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January 25, 2022

Douglas Stearn
U.S. Food and Drug Administration
Deputy Director for Regulatory Affairs
Center for Food Safety and Applied Nutrition
5001 Campus Drive
College Park, MD 20740

Re: Docket Number FDA-2021-P-0523; November 24, 2021 Food and Drug Administration Letter

The Council for Responsible Nutrition (CRN)[1] provides this letter as a follow-up to its January 4, 2022 Letter[2] and further response to the Food and Drug Administration's ("FDA" or "Agency") November 24, 2021 Letter[3] regarding the June 1, 2021 CRN citizen petition (Docket Number FDA-2021-P-0523). As was reiterated in CRN's January 4, 2022 Letter, CRN's citizen petition requested "that the FDA revert to its longstanding policy of allowing manufacturers to market dietary supplements containing [N-acetyl-L-cysteine ("NAC")] and rescind the legally invalid position included in warning letters that NAC is precluded by section 201(ff)(3)(B)(i) of the [Food, Drug, and Cosmetic Act (FDCA)] from being a legal dietary ingredient in dietary supplements".[4]

CRN raised a number of concerns in its January 4, 2022 Letter regarding the Agency's continued failure to address the single legal issue that was first raised by CRN in December 2020 and restated in CRN's June 2021 citizen petition – whether the drug preclusion provision in section 201(ff)(3)(B)(i) properly precludes NAC from being marketed in dietary supplements. The issues raised by CRN about FDA's non-responsive November 24, 2021 Letter included the following:

- FDA has inappropriately combined CRN's request for legal clarity on its NAC policy reversal with a second NAC citizen petition that asks for a different resolution from FDA on this issue.[5] In this second citizen petition, filed by the Natural Products Association (NPA), as an alternative to asking FDA to address the legality of its NAC position, NPA asks FDA to develop a regulation finding NAC lawful using the Agency's rulemaking authority under section 201(ff)(3)(B). That request presupposes that FDA has reached a final decision on the legal interpretation of

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1 The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers, and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Learn more at www.crnusa.org.

2 *See* January 4, 2022 Letter from S. Mister and M. Olsen, CRN, to D. Stearn, FDA ("January 4 Letter").

3 *See* November 24, 2021 Letter from D. Stearn, FDA, to S. Mister and M. Olsen, CRN ("November 24 Letter").

4 *See* Citizen Petition from S. Mister and M. Olsen, CRN, submitted to the Division of Dockets Management, FDA, dated June 1, 2021.

5 *See* Citizen Petition from the Natural Products Association (NPA), filed August 18, 2021 (Docket Number FDA-2021-P-0938).

201(ff)(3)(B) and found that NAC is precluded from use in supplements by that provision. CRN reiterates that it is inappropriate for FDA to review the two citizen petitions concurrently, as they request different actions from the Agency. Further, by introducing concurrent review, FDA appears to be disregarding the legal challenges to the NAC position raised by CRN, and intimating that it has declined CRN's request for legal review without the Agency actually formally stating this.

- FDA is requesting information on safety and current market evaluation that is not relevant to the legal points raised by CRN and not necessary for the Agency to address the legality of its position. Further, as we noted in our January 4, 2022 Letter, this information does not even appear to be relevant to the NPA request for rulemaking, given that the FDCA makes no reference to a safety evaluation when granting this rulemaking authority. By requesting this information, FDA has continued to delay a substantive response to consumers and industry on the legal challenges raised by CRN. Continued delay by the Agency in resolving this matter is harming both consumers and businesses, as we have noted to FDA on multiple occasions, by limiting consumer access to this safe and beneficial ingredient.

Nonetheless, while CRN contends that the safety and grandfathered status of NAC are so well established as to be beyond question at this point, we point to evidence provided in this letter by CRN and other industry stakeholders. We again ask FDA to commit to substantively responding to the concerns raised by CRN in its June 2021 citizen petition within 30 days of this letter. The Agency has had ample time and the necessary information to provide clarity on this issue.

NAC is a Clearly Grandfathered Ingredient

Industry stakeholders have already provided the Agency with evidence of NAC's grandfathered status (i.e., that NAC was marketed as a dietary supplement prior to the October 1994 passage of the Dietary Supplement Health and Education Act (DSHEA)).[6] More evidence of NAC's grandfathered status has been provided by additional stakeholders in response to the FDA's November 24, 2021 Letter.[7] This evidence, which includes numerous references to NAC in mail order catalogs and sales brochures, is the exact type of documentation that FDA references as being relevant to demonstrating grandfathered status in its 2016 draft guidance on new dietary ingredient notifications.[8]

Specifically, FDA notes as follows:

> **What documentation does FDA recommend to show that a dietary ingredient was marketed prior to October 15, 1994?**

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6 *See e.g., Comments of the American Herbal Products Association on the Citizen Petition of the Council for Responsible Nutrition Regarding the Regulatory Status of N-acetylcysteine (Dkt No. FDA-2021-P-0523)*, October 8, 2021.

7 *See* January 25, 2022 Letter from B. Ritz, Pure Encapsulations, LLC to D. Stearn, FDA.

8 FDA Draft Guidance, *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry*, August 2016.

> Documentation to show that a dietary ingredient is not an NDI should consist of written business records, promotional materials, or press reports with a contemporaneous date prior to October 15, 1994. Examples include sales records, bills of lading, sales contracts, manufacturing records, commercial invoices, magazine advertisements, ***mail order catalogs, or sales brochures***. Documentation should include adequate information to establish that marketing took place in the U.S.: the identity (e.g., chemical or botanical name) of the marketed ingredient, including its form (e.g., ground herb, water extract, oil), and whether the ingredient was marketed as a dietary ingredient or for some other purpose. For example, advertising in body building magazines could be adequate evidence of marketing as a dietary ingredient.[9]

The evidence provided to FDA includes numerous documents from as early as 1991 that clearly identify "N-acetyl-L-cysteine" being marketed in the U.S. as "nutritional products", "nutritional supplements", and similar products that demonstrate NAC's use as a dietary ingredient prior to October 15, 1994.[10] These examples also point to the existence of other products containing NAC on the market prior to October 1994.[11] Further, one of the stakeholders – the American Herbal Products Association (AHPA) – points to evidence that FDA itself was aware of NAC's presence in dietary supplements prior to DSHEA,[12] which continues to demonstrate the clearly grandfathered status of this ingredient. Given the extensive evidence of NAC supplement marketing in the 1990's, it is likely that NAC was being marketed as a dietary supplement long before this. Companies having to demonstrate grandfathered status for new dietary ingredient purposes, however, would only have needed to keep documentation of use prior to October 1994 and DSHEA's passage. This demonstrates another reason FDA's policy reversal on NAC is legally invalid – by trying to apply the drug preclusion provisions of DSHEA retroactively over 25 years after DSHEA's passage, companies were never given the opportunity to preserve documentation that would counter FDA's current, legally invalid position on NAC.

NAC Dietary Supplements Have a Long History of Safe Use

With regard to safety, CRN is not aware of FDA raising safety concerns about NAC in its decades-long history of use as a dietary supplement. FDA has had ample opportunity in this time to identify safety concerns and, as CRN has noted, FDA already has ready access to the requested safety information through the FDA Adverse Event Reporting System, manufacturing facility inspections, and other tools. The safety of NAC is supported by its long history of use as an ingredient in dietary supplements, as well as data from unpublished and publicly available research studies conducted on NAC or NAC-containing formulations. While the safety of NAC is not relevant to its status as a legal dietary ingredient under FDCA section 201(ff)(3)(B)(i), we discuss some examples of the supporting information below.

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9 *Id.* IV.A.9 (emphasis added).

10 *See* Pure Encapsulations January 25, 2022 Letter and AHPA October 8, 2021 Comment.

11 AHPA October 8, 2021 Comment, noting that Attachment D includes a catalog advertisement referencing other NAC products on the market ("Compare our 600 mg with smaller size or lower potency competitors").

12 *Id.*, citing to an FDA enforcement report that included NAC in examples of dietary supplements. *See* AHPA October 8, 2021 Comment, n. 4.

Companies manufacturing and marketing NAC-containing dietary supplement products collect adverse event data as required by law, as well as industry best practices. These reports provide compelling real-world evidence of NAC safety. As one example, Pure Encapsulations (a brand marketed by Nestlé Health Science, a CRN member company) has compiled over nine years of adverse event data for its dietary supplement products containing NAC, as described in its submission.[13] From 2013 to present, the adverse event rate per unit sold of NAC-containing products was only 0.002%. Adverse events were extremely rare, mild, non-serious, and resolved on their own. A NAC-containing dietary supplement product marketed by Sevo Nutraceuticals had a similar adverse event rate, with less than 10 reported adverse events for approximately 500,000 units sold.[14] CRN again notes that FDA has access to adverse event information through the Adverse Event Reporting System and facility inspections – FDA has never raised a concern about NAC safety.

Companies have invested in scientific research on NAC, and academic programs investigating NAC provide further evidence of its safety for use as a dietary supplement ingredient.[15] Research includes studies conducted in healthy individuals, as well as in those with medical conditions. In one example, researchers conducted eight clinical studies on a formulation containing 300 mg NAC per serving and reported no serious adverse events in over 350 participants consuming the formulation daily for periods ranging from 2 weeks to 2.4 years.[16] These studies were undertaken in a range of individuals, including healthy subjects, those with Mild Cognitive Impairment, and those diagnosed with Alzheimer's disease.

Research published in peer-reviewed journals also includes safety information pertaining to NAC. Typically, these publications report the effects of NAC either alone or in combination with other ingredients on various health conditions or diseases, as well as in healthy individuals. Several recently published review articles and meta-analyses are briefly mentioned below as examples and do not reflect a comprehensive overview of the available body of evidence.

In one review article on different therapeutic uses of NAC, the authors stated that "an extensive review of multicentric medical records has shown that intravenous and oral NAC is associated with minimal side-effects," with the most common adverse effects of oral NAC administration being gastrointestinal symptoms such as nausea and vomiting.[17] The unpleasant smell and taste of NAC contribute to these effects. Another recent review article indicated that NAC "appears to be well tolerated with minimal side effects when used as a supplement or in treatment of various disorders."[18] A publication reviewing

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13 Pure Encapsulations January 25, 2022 Letter.

14 *See* Letter from Dr. Thomas Shea to FDA, January 25, 2022. Dr. Shea has conducted relevant research on NAC safety at the University of Massachusetts Lowell and as the Science Officer for Sevo Nutraceuticals. In 2016, Dr. Shea submitted a qualified health claim petition for a dietary supplement containing NAC. In response to that petition, FDA specifically noted that NAC is a dietary supplement. *See* Letter from D. Balentine, FDA, to Dr. Shea, available here.

15 *See* Pure Encapsulations January 25, 2022 Letter; Shalchi H. GlyNAC improves strength and cognition in older humans. Baylor College of Medicine. https://www.bcm.edu/news/glynac-improves-strength-and-cognition-in-older-humans. Published Mar 29, 2021. Accessed January 25, 2022; and Dr. Shea January 25, 2022 Letter.

16 Id.

17 Tenório MCDS, Graciliano NG, Moura FA, Oliveira ACM, Goulart MOF. N-Acetylcysteine (NAC): Impacts on human health. Antioxidants (Basel). 2021;10(6):967. Published 2021 Jun 16. doi:10.3390/antiox10060967.

18 Schwalfenberg GK. N-Acetylcysteine: A review of clinical usefulness (an old drug with new tricks). J Nutr Metab. 2021;2021:9949453. Published 2021 Jun 9. doi:10.1155/2021/9949453.

the use of NAC for the treatment of psychiatric disorders reinforced NAC's excellent safety profile and cited systematic reviews that "found N-acetylcysteine to be a well-tolerated oral therapy without any considerable adverse effects."[19] Additionally, in a systematic review and meta-analysis of clinical trials to evaluate the safety and benefits of NAC for chronic kidney disease, researchers concluded that "NAC appears to be safe without obvious adverse events."[20] The lack of adverse effects in individuals with different health conditions or diseases lends further support to the safety of NAC for use as a dietary ingredient. The aforementioned publications are provided simply as a few examples of the publicly available, peer-reviewed safety information on NAC that can be readily accessed by FDA.

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CRN again asks FDA to (1) reverse its position to review the CRN and NPA citizen petitions concurrently; and (2) provide a substantive response addressing CRN's legal concerns within 30 days. By requesting safety and marketplace information, CRN is concerned that FDA could push back any response date to CRN's legal arguments by months, if not longer. Much of the safety information that CRN has discussed is already available to FDA, and additional data provided by stakeholders demonstrate the long history of safe use of NAC. Safety is not an issue, nor is it relevant to addressing CRN's concerns. By committing to a quick response on CRN's legal challenge, FDA would provide a timely resolution of this issue that CRN and numerous other stakeholders have requested.

[19] Ooi SL, Green R, Pak SC. N-Acetylcysteine for the treatment of psychiatric disorders: A review of current evidence. Biomed Res Int. 2018;2018:2469486. Published 2018 Oct 22. doi:10.1155/2018/2469486.

[20] Ye M, Lin W, Zheng J, Lin S. N-acetylcysteine for chronic kidney disease: a systematic review and meta-analysis. Am J Transl Res. 2021;13(4):2472-2485. Published 2021 Apr 15.

We look forward to receiving a commitment by the Agency to bring clarity to CRN's legal concerns in a timely manner and receiving the Agency's substantive response.

Sincerely,

Steve Mister, President & CEO, CRN

Megan Olsen, Vice President & Associate General Counsel, CRN

Cc: Greg Noonan, Acting Director, ODSP, FDA
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