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January 4, 2022

Douglas Stearn
U.S. Food and Drug Administration
Deputy Director for Regulatory Affairs
Center for Food Safety and Applied Nutrition
5001 Campus Drive
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Re: Docket Number FDA-2021-P-0523; November 24, 2021 Food and Drug Administration Letter

The Council for Responsible Nutrition (CRN)[1] writes in response to the Food and Drug Administration's ("FDA" or "Agency") November 24, 2021 letter[2] regarding the CRN citizen petition dated June 1, 2021 (Docket Number FDA-2021-P-0523). 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".[3]

The Agency's nonresponsive November 24th response does not address the single legal issue first raised by CRN in December 2020 and restated in CRN's June 1st citizen petition: whether the drug preclusion provision in section 201(ff)(3)(B)(i) properly precludes NAC from being marketed in dietary supplements. Instead the Agency has attempted to deflect the facial legal defects of its position with a detour into safety concerns that do not exist and are not relevant to this inquiry. As such, the Agency is now also in violation of its own requirement to respond to CRN's citizen's petition within 180 days of receipt.

CRN first raised significant concerns with the legality of FDA's policy to block NAC from use in dietary supplements with the Agency in December 2020.[4] FDA took the position that NAC was not a legal dietary ingredient under section 201(ff)(3)(B)(i) in warning letters issued in July 2020 to companies making hangover claims for dietary supplement products containing NAC.[5] According to the July 2020 warning letters, FDA believes NAC is precluded from being a dietary ingredient because it is the same

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

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

4 *See* December 4, 2020 Letter from S. Mister and M. Olsen, CRN, to S. Tave, FDA ("December 4, 2020 Letter").

5 *See* FDA News Release, *FDA Warns Companies Illegally Selling Hangover Remedies*, July 29, 2020.

article that was first approved as a drug in 1963, before being marketed as a dietary ingredient. This position reversed decades long precedent of FDA allowing the sale of NAC as a dietary ingredient.

CRN has alleged that the Agency's sudden policy change is legally invalid on multiple grounds. First, it is not even clear, from FDA records, whether section 201(ff)(3)(B)(i) applies to NAC as a dietary supplement. The decades-old records for NAC drug approval contain unreliable information, such as handwritten dates, and unverifiable information. Second, NAC drugs approved prior to 2016 appear to comprise different forms of NAC from that which is found in a dietary supplement. Even if the drug approval records are valid, FDA's position ignores the differences in delivery forms and dosage levels of the products at issue. Third, interpreting section 201(ff)(3)(B)(i) to prohibit the marketing of dietary supplements containing NAC violates the well-established presumption against statutory retroactivity. CRN's review of the questionable drug approval records for NAC, and subsequent discovery of unreliable and conflicting information, demonstrates one of the significant dangers of statutory retroactivity. Further, section 201(ff)(3)(B)(i) was created by Congress, as part of the Dietary Supplement Health and Education Act (DSHEA) to protect commercial drug interests necessary to incentivize new drug development. Drug marketers could not have invested in clinical research prior to 1994 in reliance on an expectation of monopoly interest for NAC prior to the passage of DSHEA, which created that expectation. Fourth, FDA's policy change is an arbitrary and capricious agency action that is invalid under the Administrative Procedure Act (APA). And finally, the equitable defense of laches prevents FDA from enforcing its new policy. These are purely legal issues for FDA's evaluation.

Over a year after CRN first raised concerns regarding the legality of FDA's policy reversal on NAC, FDA has failed to substantively respond to CRN's concerns and, with the announcement in the November 24 Letter, has extended any response date until after January 25, 2022. Meanwhile, dietary supplement companies that have been selling NAC as a dietary ingredient for decades with no objections from FDA are experiencing significant economic harm from FDA's statements. CRN has provided FDA with specific examples of this economic harm in multiple documents and meetings, including that the largest U.S. ecommerce retailer, Amazon, stopped selling NAC in spring 2021 in reliance on FDA statements. In the last few months, large payment processing platforms that businesses and consumers have come to rely on for safe and efficient online payment transactions, Paypal and Shopify, have followed Amazon's lead, and blocked the use of their platforms for NAC dietary supplement sales.

FDA has now combined CRN's request for legal clarity on its NAC policy reversal with a second NAC citizen petition that was filed by the Natural Products Association (NPA) on August 18, 2021 (Docket Number FDA-2021-P-0938). The NPA citizen petition asks in the alternative for FDA to either: 1) address the legality of its NAC position; or 2) develop a regulation finding NAC lawful under the FDCA using the authority under section 201(ff)(3)(B). By introducing the possibility that FDA could disregard the legal challenge to its position regarding section 201(ff)(3)(B)(i) and proceed to exercise its statutory discretion by instigating a rulemaking, NPA's citizen petition raises issues beyond the facial legal challenge presented by CRN.

It is inappropriate for FDA to review the CRN and NPA citizen petition's concurrently, as they request different actions from the Agency. CRN asks only for a review of the applicability of section 201(ff)(3)(B)(i) to NAC. CRN also is very concerned with FDA's request in the November 24, 2021 Letter

for extensive and irrelevant NAC marketing and safety information. The requested information is not relevant to the legal points raised in CRN's correspondence and is not needed by the Agency to respond to the legality of its position. Safety and current market evaluation are not relevant factors in the determination of whether section 201(ff)(3)(B)(i) is applicable to NAC and can be applied retroactively. It is questionable whether they are even relevant to NPA's alternative request for a rulemaking given that section 201(ff)(3)(B) makes no reference to a safety evaluation to establish "that the article would be lawful under this chapter [Title 21, chapter 9]."

In May 2021, FDA acknowledged CRN's legal arguments and noted that the Agency was "closely reviewing the information provided in your [December 4, 2020 Letter] and will provide a more substantive response once our evaluation is complete."[6] Over 6 months later, not only has the Agency not addressed CRN's legal arguments, but also appears to be suggesting through its November 24, 2021 Letter that it will not address these legal arguments if it commences an NAC rulemaking as requested by NPA. CRN again reiterates the inappropriate nature of FDA's decision to review the CRN and NPA petition concurrently – prior to the NPA citizen petition, FDA appeared willing to address CRN's legal concerns. The CRN and NPA citizen petitions ask for different actions and should be addressed as two different matters before the Agency.

With regard to when NAC was first marketed as a dietary supplement, CRN and other stakeholders already have provided the agency with evidence that NAC is clearly grandfathered and was marketed before DSHEA was passed on October 25, 1994.[7] 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, and FDA has ready access to the requested information through the FDA Adverse Event Reporting System and manufacturing facility inspections.

By requesting this information, FDA has pushed back any response date to CRN's concerns by months, if not longer. CRN believes that FDA should reverse its position to review the CRN and NPA citizen petitions concurrently and provide a substantive response addressing CRN's legal concerns that the Agency indicated it would provide in its May 6, 2021 Letter. At a minimum, however, CRN requests that FDA commit to substantively respond to the concerns raised in CRN's June 2021 citizen petition within 30 days of the January 25, 2022 comment deadline. Such a commitment would recognize the need for a timely resolution of this issue that CRN and numerous other stakeholders, including Senator Mike Lee and Representative Jeff Duncan have requested. CRN also is reserving the right to provide additional responses and information to FDA by January 25, 2022 if the Agency has not addressed CRN's legal arguments by that time.

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[6] *See* May 6, 2021 Letter from C. Welch, FDA, to S. Mister and M. Olsen, CRN ("May 6, 2021 Letter").

[7] *See* December 4, 2020 Letter at n. 17. The American Herbal Products Association (AHPA) also provided extensive evidence of NAC's pre-1994 dietary supplement marketing as a comment to the CRN citizen petition docket. *See 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.

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
Cara Welch, Acting Deputy Director, ODSP, FDA
Dr. Janet Woodcock, Acting Commissioner, FDA
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