January 19, 2022

Via Electronic Submission

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland, 20852

Comments from the American Association of Naturopathic Physicians Regarding the Regulatory Status of N-acetylcysteine (Docket No. FDA-2021-P-0938)

Dear Sir or Madam:

The American Association of Naturopathic Physicians (AANP) respectfully submits these comments in response to FDA's request, dated November 24, 2021, for information regarding N-acetyl-L-cysteine (NAC) in products marketed as dietary supplements in reference to the subject docket.

FDA specifically requested "information on the earliest date that NAC was marketed as a dietary supplement or a food, the safe use of NAC in products marketed in dietary supplements, and any safety concerns."[1]

The terms "Dietary Supplements" and "dietary ingredients" were not defined until passage of DSHEA in October1994[2], after which they became regulated under the Food, Drug, and Cosmetic Act. Since oral use of NAC in nutritional products sold to healthcare professionals for dispensing to their patients existed well before DSHEA, our comments and evidence will reflect those materials facts.

Who We Are:

The AANP is the national professional association representing 8,000 licensed and licensable Naturopathic Doctors (NDs) who are licensed or regulated in 25 states and territories. Licensed naturopathic physicians provide care to over 4 million patients annually, with a focus on primary

[1] https://www.fda.gov/food/cfsan-constituent-updates/fda-requests-information-relevant-use-nac-dietary-supplement
[2] https://ods.od.nih.gov/About/DSHEA_Wording.aspx

care, and preventing and managing chronic diseases and pain through strategies that emphasize natural and non-pharmaceutical approaches to restore health.

Naturopathic medicine has been recognized by Congress as safe, effective and affordable healthcare.[3] Licensed naturopathic physicians are trained in the art and science of both natural and conventional medicine to provide evidence-based patient-centered care. Naturopathic physicians emphasize early interventions and non-invasive treatments that address underlying causes of diseases, as opposed to focusing solely on treating symptoms. Treatment plans emphasize clinical nutrition, exercise, stress prevention and reduction, toxic load, and other lifestyle measures through advocacy and education.

To better assist FDA in understanding the scientific history of the nutritional research and functional use of oral NAC as a food ingredient, we have included references to published research studies. These studies date back to the 1960s and are often used to teach medical students in post-graduate medical programs. We hope this information will help the FDA better understand the scientific foundation of NAC as an amino acid precursor. NAC has evolved over fifty years to be widely used in the United States as an over-the-counter supplement to improve glutathione levels in healthy consumers to optimize health safely and as a prescription for patients under the care of all healthcare professionals, including Naturopathic Physicians.

NAC – Definition:

NAC is Acetylcysteine, an antioxidant and glutathione inducer indicated for mucolytic therapy and the treatment of acetaminophen overdose. Acetylcysteine has also been studied for a wide variety of off-label indications with mixed results.[4] Studied for at least five decades, NAC has a molecular formula of $C_5H_9NO_3S$, and an average mass of 163.195 Da.[5] Indexed in ChemSpider (ID 11540), commercially available NAC products are listed in the NIH Dietary Supplement Label Database. They are also listed in UPC databases, NDC databases, and, in all medical and commercial knowledge bases, either as “n-acetyl-cysteine,” “N-acetyl-l-cysteine,” or “N-acetylcysteine” which are all designations for the same compound, which is abbreviated as NAC.

The evidence we submit herein is consistent with and fully supports this safety assessment from another branch of the U.S Department of Health and Human Services, the “largest biomedical research agency in the world:” the National Institutes of Health, Office of Dietary Supplements:

[3] Naturopathic Medicine Week, S.Res.221, 113th Congress, (2013).
[4] https://go.drugbank.com/drugs/DB06151#reference-L31378
[5] https://go.drugbank.com/drugs/DB06151#reference-L31378

"No safety concerns have been reported for products labeled as dietary supplements that contain NAC".[6]

NAC Regulatory History:

The New Drug Application for "Acetylcysteine 20% Sterile Solution, (Mucomyst sterile solution for aerosolization), a mucolytic agent from Mead-Johnson," was received and acknowledged by FDA on April 6, 1966.[7] It was approved by the FDA on January 31, 1985 (NDA 13-601).

Dr. Barry Rumack, MD of the Rocky Mountain Poison Control Center, began working on NDA 13-601 in 1974. He also developed the protocol for treating acetaminophen overdoses using enteral NAC in 1976 for its use as an inhaled respiratory mucolytic, years earlier than the January 1985 FDA drug approval and well in advance of the approved IV use of NAC via the NDA approval by Cumberland for Acetadote™. [8,9,10]

Dr. Rumack and his colleagues began using NAC enterally due to the established fact that this safe nutritional substance increases hepatic glutathione levels, which are depleted by acetaminophen in a dose-dependent manner. It is through that biological function that lives were saved.

Also relevant is the fact that NAC (PO) was added as a treatment intervention on January 1, 1985[11] in the Poison Control Centers Database well before any NAC NDA was approved by FDA for marketing, either as a respiratory mucolytic agent or as an antidote for acetaminophen poisoning.

As demonstrated in numerous case reports, physicians have successfully utilized oral NAC as a food ingredient for the past 37 years, well before any drug approval. Physicians employ it to treat patients due to the vast amount of science demonstrating its functional use and safety and continue to do so in a manner consistent with state laws and the congressional findings in Public Law 103-417 §2, such as:

---

[6] https://ods.od.nih.gov/factsheets/COVID19-HealthProfessional/#en139
[7] Federal Register, Volume 31, Number 131, Friday, July 8, 1966. page 9370
[8] Personal Correspondence, Dr. Barry Rumack and Michel D. Levin, June 11, 2021 on file at Health Business Strategies, LLC, Clackamas, OR
[9] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-539_Acetadote_Admindocs.pdf
[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3189485/
[11] 2019 Annual Report of the American Associations off Poison Control Centers' National Poison Data System, Clinical Toxicology, (2020),58, No. 12, page 1540

(1) improving the health status of United States citizens ranks at the top of the national priorities of the Federal Government;

…

(5) preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health care expenditures;

(6)(A) promotion of good health and healthy lifestyles improves and extends lives while reducing health care expenditures; and (B) reduction in health care expenditures is of paramount importance to the future of the country and the economic well-being of the country;

(7) there is a growing need for emphasis on the dissemination of information linking nutrition and long-term good health;

(8) 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;

(9) national surveys have revealed that almost 50 percent of the 260,000,000 Americans regularly consume dietary supplements of vitamins, minerals, or herbs as a means of improving their nutrition;

…

(13) although the Federal Government should take swift action against products that are unsafe or adulterated, 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;

(14) dietary supplements are safe within a broad range of intake, and safety problems with the supplements are relatively rare; and

(15)(A) legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness; and (B) a rational Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements.

Comment on the Research and Safety of NAC Prior to DSHEA:

Naturopathic Medical schools teach aspiring physicians the science and research on nutritional interventions to safely improve the lives of their future patients. Notable among the many nutritional scholars are textbooks written by Alan R. Gaby, MD,[12] Joseph E. Pizzorno, ND,[13] and Melvyn R. Werbach, MD.[14]

[12] Alan R. Gaby, MD, "Nutritional Medicine, Second Edition" (N-acetylcysteine biochemistry begins on page 209)
[13] Joseph E. Pizzorno, N.D with Michael T. Murray, N.D, "Textbook of Natural Medicine, Fourth Edition", 2012
[14] Melvyn R. Werbach, M.D., "Textbook of Nutritional Medicine", 1999

Their teachings cite extensive research from many sources, including many found in the National Library of Medicine. For example, a study on the oral toxicity of NAC from 1971 found that the oral NAC LD50 in rats was 5050mg/kg.[15] In contrast, a 70kg adult taking 3000 mg a day consumes less than 1/100th of that amount. Decades of evidence of oral NAC research confirm the extraordinary safety of this ingredient when taken orally.

In summary, as supported by decades of global experience with this amino acid precursor by multiple routes of administration, the overwhelming evidence regarding the safety and value of this dietary ingredient is irrefutable.

NAC – Survey of Licensed Naturopathic Physicians, Date of Earliest Use:

We conducted a survey of licensed Naturopathic Physicians between December 24, 2021 and January 11, 2022. Naturopathic physicians were asked to provide the earliest year that they began using NAC in their practice and to describe their clinical experience with NAC, safety, dose/duration, number of patients/etc. As physicians qualified by education and training, they shared their expert medical opinion based on their direct professional and clinical experience.

Of the 126 responses received, the earliest dated back to 1990, thus evidencing pre-DSHEA availability and use of NAC as a food ingredient in the United States. That physician commented:

1) *"I use NAC in dosages of 600-2400 mg a day…I use it frequently. It is safe, has many studies supporting use, and has never caused any problem."* [Earliest use, 1990].

A similar comment from a physician who first began using NAC in 1993:

2) *"I have used NAC personally for ages. I used it in patients - often long term with no observable adverse effects."*

This comment is from a physician who first began recommending NAC in 1996:

3) *"I have had significant success with NAC and have not in my entire practice had any adverse reactions to this product. I usually prescribe 600 mg twice daily. I have used it in smaller doses in children and do not have any problem with that patient population either. If NAC were to be removed from the market, I would have to alter my prescribing to favor glutathione, which tends to be much more expensive for patients to the point that*

[15] Toxicology and Applied Pharmacology., 18(185), 1971 [PMID:5542824]

they would probably not continue to use it. Pharmacodynamics are also not as good for the glutathione products."

This physician respondent began using NAC twenty-five years ago, in 1997:

4) *"Typically, I have about fifty patients at least utilizing NAC as part of their supplement regime or to have on hand, for example if they feel the need for extra lung support or overall immune support. Typical dose is 600 mg to 900 mg/day. I have never heard any of my patients complain of negative effects, only positive experiences."*

This physician began recommending NAC in 1999, continues to do so, and notes one minor patient complaint:

5) *"I have used NAC more than 500 times in my career and the only problem that has emerged is that it tastes like sulfur, which some patients don't tolerate- Typically I Rx at 600mg two-three-times per day."*

This physician has recommended NAC since 1991:

6) *"I recommend NAC almost weekly in my practice; it is one of the most widely recommended supplements that I use. I primarily use it to help with Glutathione production…I have never had any side effects with the amino acid. I find it highly successful."*

This physician reports no adverse effects in patients under his direct care with "use up to 3000 mg doses".

7) *"I use it regularly with at least 30% of my patients at some point during my time working with them…I have had no patients report any adverse effects and regularly use up to 3000 mg doses."*

Additional comments:

8) *"I use NAC as a supplement to support healthy detoxification. This is a nutrient used by the body in liver and cellular detoxification pathways. There have never been any adverse reactions in the hundreds of patients that have used NAC in my practice. An average daily dosage is around 600 mg. Dosages up to 1200 mg per day are also sometimes used and are safe and effective in my patient population. I also use 300-500 mg daily dosages of NAC to support children. Again, there are no adverse reactions. Patients tolerate this nutrient well and it supports their health through the mechanism of healthy detoxification from pollutant and chemical exposures. It is important that this nutrient continues to be available for physicians and their patients."*

9) *"I have successfully and safely used NAC in MANY patients… I have years of experience PRIOR to being an ND using NAC in my nursing career for acetaminophen overdoses - at no point have I seen any adverse effects of the substance, and have seen too many successful treatments to count."*

10) *"I have been using NAC in practice… for over 11 years. I have never reported a single adverse reaction or side effect with doses up to 3 grams per day. I have administered NAC orally, intravenously and through nebulization."*

11) *"Clinically effective as a mucolytic and glutathione precursor. We use 600 mg twice daily. I have never seen any side effects, only beneficial results. I probably have about 15 patients on NAC at this point in time."*

12) *"I have used an NAC in a product that is a combination of NAC, quercetin, and nettle … for years now. I use a chewable with children and capsules for adults. People swear by this product, …The supplements get to the root of the issue."*

Our physicians with decades of experience recall recommending finished products formulated with NAC to patients prior to 1994 that were produced by companies that included Allergy Research, NF Formulas, Tyler Encapsulations, and Thorne Research, as representative examples.

Comment on the Current Availability of Dietary Supplements Containing NAC:

NAC has and continues to be widely sold, safely used, and has delivered substantial health benefits to consumers in the United States in dietary supplements since DSHEA passed in 1994. To our knowledge, FDA never questioned its legal status until 2020, in the form of Warning Letters sent to companies who marketed consumer products labeled for the treatment or prevention of "hangovers," which we understand can be argued is an unlawful health claim. We are not lawyers. We only represent physicians and the best interest of the patients they serve.

After FDA Warning Letters began to appear regarding NAC, certain companies serving the naturopathic community opted to remove NAC from their products and reformulate rather than risk receiving a warning letter. This significantly and immediately impacted the availability of this useful ingredient. Costs also increased when a more expensive alternative was used, thus increasing consumer prices.

Out of an abundance of caution, Amazon also began removing hundreds of products containing NAC from their website[16] last year, reportedly based on the Warning Letters. We bring this point

[16] https://www.naturalproductsinsider.com/regulatory/amazon-confirms-plans-removing-nac-supplements

to your attention because the unintended consequences of your actions unnecessarily reduced access to these important products, including to those patients and other consumers who wished to purchase these products from Amazon.

Request:

Until recently, FDA has consistently and affirmatively permitted manufacturers to market products with NAC. The impact of the FDA's Warning Letters has been to restrict patient access to NAC - a critical nutritional supplement - which negatively affects the health of patients by limiting treatment options and forcing them to resort to more invasive and expensive pharmaceutical treatments. We urgently request that the FDA exercise its authority[17] to reverse this policy change and again allow manufacturers to market dietary supplements containing NAC as has been safely done for over 40 years.

We also request that the drug exclusion provision in DSHEA be revised to clarify Congressional intent and give all stakeholders clearer guidance. Specifically, the language should limit the scope of the protection based upon route of administration and intended use, and specifically exclude from protection all other routes of administration and intended uses.

Thank you for your consideration of this matter.

Respectfully,

Laura Farr
Executive Director
American Association of Naturopathic Physicians

[17] U.S.C. 321 (ff)(3)(A) and FFDCA 201(ff)(3)(A)