determination is legally erroneous, arbitrary, and capricious under 5 U.S.C. § 706(2) and should be vacated and set aside.

REQUEST FOR RELIEF

NPA requests the following relief:

a. judgment in its favor on all claims against Defendants;

b. a declaratory judgment pursuant to 28 U.S.C. § 2201(a) in favor of NPA and against Defendants declaring that the drug exclusion in 21 U.S.C. § 321(ff)(3)(B)(i) does not apply, retroactively or otherwise, to the dietary ingredient NAC and any informal attempt by FDA to avoid this result would be contrary to law and arbitrary and capricious;

c. to the extent necessary, a declaratory judgment pursuant to 28 U.S.C. § 2201(a) in favor of NPA and against Defendants declaring that the drug exclusion in 21 U.S.C. § 321(ff)(3)(B) does not apply to NAC, at least because: (1) NAC was marketed as a dietary supplement or food prior to acetylcysteine's approval in 1963; (2) NAC's route of administration as an inhalant in 1963 cannot be used as a reference to exclude orally administered dietary supplements containing the dietary ingredient NAC from the definition of dietary supplements under DSHEA; and/or (3) NAC was marketed as a dietary supplement or as a food prior to acetylcysteine's drug approvals in 1982 and/or 1985.

d. a preliminary and permanent injunction prohibiting Defendants from taking any regulatory action against manufacturers, sellers, or distributors of NAC-containing dietary supplements based on the claim that the drug exclusion in 21 U.S.C. § 321(ff)(3)(B)(i) is retroactive and applies to NAC and any informal attempt by FDA to avoid this result would be contrary to law and arbitrary and capricious;

e. reasonable attorneys' fees as allowed by law;

f. costs pursuant to Fed. R. Civ. P. 54(d) or otherwise provided by law; and

g. such other relief as the Court deems just and appropriate under the circumstances.

Dated: February 21, 2022

Respectfully submitted,

/s/ Kevin M. Bell

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that on February 21, 2022 the foregoing was served on counsel for all parties through the Court's ECF system.

/s/ Kevin M. Bell
Kevin M. Bell