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In NAC Docket, NAD+ Drug Firm Suggests US FDA Get Serious About Dietary Ingredient Regulations

by Malcolm Spicer

MetroBiotech argues it and other drug developers and manufacturers are harmed as FDA allows NAD+ use in dietary supplements without requiring new dietary ingredient notifications and despite DSHEA's preclusion clause.

It didn't take long for the US pharma industry to respond to the Food and Drug Administration's request for comments on whether the amino acid N-acetyl-L-cysteine is safe for use as a dietary ingredient.

The first comment published by the agency since it announced a docket for comments came from Metro International Biotech LLC, which informs the FDA that it is a clinical-stage pharma "that has established the most comprehensive portfolio of proprietary nicotinamide adenine dinucleotide (NAD+) precursors in the world" and has instituted publicly available clinical trials with the ingredient.

The Birmingham, MI, firm, which operates as MetroBiotech, suggests the FDA apply to the use of NAD+ in supplements the same scrutiny it's showing concerning N-acetyl-L-cysteine (NAC) in the products.

Through corporate counsel Michael Willis, MetroBioTech also suggests dual enforcement of separate FDA rules under the Dietary Supplement Health and Education is appropriate concerning the use of NAD+ in supplements.

Willis noted the requirement for notifications for new dietary ingredient with proof of a reasonable assurance of safety for their intended use for ingredients not available in the US food supply before Congress passed DSHEA in October 1994 and the preclusion rule imposed by the act prohibiting, before their use in food or supplements was known, ingredients studied as or

approved as drugs from being used as dietary ingredients.

The comments suggest MetroBiotech and other drug ingredient developers and manufacturers are harmed as NAD+ is used in dietary supplements without requiring new dietary ingredient notifications with proof of a reasonable assurance of safety for their intended use.

The firm suggests the FDA "take ... seriously" the preclusion rule "to protect the right of companies that have spent significant time and research to develop drugs products from competition from dietary supplements that are clearly new dietary ingredients that have never filed a new dietary ingredient notification prior to the institution of substantial clinical trials."

In its comments, MetroBiotech makes a more narrowly focused recommendation than the Pharmaceutical Research and Manufacturers of America trade group in 2019 made in comments to the FDA's "Responsible Innovation in Dietary Supplements" *docket*. PhRMA recommended that the FDA adhere to the clear definitions in agency regulations under DSHEA that determine whether substances are eligible for use as dietary ingredients. (Also see "*Drug Innovation Needs Exclusivity For Some Natural Substances, PhRMA Recommends*" - HBW Insight, 25 Jul, 2019.)

NAD+ 'Broad Pharmaceutical Potential'

NAD+, according to a January 2019 report in the journal Antioxidants & Redox Signaling, is an essential pyridine nucleotide that is an essential cofactor and substrate for multiple critical cellular processes involved in oxidative phosphorylation and adenosine triphosphate production, DNA repair, epigenetically modulated gene expression, intracellular calcium signaling and immunological functions.

MetroBiotech, describing its work on its website, states: "NAD+ levels have been shown to decline as humans age and increasing NAD+ to preserve health and normal metabolism is believed to have broad pharmaceutical potential."

According to labels on numerous dietary supplement promoted for healthy aging, including products provided exclusively for sale at Walmart stores, NAD+ production in the body is boosted by dietary ingredients including nicotinamide riboside chloride. (Also see "*Attention Shoppers And Investors: ChromaDex Makes Tru Niagen Available At Walmart*" - HBW Insight, 7 Jun, 2021.)

Two firms with businesses centered on nicotinamide riboside ingredients, ChromaDex Corp. and Elysium Health Inc., are engaged in extended litigation across multiple federal district courts alleging false advertising and patent infringement. (Also see "*Split Decision In Breach-of-Contract Battle Of Litigation War Between ChromaDex, Elysium*" - HBW Insight, 6 Oct, 2021.)

NAC Approved As Drug In 1963

According to the docket on regulations.gov – *FDA-2021-P-0938-0006* – MetroBiotech's comment

posted on 6 December is the first published since the FDA on 24 November announced that it needed information to "determine if rulemaking to make NAC lawful as a dietary supplement is appropriate." (Also see "*Window Of Opportunity Opened Narrowly For Continued Use Of NAC As Dietary Ingredient In US*" - HBW Insight, 24 Nov, 2021.)

The American Herbal Products Association submitted comments to the docket in October, when the FDA used the docket number for comments on the Natural Products Association's citizen petition submitted in August asking to halt to warnings and other enforcement against firms marketing supplements containing NAC. (Also see "*AHPA Offers Hard Copy Supporting NAC's Use In Dietary Supplements Pre-DSHEA*" - HBW Insight, 13 Oct, 2021.)

AHPA's comments also went to a separate docket for the Council for Responsible Nutrition's June petition asking for the same action. (Also see "*US FDA Put On The Clock About NAC's Use As Dietary Ingredient After Amazon Ends Sales*" - HBW Insight, 2 Jun, 2021.)

The Office of Dietary Supplement Program in the FDA Center for Food Safety and Applied Nutrition submitted tentative responses informing the CRN and the NPA it is requesting additional information from the petitioners and interested parties and that it "needs additional time to carefully and thoroughly review the complex questions posed in these petitions."

The ODSP asks for comments with information on the earliest date NAC was marketed as a dietary supplement or as a food; its safe use in products marketed as a dietary supplement; and "any safety concerns." The office didn't ask for comments on the safety of other ingredients used in dietary supplements. (Also see "*NAC's Longevity In US Dietary Supplement Market Swings On Comments As NDI Notifications*" - HBW Insight, 29 Nov, 2021.)

With NAC commonly used in myriad supplements available in the US, the FDA in July 2020 revealed that it no longer considered NAC eligible for e a dietary ingredient in warning letters to seven firms in July 2020. (Also see "*Widely Available Unapproved Hangover Remedies Concern US FDA As Encouraging Overindulgence*" - HBW Insight, 30 Jul, 2020.)

The agency warned each firm about making violative claims for their products as hangover remedies while also advising each that NAC-containing products are "excluded from the dietary supplement definition" under DSHEA because the ingredient had been approved as a new drug before the legislation was passed in 1994.

"NAC was approved as a new drug ... 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," stated the CFSAN Office of Compliance in each warning.

The deadline for comments to the agency's NAC docket is 5 January.