March 7, 2023

CITIZEN PETITION REGARDING REGULATORY STATUS OF ß-NICOTINAMIDE MONONUCLEOTIDE

The undersigned, on behalf of the Natural Products Association ("NPA") and the Alliance for Natural Health USA ("ANH-USA"), (collectively referred to herein as "Petitioners,") submit this petition under 21 U.S.C. § 321(ff) and 21 C.F.R. § 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs, based on the facts and arguments set forth herein, either (1) determine that ß-Nicotinamide Mononucleotide ("NMN") is not excluded from the definition of a dietary supplement under section 21 U.S.C. § 321(ff)(3) of the Food, Drug, and Cosmetic Act (the "Act"), or (2) commit to exercise enforcement discretion in connection with the marketing and selling of NMN in or as a dietary supplement. Alternatively, Petitioners request that FDA recommend that the Secretary of the Department of Health and Human Services ("HHS") exercise his discretion to promptly issue a regulation, after notice and comment, finding that NMN would be lawful in or as a dietary supplement under the Act.[1]

I. ACTION REQUESTED

For the reasons that follow, Petitioners respectfully request that the Commissioner of Food and Drugs, based on the facts and arguments provided herein, either (1) determine that NMN is not excluded from the definition of a dietary supplement under section 21 U.S.C. §321(ff)(3)(B) of the Act or (2) commit to exercise enforcement discretion in connection with the marketing and selling NMN in or as a dietary supplement. Alternatively, Petitioners request that FDA recommend that the Secretary of the Department of Health and Human Services ("HHS") exercise his discretion to

[1] Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301, *et seq.*

promptly issue a regulation, after notice and comment, finding that NMN would be lawful in or as a dietary supplement under the Act.

II. STATEMENT OF GROUNDS

1. Petitioners

a. NPA

Founded in 1936, NPA is the nation's largest and oldest nonprofit organization dedicated to the natural products industry. Natural products are represented by a wide array of consumer goods that grow in popularity each year. These products include natural and organic foods, dietary supplements, pet foods, health and beauty products, "green" cleaning supplies and more. Generally, natural products are considered those formulated without artificial ingredients and that are minimally processed. NPA advocates for the right of consumers to have access to products that will maintain and improve their health, and for the right of retailers and suppliers to sell these products. NPA represents over 1,400 members, accounting for more than 10,000 retail, manufacturing, wholesale, and distribution locations of natural products, including foods, dietary supplements, and health/beauty aids. NPA unites a diverse membership, from the small health food stores to large dietary supplement manufacturers.

NPA played a key role in the passage of the Dietary Supplement Health and Education Act of 1994 ("DSHEA").[2] This important legislation struck a balance between the need for consumers to have access to and information about safe and effective dietary supplements while also preserving the government's interest in protecting the public from unsafe products and false and misleading claims. Currently, NPA advocates before Congress, the Food and Drug Administration,

[2] Pub. L. No. 103-417, 108 Stat. 4325.

the Federal Trade Commission, and other federal and state agencies, legislatures, state attorneys' general and the court.

b. ANH-USA

Representing one million supporters across the U.S., the Alliance for Natural Health USA ("ANH") is the largest organization in the U.S. and abroad working to protect consumer access to safe, effective natural health options. Founded in 1992, ANH is a United States affiliate of an international, non-profit, non-governmental organization, and is the successor to the American Association for Health Freedom.

ANH is dedicated to promoting natural, sustainable healthcare through good science and good law. We protect the right of natural health practitioners to practice and the right of consumers to choose the healthcare options and treatment modalities they prefer, including complementary and alternative medicine. Central to this type of medicine is a broad range of high-quality dietary supplements. ANH supporters include health care practitioners, medical doctors, scientists, business entities, consumers, and patients across the United States, many of whom recommend, manufacture, or consume NMN supplements. Thus, ANH's supporters would directly suffer if they lost access to NMN in dietary supplements.

2. Exclusion From The Definition Of A Dietary Supplement Under 21 U.S.C. §321(ff)(3)(B)

Section 201(ff) of the Act, as amended by DSHEA, specifically defines what it means to be a "dietary supplement." Section 201(ff)(3)(B) excludes the following from the definition of dietary supplement:

> (i) an article that is approved as a new drug under section 505, certified as an antibiotic under section 507, or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or
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> (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,
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> which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless the Secretary, in the

Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act.

21 U.S.C. § 321(ff)(3)(B). This section of the Act has come to be known in the industry as creating a "race-to-market" between those interested in investigating an article as a drug and others interested in marketing the same article in products labeled as dietary supplements. This section purportedly is intended to preserve the financial incentives to both bring innovative dietary ingredients to market and to conduct research on new drugs.

The second race-to-market exclusion, the authorized for investigation clause, is the one most relevant to this Citizen Petition. Under the plain language of the statute, that exclusion does not apply to an article that was either (1) marketed as a dietary supplement or food before authorization for investigation, or (2) is the subject of a HHS regulation finding that the article would be lawful under the Act.

3. FDA's Interpretation And Application Of 21 U.S.C. § 321(ff)(3)

In passing the Act, Congress charged the FDA to "protect the public health" by ensuring that "foods are safe, wholesome, sanitary, and properly labeled." 21 U.S.C. § 393(b)(2)(A). In 1994, DSHEA established a new category of food products – dietary supplements – that have unique, comprehensive safety, labeling, manufacturing, and other related standards. DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of products that it defined as dietary supplements.[3]

a. "Old" and "New" Dietary Ingredients

As noted above, DSHEA established the definition of a dietary supplement under Section 201(ff) of the Act.[4] Under this definition, a dietary supplement must, among other things, contain

[3] *See, e.g.*, 103 CONG. REC. S17049 (daily ed. Nov. 23, 1993) (statement of Sen. Hatch).
[4] 21 U.S.C. § 321(ff).

at least one dietary ingredient, be swallowed, not be intended to replace a meal, and not contain an ingredient found to be excluded under the race-to-market clause. DSHEA also established, under Section 413(d) of the Act, the definition of a "new dietary ingredient" ("NDI") to mean a dietary ingredient that was not marketed in the United States before October 15, 1994.[5] Although there is no statutory or regulatory definition, the term "old dietary ingredients" ("ODIs") has come to describe ingredients that were on the market prior to DSHEA and would satisfy the definition of a dietary ingredient under DSHEA.[6] There is no authoritative list of ODIs that were marketed before October 15, 1994. Even more, the entire category of food we now call dietary supplements, nor any of the requirements for a food to be classified as one, including the race-to market clause, existed prior to October 15, 1994. The statutory interplay between the race-to-market clause and the effective date of the pertinent sections of DSHEA results in a situation in which an ingredient, legally marketed pre-DSHEA (before October 15, 1994), could retroactively have become violative of the Act because of the race-to-market clause. Prior to DSHEA, there was no need for a responsible distributor or manufacturer to be concerned with the approval date of a drug/biologic or when an article was authorized for investigation. Essentially, the distributor or manufacturer of what was a legal ingredient, pre-DSHEA, could be forced off the market because of losing a race-to-market that did not exist when they first placed the ingredient into commerce. NPA has previously asserted that a retroactive application of the race-to-market clause, or any aspect of DSHEA, is improper.[7]

b. Authorized For Investigation

[5] 21 U.S.C. 350b(d).
[6] 21 U.S.C. § 321(ff)(1).
[7] *See, e.g., First Amended Complaint in Natural Products Ass'n v. FDA*, Case No. 21-cv-3112 (D. Md).

As noted above, other than the date of approval for a new drug, antibiotic, or biologic, the date an article is authorized for investigation as a new drug, antibiotic, or biologic is relevant to whether a dietary ingredient placed into commerce by a distributor or manufacturer would be excluded from the definition of a dietary supplement under section 201(ff)(3)(b). The FDA has taken a position that Congress, in DSHEA, intended the term "an article authorized for investigation" to mean an article that is subject of an Investigational New Drug Application ("IND") that has gone into effect.[8] This interpretation and application of the Act is troubling for at least two reasons: (1) INDs are not authorized by FDA, and (2) to Petitioners' knowledge, there is no public access to a database or list of current articles that are the subject of an IND. In fact, FDA's regulations prevent it from publicly revealing the effective date of an IND or the source of the IND.[9] To Petitioners' knowledge, there is no way for anyone – the public, industry, and other stakeholders – other than the IND holder or someone at FDA with access to the records, to know that an IND has become effective until either a clinical study begun under it is listed on clinicaltrials.gov, or there is a publication relating to it.

In this situation, it is perplexing that FDA has determined that Congress intended the phrase "authorized for investigation" to mean the date an IND became effective. Under 21 C.F.R. Part 312, the regulations pertaining to IND applications, the FDA can only respond to an IND application by either placing it on clinical hold or simply allowing it to become effective 30 days after it was submitted for review to the agency. Equally perplexing is FDA's determining that Congress would set up a regulatory race-to-market between those wishing to distribute/manufacture dietary ingredients/supplements and those investigating articles as drugs,

[8] FDA, *Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance for Industry* at 44 (Aug. 2016).
[9] 21 C.F.R. 312.130(a).

but not intend for both sides to have access to the relevant date that would be absolutely necessary to make any determination as to the regulatory status concerning the marketability of an ingredient. Considering that DSHEA was introduced to counteract unnecessarily stringent federal intervention into the manufacturing, sale, and labeling of dietary supplements, it is hard to understand the basis for FDA's interpretation of the will of Congress.

4. NMN

NMN is a naturally occurring molecule that belongs to the family of nucleotides. It is an intermediate in the biosynthesis of nicotinamide adenine dinucleotide (NAD+), which is an essential coenzyme involved in numerous biological processes. NMN is a derivative of vitamin B3 (niacin) and synthesized through several enzymatic reactions in cells. Research has shown that β-NMN has potential health benefits, including anti-aging and metabolic benefits. NMN is the subject of a Structure/Function Claims Notification filed with the FDA in June 2020.[10]

It is Petitioners' understanding that FDA has been informed and provided a basis demonstrating that NMN capsules were offered for sale in Japan as early as 2016. Further, on April 6, 2016, Shinkowa Pharmaceutical Co. Ltd. announced that its NMN dietary supplement had been available for sale in Japan in 2015 and that the product was being offered for sale in the United States through Amazon.[11] By no later than the end of 2018, NMN was marketed in the United States by Nutraland as an article for use in food, beverage, and supplement products. Moreover, Nutraland announced on December 19, 2018, that its NMN product had self-affirmed GRAS status.[12] Another company, Cellmark, announced self-affirmed GRAS status for its NMN in

[10] SFC No. 2020-000700 June 22, 2020.
[11] *See, e.g.*, attached Ex. 1.
[12] *See, e.g.*, attached Exs. 2-3.

September 2020.[13] In addition, there are a plethora of labels for supplement products containing NMN in the National Institutes of Health Dietary Supplement Label Database.

In May 2022, the FDA acknowledged without objection a new dietary ingredient notification filed by SyncoZymes (Shanghai) Co., Ltd.[14] On November 4, 2022, the FDA notified the company that it changed its mind: "Based on new information that came to light when we were reviewing another notification, FDA initiated a review of past notification responses for NMN and concluded that NMN is excluded from the definition of a dietary supplement. This means that NMN may not be marketed as or in a dietary supplement."[15] The FDA took the position that NMN is excluded from the statutory definition of a dietary supplement because it was allegedly authorized for investigation under an effective IND before being lawfully marketed as a dietary supplement or as a food in the United States. As discussed above, the FDA cannot identify the date of the alleged "authorization" it is using to attack NMN. The FDA also objected to NDINs on NMN submitted by other companies.

As a result of the FDA's action, Amazon announced on February 16, 2023, that it would no longer allow dietary supplements containing NMN to be sold on its platform.[16]

5. The FDA Has Misconstrued And Misapplied Section 201(ff)(3) Of The Act To NMN.

As a rationale for its decision concerning the regulatory status of NMN in or as a dietary supplement, the FDA contends that section 201(ff)(3)(B) of the Act requires that the article be "marketed as a dietary supplement or as a food" **in the United States**. There is nothing in the plain

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[13] https://www.cellmark.com/2020/09/22/cellmark-announces-self-affirmed-gras-at-nyift-2020/ (last visited Mar. 3, 2023).
[14] NDIN 1247, FDA-2022-S-0023-0027.
[15] *Id.*
[16] https://www.npanational.org/wp-content/uploads/2023/02/Amazon-letter.pdf (last visited Mar. 3, 2023).

language of the statute that requires the prior marketing of the article to **only** have occurred **in the United States**. The FDA is improperly trying to import a limitation into the statute that does not exist. And the FDA has not cited any prior regulatory document that adopts its argument. In fact, the 2016 Draft Guidance on NDINs provides (at page 68) that the data and information to substantiate a history of safe use is not limited to the United States: "This history of use could be from the United States or another country, as long as the substance was consumed as a food, dietary supplement, or, in the case of foreign history of use, category of product comparable to a dietary supplement in the U.S." Further, Congress was clear in its intent when it drafted the definition of a NDI in Section 413(d) of the Act – namely, that an ingredient could only avoid being classified as an NDI if it was marketed in the U.S. before a specific date. It seems odd that FDA would infer Congress's silence on the issue of where marketing must occur under a reading of Section 201(ff)(3) to indicate that Congress intended the "marketing as a dietary supplement or as a food" to be limited to only U.S. commerce.

The FDA's argument that it would be a burden to keep track of supplement and food product launches around the world is way off the mark. A company that submits a NDIN to the agency would have the opportunity to bear the burden of providing the requisite evidence of any marketing in foreign countries in order to avoid falling within the exclusion.

The FDA erred in arbitrarily or capriciously misinterpreting the Act and rejecting evidence of marketing and safe use of NMN in Japan.

The FDA further erred when it found that it would not consider evidence of marketing for a product on which no NDIN had been submitted. In its supplemental response letters to companies that submitted NDINs, the FDA concede that the Act does not contain that language. As to any

safety concerns, the NMN product has self-affirmed GRAS status.[17] Further, the agency did not take into consideration the policy it announced in May 2022 to exercise enforcement discretion in certain circumstances to encourage manufacturers, distributors, or others to file NDINs.[18] The policy stated that: "we generally do not intend to take enforcement action based on a failure to comply with the requirement to file an NDI notification in a timely fashion against firms marketing products within the scope of this enforcement discretion policy."[19] There is no reason that enforcement discretion as to the marketing of qualifying NMN products under the policy should be more limited than other products.

The FDA's action on NMN is confusing consumers and industry stakeholders and has caused significant economic harm. And it is doing so without any suggestion that NMN presents a safety risk. Indeed, NMN is the subject of multiple GRAS affirmations. By its erroneous and inconsistent actions, the FDA will likely deter companies from spending the significant time and money to submit NDINs or obtain GRAS status.

III. CONCLUSION

FDA's sudden and contradictory announcement relative to the regulatory status of NMN as a dietary ingredient that is excluded from the definition of a dietary supplement, along with the arbitrary, erroneous, unreasonable, and inequitable interpretation of the Act it relied on, adversely affects the entire dietary supplement stakeholder community. The current situation with NMN is yet another example of the inconsistent and mercurial way in which FDA chooses to both interpret DSHEA and use its limited resources to supposedly protect the public health. FDA has not

[17] *See, e.g., Center for Food Safety v. Becerra*, 565 F.Supp.3d 519 (S.D.N.Y. 2021).
[18] FDA, *Policy Regarding Certain New Dietary Ingredients and Dietary Supplements Subject to the Requirement for Premarket Notification: Guidance for Industry* (Draft, May 2022).
[19] *Id.* at 4.

articulated any risk to the safety of the public posed by NMN when marketed as a dietary ingredient or dietary supplement.

For the foregoing reasons, FDA should reverse its arbitrary or capricious position that NMN is excluded from the definition of a dietary supplement under Section 201(ff)(3)(B)(ii) of the Act. Petitioners respectfully request that the Commissioner of Food and Drugs either determine, based on the facts and arguments provided herein, (1) that NMN is not excluded from the definition of a dietary supplement under 21 U.S.C. §321(ff)(3)(B), or (2) commit to exercise enforcement discretion in connection with the marketing and selling of NMN in or as a dietary supplement. In the alternative, Petitioners respectfully request that the Commissioner of Food and Drugs recommend to the Secretary of HHS that he exercise his discretion and promptly issue a regulation, after notice and comment, finding that NMN would be lawful in or as a dietary supplement under the under the Act.

IV. ENVIRONMENTAL IMPACT

The Petitioners claim a categorical exclusion from the requirements for an Environmental Assessment under 21 CFR § 25.32 in light of the fact that FDA granting this petition will not affect the environment.

V. ECONOMIC IMPACT

Information on the economic impact of the action(s) requested by this Citizen Petition will be submitted if requested by FDA.

VI. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

If the undersigned received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, they received or expect to receive those payments from the following persons or organizations: NONE.

The undersigned verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

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