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UNPA

UNITED NATURAL
PRODUCTS ALLIANCE®

January 24, 2022

Via Regulations.gov and FedEx (overnight)

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

RE: Docket number [FDA-2021-P-0938], Request that the FDA determine, based on the facts provided herein, that NAC is not excluded from the definition of a dietary supplement under 21 U.S.C S321(ff)(3)(B) of HHS, that, in their discretion, they issue a regulation, after notice and comment, finding that NAC would be lawful under the Act.

Dear Sirs/Madames:

The United Natural Products Alliance (UNPA) welcomes this opportunity to submit comments on behalf of our members.

UNPA is a dietary supplement trade association founded in 1992 and based in Salt Lake City, Utah. UNPA members represent approximately 120 companies/organizations including dietary supplement and natural products brands plus our science, technology, and service partners. We serve our membership by providing quality, regulatory, and legislative support, training, and by providing assistance with international export programs. Our vetted members have the same corporate values including providing reliable, high quality, complaint, and science-based dietary supplement products to the consumer. We support the full and faithful implementation of the Dietary Supplement Health and Education Act of 1994 (DSHEA).

We submit these comments in response to the FDA *Constituent Update*, *FDA Requests Information Relevant to the Use of NAC as a Dietary Supplement,* issued on November 24, 2021.

This FDA *Constituent Update* 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."

The term "dietary supplement" was initially defined by the Dietary Supplement Health and Education Act of 1994 (DSHEA) (October 15,1994).

Our comments have been drafted with the goal of providing FDA marketing and safety data to substantiate the human use of NAC as a dietary supplement.

UNPA submits these comments and the accompanying information in the spirit of cooperation with the agency. We are providing a significant collection of marketing and sales information from our member companies and other members of the broader dietary supplement industry. However, it is our view that FDA, in attempting to exclude NAC from the dietary supplement market, is acting in excess of its statutory jurisdiction and authority.

Salt Lake City, Utah 84105

This is because FDA does not have the legal or statutory authority or right to interpret section 201(ff)(3)(B)(i) as prohibiting the marketing of dietary supplements containing NAC because such interpretation violates the well-established presumption against statutory retroactivity. If Congress had wanted this provision to apply retroactively, they could have so stated, but they did not. In fact, we believe Congress intended the exclusionary clause to be forward-looking, notwithstanding that the legislative history is limited to the Statement of Agreement to the DSHEA.

UNPA members, and collaborators to this response, believe rule making is inappropriate. UNPA wishes to advise FDA that it intends to submit additional comments on this topic.

In response to the November 2021 *Constituent Update*, we have collected evidence from our members and industry partners to support the earliest oral use of NAC as a dietary supplement. Some of this evidence is for products on the market prior to DSHEA (Oct 15, 1994); however, these products meet the current definition of a dietary supplement.

The below section was written in collaboration with Daisy Herpin, a dietary supplement subject matter expert:

> "We feel confident the information supplied herein will reverse FDA's interpretation and position regarding NAC. We believe recent statements in Warning Letters, issued by the agency, stating NAC is excluded from the definition of a dietary supplement were in error. In fact, we (UNPA collaborators) believe NAC is a lawful dietary supplement under the Federal Food, Drug, and Cosmetic Act.
>
> As previously stated in the Docket (FDA-2021-P-0938),*"Under section 201(ff)(3)(B) of the Act (21 U.S.C. 321(ff)(3)(B)), an article that has been approved as a new drug under section 505 of the Act (21 U.S.C. 355), licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or has been authorized for investigation as a new drug or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, then products containing that article are outside the definition of a dietary supplement unless an exception applies. There is an exception if the article was marketed as a dietary supplement or as a food before such approval, licensing, or authorization."*

NAC was on the market pre-DHEA

Attached and summarized below is the evidence received by UNPA for the use of oral NAC as a dietary supplement pre-DSHEA (prior to October 15, 1994) including labeling (advertising, marketing, and printed literature), manufacturing records, formulas, testing documents, and invoices for Interstate sales.

Please note, as the industry evolved, marketing and advertising of these dietary supplement products has shifted into compliance with Structure/Function claims and with FDA label and labeling requirements. Additionally, some of the literature presented within this response was initially utilized for educational purposes to licensed doctors and professional health care providers. This literature was intended for use by doctors, and it was not provided to the general public.

We want to emphasize to FDA staff and reviewers; a significant time gap has transpired since NAC was introduced to the market as a "nutritional" supplement. Nutritional supplement was

redefined as dietary supplements by DSHEA. We have done our best to review all available paper records and electronic storage systems in preparing this response. Due to the limitations of physical records storage and the legal limits for records retention, many of the historical documents to support this topic, are simply no longer available. Some of the potential NAC records are within out-of-date software/electronic storage systems or the paper records have been destroyed long ago. Current requirements for most (legal) record retention systems is seven years. We are well beyond seven years regarding the introduction of NAC to the dietary supplement market.

Chemical description of NAC

- N-acetyl-L-cysteine (NAC), IUPAC N-acetyl-DL-cysteine, molecular formula $C_5H_9NO_3S$, molecular weight 163.195 Da, CAS [616-91-1] (synonyms include n-acetylcysteine; mercapturic acid; Acetadote; L-acetylcysteine; Mucomyst; 2-acetamido-3-sulfanylpropanoic acid; 2-acetamido-3-mercaptopropanoic acid; acetylcysteine; L-alpha-acetamido-beta-mercaptopropionic acid, acetein; Nacetyl-3-mercaptoalanine, airbron, broncholysin, fluimucetin, fluimucil, flumicil, inspir, mercapturic acid, mucolyticum, mucolyticum lappe, mucolytikum lappe, mucomyst, mucosolvin, NAC, NAC-TB, NSC 111180, parvolex, respaire),
- a plant antioxidant commonly found in plants of the Allium species (onion)[1],
- is the N-acetyl derivative of the amino acid L-cysteine, a low molecular weight nucleophilic thiol which forms glutathione, cystine, l-methionine and mixed disulfides *in vivo*.[2]
- is commonly obtained from the acetylation of cysteine from human or animal hair and is a precursor of the antioxidant glutathione in the body.[3]
- NAC has been shown to be bioequivalent to an isomolar amount of L-cystine.

Functional Use of NAC

- It is a scavenger of free radicals and mucolytic agent.
- NAC is extensively metabolized by the liver, CYP450 minimal. Excretion in the urine is 22-30% with a half-life of 5.6 hours in adults and 11 hours in neonates.
- It is currently supplied by over 59 chemical vendors worldwide.
- NAC was initially patented in 1960 and came into medical use in 1968.[4]
- It has been used as a substitute for L-cysteine in foods because the acetylation of L-cysteine improves the palatability of the product and enhances patient compliance with the diet without compromising the cysteine content of the formulation.
- It has been used for the dietary supplementation, for example, and in sports nutrition and food supplements.

References for the above chemical and functional use sections:

1. Medical and Dietary Uses of N-Acetylcysteine May2019 Antioxidants (Base!) 8(5):111 Spela Salamon, Barbara Kramar, Tinkara Pirc Marold, Borut PolJsak, and Irina Milisav.
2. NAC Evidence Record 1A –Nautal Antioxidants Effects of N-Acetyl-L-Cysteine, Quercetin & Standardized Ginkgo Biloba Extract. Townsend Letter for Doctors July 1993 Sponsored by Tyler Encapsulations.
3. N-ACETYL-L-CYSTEINE Product Information" (PDF). *Sigma*. Sigma-aldrich. Archived from the original (PDF) on 11 June 2014. Retrieved 9 November 2014.
4. US patent 3091569, Aaron Leonard Sheffner, "Mucolytic-nu-acylated sulfhydryl compositions and process for treating animal mucus", published 1963-05-28, issued 1963-05-28, assigned to Mead Johnson & Co

The outline of UNPA comments is as follows:

A. Evidence use of NAC as a nutritional supplement Pre-DSHEA (prior to October 15, 1994)
B. Safety information related to the use of oral NAC

Exhibits and attachments provided here are "Confidential and Exempt from Public Disclosure under FOIA."

Evidence of use for NAC as a dietary supplement pre-DSHEA
We have reviewed documentation from at least eight companies for pre-DSHEA use of NAC. Pre-DSHEA is defined as to October 15, 1994. These nutritional supplements meet the current definition of a dietary supplement as defined in DSHEA 1994.

Pre-DSHEA Product Name	Company	Date	Document	Significance	Exhibit # **
Cysteplus (Item/code 560) Dietary Supplement, containing 500 mg N-Acetyl-L-Cysteine, 90 count	Thorne Research	11/02/93	Invoice #16947	Pre-DSHEA (November 1993). Interstate (IS) sale of 4 bottles of Cysteplus (Lot Numbers: 930906) documenting IS from Sandpoint, ID to Santa Rosa, CA via FedEx. The formula for this product is shown below as "Master Formula". Label images are shown below in the "Product Book"*	1
Cysteplus (Item/code 560) Dietary Supplement, containing 500 mg N-Acetyl-L-Cysteine, 90 count	Thorne Research	03/18/91	Invoice #25991	Pre-DSHEA (March 1991). Interstate (IS) sale of 9 bottles of Cysteplus (Lot Numbers: 940057) documenting IS from Sandpoint, ID to Parsippany, NJ via FedEx.	2
Cysteplus (Item/code 560) Dietary Supplement, containing 500 mg N-Acetyl-L-Cysteine, 90 count	Thorne Research	12/15/1993	Invoice #19922	Pre-DSHEA (December 1993). Interstate (IS) sale of 2 bottles of Cysteplus (Lot Numbers: 930931) documenting IS from Sandpoint, ID to Santa Rosa, CA via FedEx.	3
Cysteplus (Item/code 560) Dietary Supplement, containing 500 mg N-Acetyl-L-Cysteine, 90 count	Thorne Research	10/21/1993	Invoice #16171	Pre-DSHEA (October 1993). Interstate (IS) sale of 3 bottles of Cysteplus (Lot Numbers: 930906) documenting IS from Sandpoint, ID to Seattle, WA via FedEx.	4
Cysteplus (Item/code 560) Dietary Supplement, containing 500 mg N-Acetyl-L-Cysteine, 90 count	Thorne Research	11/23/1993	Invoice #18383	Pre-DSHEA (November 1993). Interstate (IS) sale of 3 bottles of Cysteplus (Lot Numbers: 931012) documenting IS from Sandpoint, ID to Oakland, CA via FedEx.	5
Cysteplus, 500 mg 90's (AKA 90 count bottles) (Item/code 560)	Thorne Research	"Effective Aug 15, 1993", and "Ship Date: Nov 1/93"	Professional Product Order Form for "ACAM-Product Display"	Pre-DSHEA (November 1993) order with "Ship Date Nov 1/93" for 7 bottles of Cycteplus.	6

Product Name	Company	Date	Document	Significance	Exhibit # **
Cysteplus, 500 mg 90's (AKA 90 count bottles) (Item/code 560)	Thorne Research	This Product Order form reads in part "Effective Apr 1, 1993." and "Order Date: 10/18/93"	Product Order for [redacted] (Rancho Sante Fe, CA)	Pre-DSHEA (October 1993) order for a shipment of a NAC containing dietary supplement with IS sales from Sandpoint, ID to Rancho Sante Fe, CA	7
CystePlus [500 MG] (Item/code 560) and **CystePlus II** [300 mg]	Thorne Research	"EFFECTIVE OCTOBER 15, 1992"	THORNE RESEARCH, INC. PATIENT ORDER FORM including two products contain 500 mg and 300 mg of NAC respectively.	Pre-DSHEA (October 1992). Documentation of NAC containing products on the market. This order was shipped from Sandypoint, ID to Akron, OH.	8
CYSTEPLUS capsules containing N-ACETYLCYCTEINE. (Item/code 560)	Thorne Research	Copyright 1995 is shown on the front page, on the last line.	Product Book	This Product Book contains label images and product description for the Cycteplus and Cysteplus II. These products are shown above in the provided invoices (IS shipments).	9
N-Acetyl Cysteine (code SA560) containing 500 mg NAC	Thorne Research, Inc	The record Effective date reads "1/25/90" and the signature on the "Master Formula" reads "1/25/90"	Master Formula	Pre-DSHEA (January 1990) manufacturing record (Master Formula).	10
CystePlus II [300 mg] LOT NUMBERS: 930931	Thorne Research, Inc	02/07/94	Commercial Invoice #23255	Pre-DSHEA (Feb 1994) record including invoice, packing list, air bill #400-3607 1136, for a supplement shipment containing 2 bottles of NAC from Throne Research, Inc (Sandpoint, ID) to Dr. Claus Frandsen (Lyngby, Denmark)	11

Product Name	Company	Date	Document	Significance	Exhibit # **
NAC (N-Acetyl-L-Cysteine)	Allergy Research Group / Nutricology. Nutri-cology is a brand of Allergy Research Group.	"91-10c" which is equal to October 1991 The final page (page 3) includes a Copyright of 1991, NutriCology, Inc.	NAC (N-Acetyl-L-Cysteine) Background	Pre-DSHEA (October 1991). This information sheet was utilized to provide background and education to doctors and health care providers regarding the science of specific nutrients. Note, in the Townsend Letter information (discussed below) there is label provided for this product as Exhibit 19 A-T.	12
n-Acetyl L-Cysteine	Ortho Molecular Products, Inc	Printed date reads "Clinical Nutrition For The Nineties...And Beyond"	Catalog	Pre-DSHEA labeling (~1991). Dietary supplement product catalog for doctors and health professionals containing two NAC products.	13
NAC N-ACETYL CYSTEINE WITH SUPPORTING NUTRIENTS containing 600 mg NAC (N-Acetyl Cysteine)	NOW NATURAL FOODS	Printed date reads "October 1993 Specials"	Ad	Pre-DSHEA (1993) nutritional supplement containing NAC	14
NAC 600 mg (N) (N-Acetyl Cysteine, Selenium, Molybdenum)	NOW Foods	The printed date reads "Summer 1994 Wholesale Catalog"	"Summer 1994 Wholesale Catalog"	Pre-DSHEA (Summar 1994). The page titled "Amino Acids/Vitamins A&D" includes NAC, 100 caps.	15

Product Name	Company	Date	Document	Significance	Exhibit # **
N-Acetyl-L-Cysteine (NAC) Powder, Item #50086	NOW Foods	Printed date reads "Date Issued: 12-29-99" and "Supersedes 10-05-98"	"Spec 1999"	Specification sheet (spec) for NAC as a raw material. This document describes the article utilized in dietary supplements.	16
N-Acetyl-L-Cysteine USP	Seltzer Chemicals (supplier) for NOW Foods	Printed date reads "12/22/99"	Raw Material Specification provided by the supplier to NOW Foods	This document describes the article utilized in dietary supplements.	17
Super Thisilyn containing NAC	Nature's Way	Printed dates read "Published for Opposition July 12, 1988" Trademark "Registration Date October 4, 1988". S/F notice submission date April 29, 2020."	Trademark information. https://tmsearch.uspto.gov/bin/showfield?f=doc&state=4805:6iyip2.2.1 A label for this product containing 50 mg of N-Acetylcysteine is also provided.	Pre-DSHEA (Feb 1988). Documentation of use of NAC as "NUTRITIONAL DIETARY SUPLEMENTS. FIRST USE: 19880201. FIRST USE IN COMMERCE 19880201." 19880201 is equal to the year, month, and day or February 01, 1988.	18

* There are many invoices from Thorne Research these additional documents apply to all Cysteplus items shown below.

**** NOTE: Exhibits will not be submitted to the Docket in the electronic submission. They will be included in the mailed hard copy only. Exhibits will be marked confidential and are not available for FOIA request.**

In addition to the information provided by UNPA member companies and collaborators, UNPA commissioned a project to audit the Townsend Letters (TL). Townsend Letter, the Examiner of Alternative Medicine, is a well-known print magazine about alternative medicine. It is published by Editor-in-Chief, Jonathan Collin, MD. The publication is written by researchers, health practitioners and patients. Per the TL website, the publication presents scientific information (pro and con) on a wide variety of alternative medicine topics.

For additional information regarding Townsend Letter see their website: https://www.townsendletter.com/about

The information obtained from the TL audit is presented in two formats below: as bullets and in a table.

The following summary of the TL audit was written in collaboration with Evelyn Cadman, FDA Compliance Simplified:

> UNPA initiated an audit of Townsend Letter issues published prior to November 1994 to identify evidence of nutritional (dietary supplement) products containing N-acetyl-L-cysteine marketed prior to October 15, 1994.
>
> The audit was conducted by Townsend Letter Editor, Julie Klotter. Ms. Klotter reviewed all issues of the Townsend Letter published between March 1983 and November 1993 and logged her findings.

See the summary of findings table for the TL audit on the following pages. This table was written by Evelyn Cadman.

The following (bullet) summary was written in collaboration with Ms. Herpin.

- An advertisement of a time-released form of N-acetyl-L-cysteine by Cardiovascular Research, Ltd Ecological Formulas, in an October 1989 issue of TL, pp. 551, is among the earliest exhibits of marketing of NAC as a Dietary Supplement.
- An ad for Formula 7454, Ultra Preventive* III Low Allergenicity Tablets containing NAC, among other dietary ingredients, produced by Douglas Laboratories is found in a later publication dated August/September 1991, pp. 638, and running in 6 subsequent publications of TL (November 1991 pp. 929, December 1991 pp. 977, January 1992 pp. 87, June 1992 pp. 477, and July 1992 pp. 659) until August/September 1992 (Exhibits A-H).
- In the February/March 1993 publication of the TL, an ad on pp. 173 by Klabin Marketing for Bio-Nutritional Formulas® of New York City introduced Premier Anti-Oxidant Formula which contained NAC. The ad ran again in April and May of 1993 (pp. 295 & 487, respectively (Exhibits I-K)).
- A July 1993 publication contained an ad on p. 711 by Tyler Encapsulations for Oxyperm™ High Potency Antioxidant Formula containing NAC (Exhibit L).
- The November 1993 publication contains an ad from Allergy Research Group on pp.1059 for Superior Antioxidant Formulations, one of which a NAC tablet.

Exhibits for the Townsend Letter at included as Exhibit 19 A-N. Exhibits will be marked confidential and are not available for FOIA request.

Table - Evidence of Pre-DSHEA Marketing of N-Acetyl-L-Cysteine from Townsend Letter					
Company	**Product**	**Published**	**N-Acetyl-L-Cysteine**	**Article Type**	**PDF Name, Exhibit# ****
Cardiovascular Research, Ltd Ecological Formulas 1061-B Shary Circle Concord, CA 94518	N-Acetyl-L-Cysteine	Townsend Letter October 1989, Page 552	N-Acetyl-L-Cysteine raw material	Advertisement	Exhibit 19A - Marketing of NAC Pre-DSHEA
Douglas LaboratoriesWabash & Main, P.O. Box 8583Pittsburgh, PA 15220	Formula 7454	Townsend Letter August/September 1991, Page 638	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19B - Marketing of NAC Pre-DSHEA
Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter November 1991, Page 929	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19C - Marketing of NAC Pre-DSHEA
Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter December 1991, Page 977	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19D - Marketing of NAC Pre-DSHEA
Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter January 1992, Page 87	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19E - Marketing of NAC Pre-DSHEA
Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter June 1992, Page 477	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19F - Marketing of NAC Pre-DSHEA
Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter July 1992, Page 659	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19G- Marketing of NAC Pre-DSHEA

Douglas Laboratories Wabash & Main, P.O. Box 8583 Pittsburgh, PA 15220	Formula 7454	Townsend Letter August/September 1992, Page 765	L-Cysteine HCl/N-Acetyl-L-Cysteine 200 mg	Advertisement to private label a formula containing N-Acetyl-L-Cysteine	Exhibit 19H- Marketing of NAC Pre-DSHEA
Klabin Marketing 115 Central Park West NY, NY 10023	Premier Anti-Oxidant (Formula)	Townsend Letter February/March 1993, Page 173	N-Acetyl Cysteine 100 mg	Advertisement to order the packaged formula	Exhibit 19I - Marketing of NAC Pre-DSHEA
Klabin Marketing 115 Central Park West NY, NY 10023	Premier Anti-Oxidant (Formula)	Townsend Letter April 1993, Page 295	N-Acetyl Cysteine 100 mg	Advertisement to order the packaged formula	Exhibit 19J- Marketing of NAC Pre-DSHEA
Klabin Marketing 115 Central Park West NY, NY 10023	Premier Anti-Oxidant (Formula)	Townsend Letter May 1993, Page 487	N-Acetyl Cysteine 100 mg	Advertisement to order the packaged formula	Exhibit 19K - Marketing of NAC Pre-DSHEA
Tyler Encapsulations 2204-8 NW Birdsdale Gresham, OR 97030	OXYPERM™ (formula)	Townsend Letter July 1993, Page 711	N-Acetyl-L-Cysteine 150 mg	Advertisement to order the packaged formula	Exhibit 19L - Marketing of NAC Pre-DSHEA
Allergy Research Group400 Preda StreetSan Leandro, CA 94577	N-Acetyl-L-Cysteine Tableted for stability (NAC)	Townsend Letter November 1993, Page 1059	N-Acetyl-L-Cysteine	Advertisement to order the packaged product	Exhibit 19M - Marketing of NAC Pre-DSHEA
Tyler Encapsulations 2204-8 NW Birdsdale Gresham, OR 97030	Natural Antioxidants Effects of N-Acetyl-L-Cysteine, Quercetin & Standardized Ginkgo Biloba Extract	Townsend Letter July 1993, Page 710 & 712.	N-Acetyl-L-Cysteine	Sponsored Article	Exhibit 19N - Marketing of NAC Pre-DSHEA

**Exhibits will be marked confidential and are not available for FOIA request.

B. Safety information related to the use of NAC

We believe the safety of NAC is well established in scientific and peer-reviewed literature. Some of the publicly available safety studies from Clinicaltrials.gov include drug end points and other studies from the same source include trials of NAC for dietary supplement support. We feel safety has been reviewed and provided previously to the FDA and therefore we will not incorporate repetitive studies within our response.

We submit the following information to further demonstrate the well-established safety data for the use of NAC orally at dosage levels similar for both categories.

Dosage in dietary supplements

We found oral NAC is dosed up to 600 mg – with 600 mg/day probably being most common. Of note, 600 mg/day is the limit per the associated monograph for this ingredient in Canada, and that is without any "known adverse reactions" (albeit some minor cautions around pregnancy, breastfeeding, and kidney stones; and contraindications with antibiotics and nitroglycerin). We found multiple companies in the US dosing up to 1000 mg/daily, but these are fewer. Lesser dosages are employed for a myriad of antioxidant functions/maintenance of cellular function, so it appears lower dosing may be utilized when mixing with more of a broad spectrum of antioxidants without increasing number of capsules per serving.

CDER Summary

Please see the attached document from the Center for Drug Evaluation and Research, *"APPLICATION NUMBER: 207916Orig1s000, SUMMARY REVIEW" DATED March 30, 2015*, for the New Drug Application (NDA) #207916 (Exhibit 20). This document, written by CDER, provides a "Benefit-Risk and Assessment". The document reads in part (page two):

> Acetylcysteine products have been on the market since the 1950's, and have a well know adverse reaction profile. There are rare hypersensitivity reactions, mainly occurring with the intravenous formulations. Occasionally severe and persistent vomiting occurs as a symptom of acute acetaminophen overdose. Treatment with acetylcysteine may aggravate the vomiting and increase the risk of upper gastrointestinal hemorrhage in at risk patients (e.g., those with esophageal varices, peptic ulcers, etc.). Gastrointestinal intolerance with nausea and vomiting are the main adverse reaction to the oral formulation and frequently patients require conversion to intravenous treatment.

An additional area of interest, from this CDER document, regarding safety is found at the end of page two to page three:

In conclusion, the bioequivalence of Cetylev (acetylcysteine) effervescent tablets for oral solution and the safety profile are the same as the currently marketed oral solution of acetylcysteine. There

2

Reference ID: 3879846

CDER Division Director Summary Review NDA # 207916
Cetylev (acetylcysteine) effervescent tablets

were no new safety issues identified. Therefore the risk-benefit assessment favors approval of Cetylev.

USP

Acetylcysteine is included in the USP-NF (drug). Acetylcysteine is also in the USP Dietary Supplement Compendium (DSC) (page 854) where other chemical names include "*L-Cysteine, N-acetyl, N-Acetyl-L-cysteine*".

Per USP staff on January 19, 2022 (paraphrased),
NAC is included in recognition to its use as a drug and excipient. As of 2009 and in subsequent editions of the DSC, it is included in recognition of its usage as a dietary ingredient.

Additionally, from USP staff:
Our admission criteria specifically indicates that:
"Determinations regarding the U.S. regulatory status of specific dietary ingredients are within the purview of the U.S. Food and Drug Administration (FDA). USP will defer to FDA with respect to such determinations and will not pursue USP-NF monograph development for a dietary ingredient where USP is aware that FDA has issued a specific opinion or taken enforcement action to indicate that there is no legal basis to market that substance in the U.S."

Per USP staff, based on the FDA decision on this topic, the DSC could potentially be updated.

"Regarding UPS standards or monographs: USP does not establish monographs for dietary supplement ingredients unless and until they have passed USP's extensive committee review process, which includes a safety review. This is a precondition to USP setting a compendial standard for an ingredient – safety must first be established. Also, the standards of USP are recognized by FDA, per various statutory and regulatory provisions, e.g., per § 201(j) of the FDC Act, the "term 'official compendium' means the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them." For dietary supplements, under § 403(s), a dietary supplement shall be deemed to be misbranded if the supplement is covered by the specifications of an official compendium [i.e., USP], and is represented as conforming to such specifications, but fails to so conform.

Also, with respect to safety, an argument could be made that NAC is safe based on marketing data and "use for a material extent and material time" which is a concept in the

FDA's OTC drug review." Per a UNPA member and practicing dietary supplement attorney.

Information from SafetyCall International:

"SafetyCall, a nationally recognized healthcare firm academically affiliated with the University of Minnesota and a leader in providing Post Market Medical Surveillance service and support to hundreds of dietary supplement companies, has monitored the safety of NAC manufactured and distributed by a number of their client companies.

SafetyCall provides the safety net for monitoring real life use and experience with NAC as a dietary supplement and has advised UNPA that to date, their experience has been that NAC containing dietary supplements are well tolerated, rarely result in any adverse effects and when seen, the effects are minor in nature. In fact, SafetyCall has not identified any SAERs involving NAC amongst the companies that have engaged them to provide post market surveillance for their entire line of dietary supplements.

They further report that their findings appear to be consistent with the data reported to the CAERS database where there has only been a handful of reported SAERs assigned with either a "suspect" or "concomitant" relationship code in the most recently available CAERS download. Amongst the few reported SAERs the absolute numbers are so low and without consistent findings that no trend or safety signal could be identified.

Lastly, SafetyCall is also a poison control center and it's clinicians routinely consult with, and advise, front line clinicians treating patients with acetaminophen poisoning and as such SafetyCall clinicians are also quite familiar with the use of NAC to treat acetaminophen overdose. CDER's summary of NAC safety for drug related indications acknowledges the known side effect of gastrointestinal intolerance but it is important to note that this is a dose dependent phenomena and associated with daily doses of drug versions of NAC of up to 39gms per day (loading dose 140mg/kg x 70kg adult = 9,800mg and 70mg/kg (q4hours) x 6 x 70kg adult = 29,400mg for a total daily dose of 39,200mg (39gms).

These doses are magnitudes in excess of what would be used in any dietary supplement version of NAC. This likely accounts for the very positive safety profile for dietary supplement versions of NAC.
For further information, FDA can contact:

Rick Kingston PharmD, Co-Founder, President, Regulatory and Scientific Affairs & Senior Clinical Toxicologist, SafetyCall International LLC
&
Clinical Professor, Department of Experimental and Clinical Pharmacology
College of Pharmacy, University of Minnesota
&
Adjunct Professor, National Center for Natural Product Research (NCNPR), University of Mississippi, College of Pharmacy"

This submission is a collaboration with UNPA members, the UNPA NAC Working Group, and the greater dietary supplement industry including:

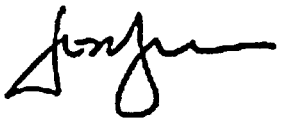
- American Association of Naturopathic Physicians
- Arizona Nutritional Supplements
- Bastyr University
- FDA Compliance Simplified
- Holistic Primary Care
- NOW Foods
- Ortho Molecular
- Thorne Research
- Whole Foods Market

Additional comments regarding safety will be provided to the Docket by the American Association of Naturopathic Physicians (AANP) and others in the UNPA NAC Working Group.

We affirm our interest in supporting and assisting the agency to these ends.

NOTE: Exhibits will not be submitted to the Docket in the electronic submission. They will be included in the mailed hard copy only. Exhibits will be marked confidential and are not available for FOIA request.

Respectfully submitted,



Loren Israelsen
President
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