November 4, 2022

(b) (4)

Dear (b) (4) :

This letter is in further response to the new dietary ingredient notification you submitted to the Food and Drug Administration (FDA or we) on July 28, 2022, on behalf of Inner Mongolia Kingdomway Pharmaceutical Limited (Kingdomway) under 21 United States Code (U.S.C.) § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act)). Your notification concerns a new dietary ingredient, "β-Nicotinamide Mononucleotide" (NMN), that Kingdomway intends to market as a bulk dietary ingredient for use in dietary supplements.

Background

New Dietary Ingredients

Under 21 U.S.C. § 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient (NDI) that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing the NDI will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. § 350b(a)(2), there must be a history of use or other evidence of safety establishing that the NDI, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. § 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the NDI does not present a significant or unreasonable risk of illness or injury.

In addition, if a dietary supplement containing an NDI subject to the notification requirement is sold before the manufacturer or distributor submits an NDI notification or less than 75 days after the firm submits an NDI notification, the dietary supplement is deemed to be adulterated under 21 U.S.C §342(f). However, if the NDI has been present in the food supply as an article used for food in a form in which the food has not been chemically altered, the dietary supplement is exempt and may be marketed without an NDI notification.

U.S. Food and Drug Administration
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Procedural History

In an October 11, 2022 letter responding to your NDI notification (October 11 NDIN Response), we informed you that NMN is excluded from the dietary supplement definition under section 201(ff(3)(B)(ii) of the FD&C Act (21 U.S.C. § 321(ff)(3)(B)(ii)) and may not be marketed as or in a dietary supplement. The definition of a dietary supplement is set forth in 21 U.S.C. § 321(ff) (section 201(ff) of the FD&C Act), which states in relevant part:

> (ff) The term 'dietary supplement' ... (3) does ... (B) not include - (i) an article that is approved as a new drug under section 355 of this title ... or (ii) an article authorized for investigation as a new drug ... for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval ... 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 chapter.

Under this provision, if an article has been authorized for investigation as a new drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, the article may not be marketed as or in a dietary supplement unless the article was marketed as a dietary supplement or as a food before being authorized for investigation as a new drug. The date an article becomes authorized for investigation as a new drug is the date the first investigational new drug application (IND) for the article goes into effect, at which time the clinical investigations described in the IND are authorized to proceed. Under FDA's IND regulations, an IND generally goes into effect thirty days after FDA's receipt of the IND or when FDA notifies the IND sponsor that the clinical investigations in the IND may begin, whichever comes first.[1]

As explained in our October 11 NDIN Response, NMN is an article authorized for investigation as a new drug by the FDA. After consulting our internal records, the clinical trials registry, and other relevant sources, we concluded that NMN is also an article for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public.[2] After carefully reviewing the information provided in your amended notification and other relevant sources, including our own records, we also concluded that NMN was not marketed as a dietary supplement, except unlawfully without an NDI notification, or as a food before FDA authorized it for investigation as a new drug. We therefore further concluded that NMN is excluded from the dietary supplement definition under 21 U.S.C. § 321(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement.

On October 19, 2022, we received a letter (the October 19 Letter) from Kingdomway's lawyers, Miriam Guggenheim, Jeannie Perron, Matthew Hegreness, and Cory Trio of Covington & Burling LLP (Covington or your counsel). Covington's letter raised several legal and factual objections to our October 11 NDIN Response and requested, among other things, that FDA withdraw the October 11

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[1] 21 CFR 312.40(b). Note that an IND does not go into effect after thirty days if FDA notifies the sponsor that the investigations described in the IND are on clinical hold.

[2] *See* "A Phase 2a Randomized Controlled Trial of MIB-626 (NAD-boosting Drug) vs. Placebo in Adults With COVID-19 Infection and Early Acute Kidney Injury," available at https://clinicaltrials.gov/ct2/show/study/NCT05038488?term=MIB-626&draw=1&rank=1; "A Proof of Concept Trial of a Sirtuin-NAD Activator in Alzheimer's Disease," available at https://clinicaltrials.gov/ct2/show/study/NCT05040321?term=MIB-626&draw=1&rank=2; "A Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia," available at https://clinicaltrials.gov/ct2/show/study/NCT04817111?term=MIB-626&draw=1&rank=3.

NDIN Response and issue a letter of acknowledgement without objection. Although we are not withdrawing the October 11 NDIN Response because we continue to believe its conclusions are correct, this letter supplements that response with further explanation of our decision and responds to the objections in the October 19 Letter.[3]

Discussion and Conclusions

1. FDA is prohibited from disclosing certain facts supporting the exclusion of NMN from the dietary supplement definition.

This response, like our original October 11 NDIN Response, does not specify the date on which NMN was first authorized for investigation as a new drug. FDA's regulations prohibit us from disclosing the existence of an IND unless it has previously been publicly disclosed or acknowledged.[4] Accordingly, although we can state our conclusions as to when NMN was first marketed as a dietary supplement or as a food and whether that date was before or after the date NMN was authorized for investigation as a new drug, we cannot specify the date of authorization or identify its source. Details about NMN's authorization as a new drug are documented in FDA's files.

2. The evidence on which Kingdomway relies to show that NMN was marketed as a dietary supplement or food before it was authorized as a new drug is too recent, not relevant, or both.

    a. Evidence of marketing as a dietary supplement in Japan does not exempt NMN from the U.S. new dietary ingredient notification requirement because dietary supplements are not part of the "food supply" under the FD&C Act.

Citing evidence showing that NMN capsules were offered for sale in Japan beginning on January 7, 2016, the October 19 Letter argues that NMN has been "present in the food supply as an article used for food" since that date, and therefore any marketing of NMN in the United States after that date did not require an NDI notification. *See* section 413(a)(1) of the FD&C Act (21 U.S.C. 350b(a)(1)) (dietary supplements that contain "only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered" do not require an NDI notification to FDA). Based on the facts Kingdomway has provided, however, we do not agree that your evidence of marketing in Japan shows that NMN has been "present in the food supply as an article used for food." Although the FD&C Act does not define the compound term "food supply," section 201(f) defines the term "food" as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article."[5] The leading case on the meaning of "food" under section 201(f)(1) of the FD&C Act interprets the definition to refer to "articles consumed primarily for taste, aroma, or nutritive value."[6] Although dietary supplements are deemed to be foods for most purposes under the dietary supplement definition in section 201(ff) of the FD&C Act,[7] they do not always meet the FD&C Act's definition of food. Dietary supplements are not typically consumed for their taste or aroma, and some do not have nutritive value or are consumed primarily for reasons other

[3] In addition to Covington's October 19 letter and attachments, we considered information that Covington provided in a meeting with FDA on October 25 and via email on October 26 and November 3, 2022.
[4] 21 CFR 312.130(a).
[5] Section 201(f) of the FD&C Act (21 U.S.C. 321(f)).
[6] *Nutrilab v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983).
[7] 21 U.S.C. 321(ff). Dietary supplements are not deemed to be foods for all purposes; for example, a dietary supplement that meets the drug definition is not deemed to be a food.

than nutrition (i.e., for other effects on the structure or function of the body). Accordingly, when Congress enacted the Dietary Supplement Health & Education Act of 1994 (DSHEA) and wanted to ensure that all dietary supplements would be regulated as foods, the drafters added a provision "deeming" dietary supplements to be foods.

Because the meaning of "food supply" derives from the FD&C Act's definition of "food," it refers to conventional foods and their ingredients. Although dietary supplements are taken by mouth, they are not typically "used for food or drink by man" or used as components of conventional foods. Accordingly, a dietary ingredient that has been "present in the food supply as an article used for food" is one that has been used as a conventional food or conventional food ingredient. Prior use in dietary supplements does not constitute "presence in the food supply." Indeed, if it did, a "new dietary ingredient," defined by DSHEA as "a dietary ingredient not marketed in the United States before October 15, 1994,"[8] could avoid the notification requirement for NDIs that entered the market long after 1994.

Under standard canons of statutory interpretation, the text of a statute must be read as a whole and in accordance with the statute's structure and purpose.[9] Interpreting "food supply" in section 413(a)(1) to include dietary supplements for purposes of the exemption from the NDI notification requirement would not be consistent with the purpose of that requirement, which is to ensure that dietary ingredients that have not been widely consumed undergo a safety evaluation before reaching the marketplace. Because dietary supplements are generally consumed by a narrower segment of the population than conventional foods and typically have a shorter history of use than conventional food ingredients, prior use in a supplement or supplements typically provides less information about a substance's safety than prior use in conventional foods. In addition, such an interpretation would expand the exception to the point that it would risk swallowing the rule, as prior use in even one dietary supplement manufactured in small quantities and distributed over a small area would exempt all dietary supplements containing the NDI from the notification requirement, even if the intake level and conditions of use were much different.

The legislative history of DSHEA also supports that "the food supply" refers to foods other than dietary supplements. For example, in explaining why "dietary substances" are included as a category of dietary ingredients,[10] Senate Report 103-417 states:

> [A] dietary supplement must be a product "intended to supplement the diet by increasing the total dietary intake". The definition is intended to encompass all those substances and materials that are presently contained in dietary supplements as well as substance[s] derived from foods. Thus, a dietary supplement must bear or contain one or more of a vitamin, a mineral, an herb or other botanical, or amino acid or another dietary substance for use by man to supplement the diet by increasing total dietary intake. This last section is meant to encompass those substances which have been *isolated from the food supply* and are being provided to increase the total dietary intake by supplementing the diet.

S. Rep. No. 103-410, at 34 (1994) (emphasis added). In this context, "the food supply" can only refer to conventional foods, i.e., foods that are not dietary supplements.

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[8] Section 413(d) of the FD&C Act (21 U.S.C. § 350b(d)).

[9] *See* 2A Norman J. Singer & J.D. Shambie Singer, *Sutherland Statutes and Statutory Construction* § 46.5 (7th ed., Nov. 2021) (discussing principle of "whole statute" interpretation).

[10] Dietary ingredients are the characterizing ingredients in dietary supplements. To be a dietary supplement, a product must contain at least one "dietary ingredient" as defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. § 321(ff)(1).

One of the principles underlying DSHEA is that articles in the human food supply, meaning articles that meet the statutory definition of food because they are "articles for food or drink for man," chewing gum, or "articles used for components of any such article,"[11] have been shown through history of use to be safe for consumption and should be allowed in dietary supplements without premarket review by FDA. Testimony from a dietary supplement trade association at one of the hearings leading up to the passage of DSHEA shows that industry endorsed this concept and shared the understanding of "food supply" as foods other than dietary supplements:

> The definition of dietary supplements should include vitamins, minerals, herbs, amino acids, and other "dietary" ingredients, i.e., ingredients intended for use to supplement the diet by increasing total dietary intake. It would include supplements sold in forms that have the characteristics of conventional food, so long as such substances were clearly labeled as intended for use to supplement the diet. This definition, however, would exclude chemical entities not commonly found in the food supply.

Hearing on the Food and Drug Administration's Regulation of Dietary Supplements Before the Subcomm. on Human Resources and Intergovernmental Relations of the House Comm. on Government Operations, 103d Cong. 141 (1993) (statement of J.B. Cordaro, president of the Council for Responsible Nutrition).

A legislative history written by two dietary supplement industry lawyers who participated in the drafting and negotiations leading up to DSHEA reflects the same understanding of "food supply" as referring to foods other than dietary supplements:

> This provision ensures that chemically unaltered ingredients from the food supply do not require any special treatment to be used as dietary supplements. Foods do not require premarket approval, and Congress wanted to maintain this approach.

I. Scott Bass & Anthony L. Young, *The Dietary Supplement Health and Education Act: A Legislative History and Analysis* 40 (1996).

The NMN products shown in Attachments B-C of Covington's October 19 Letter are all in tablet or capsule form, and each is described in promotional materials as a "supplement" or "dietary supplement." Whether or not these products in capsule and tablet form are regulated as foods in Japan, they are not part of the "food supply" under the FD&C Act because they are not used as food or drink for humans nor as components of human food or drink. This point is well illustrated by Mirai Lab's claim for NMN 1500 Pure Plus capsules: "This dietary supplement is recommended for those who wish to take a large amount of NMN at one time."[12] Thus, FDA does not agree with your contention that the marketing of these supplements in Japan establishes that NMN "has been present in the food supply as an article used for food" and is therefore exempt from the new dietary ingredient notification requirement under section 413(a)(1) of the FD&C Act. Accordingly, this evidence cannot be used to establish that lawful marketing of NMN in the United States without an NDI notification occurred in the United States before NMN was authorized for investigation as a new drug.

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[11] Section 201(f) of the FD&C Act (21 U.S.C. § 321(f)).

[12] https://mirai-lab.jpn.com/en/products/nmn_pure1500plus (last visited Nov. 1, 2022).

b. Evidence that MNM was unlawfully marketed as a dietary supplement in the United States is irrelevant under section 201(ff)(3)(B)(ii).

Citing structure/function claim notifications submitted to FDA for NMN-containing dietary supplements in September and December 2020, the October 19 Letter argues that even unlawful marketing of an article as a dietary supplement or food before the article's authorization for investigation as a new drug should defeat the exclusion from the dietary supplement definition. We disagree. Although it is true that section 201(ff)(3)(B)(ii) does not contain the word "lawful," the context in which the reference to "marketing" appears and the structure and purpose of DSHEA make clear that "marketed as a dietary supplement or as a food" refers to lawful marketing.

Under section 201(ff)(3)(B)(ii), the first date an article was marketed as a dietary supplement or food is compared to the date of the article's first "authorization for investigation as a new drug" to determine whether the threshold prerequisite for exclusion from the dietary supplement definition is met. Obtaining such authorization to conduct clinical trials is a U.S. legal requirement that a drug sponsor who wishes to trigger the exclusion must comply with by submitting an IND to FDA and waiting for the IND to go into effect before initiating any clinical investigations. Under the other dietary supplement exclusion in section 201(ff)(3)(B)(i), the comparison date for the date of first marketing as a dietary supplement or food is the date of approval as a new drug under section 505 of the FD&C Act.[13] Given this context explicitly requiring compliance with U.S. legal requirements that apply to drugs, it would be inconsistent and incongruous to interpret "marketing as a dietary supplement or as a food" to sanction marketing the article in a way that does not comply with U.S. law, such as marketing a product that requires an NDI notification without submitting such a notification.

Moreover, such an interpretation would be contrary to the statutory purpose. Allowing a manufacturer or distributor to bootstrap its way into the dietary supplement category with bad behavior -- marketing a product without complying with an important premarket safety requirement -- would defeat the purpose of that requirement, which is intended to protect public health. The Congressional findings enacted as part of DSHEA state that "the Federal Government should take swift action against products that are unsafe or adulterated."[14] As noted above, dietary supplements that are marketed without a required NDI notification are adulterated under section 413(a) of the FD&C Act. In light of Congress's statement in one part of DSHEA that FDA should take swift action against dietary supplements that are adulterated, it seems highly unlikely that Congress would have provided in another part of the statute that an unscrupulous dietary supplement firm could prevent a product from being excluded from the dietary supplement definition by marketing it in defiance of the safety provisions of DSHEA. Accordingly, the 2020 structure/function notifications cited in the October 11 Letter cannot be used as evidence that NMN was "marketed as a dietary supplement" before its authorization for investigation as a new drug because the companies in question did not submit NDI notifications for their NMN products.

[13] 21 U.S.C. § 355.
[14] Pub. L. No. 103-417, § 2(13), 108 Stat. 4325, 4325 (1994), 21 U.S.C. 321 note.

c. Evidence of marketing as a dietary supplement or food in Japan is irrelevant because "marketing" in section 201(ff)(3)(B) refers to marketing in the United States

Citing a search of Amazon.co.jp finding that NMN was marketed in Japan as a food and/or dietary supplement no later than January 7, 2016, the October 19 Letter argues that any marketing of NMN as a dietary supplement or food that took place outside the United States before the authorization of NMN for investigation as a new drug prevents NMN from being excluded from the dietary supplement definition. This reading of the statute is incorrect because it ignores the statutory context specific to the U.S. system of food and drug law regulation, the geographical limits on FDA's jurisdiction, and DSHEA's statutory purpose to establish a "rational Federal framework" rather than a "patchwork" regulatory framework for dietary supplements.[15]

According to the "whole act" principle of statutory interpretation,[16] a statute must be construed as a whole, and individual sections must be read in light of the statute's structure, object and purpose,[17] including "the physical and logical relation of its many parts."[18] Section 201(ff)(3)(B)(ii) of the FD&C Act directs FDA to compare the date an article is first authorized for investigation as a new drug with the date it was first marketed as a dietary supplement or as a food. It is evident that the first half of this comparison was drafted in the context of U.S. law and the U.S marketplace, as it refers to the U.S. drug regulatory framework and uses terms defined in the FD&C Act, such as "new drug."[19] As noted above in section 2b, the comparison date for the date of first marketing as a dietary supplement or food specified in the other dietary supplement exclusion in section 201(ff)(3)(B)(i) is the date of approval as a new drug "under section 505 of the FD&C Act."[20] This U.S.-specific context in both exclusions indicates that Congress intended "marketing as a dietary supplement or as a food" to be evaluated in the context of U.S. law and the U.S. marketplace. Under section 201(ff)(3)(B), the date of first authorization for investigation or approval as a new drug is determined under U.S. law; therefore, the date of first marketing as a dietary supplement or as a food should also be determined under U.S. law and with reference to the U.S. marketplace, rather than under some other set of legal requirements that vary depending on the country where the product is marketed.

Moreover, FDA has jurisdiction only over articles that travel in interstate commerce, defined in relevant part as commerce between a U.S. state or territory and "any place outside thereof."[21] We do not regulate products sold only in other countries and do not have comprehensive knowledge of the legal systems of foreign nations, many of which define regulatory categories like foods and dietary supplements differently than they are defined in the United States. For example, Canada has a category called "natural health products" that is considerably broader than the U.S. dietary supplement category because it includes some products (e.g., homeopathics) that are drugs under U.S. law, and others that are food additives or other non-dietary supplement foods under U.S. law.[22] A reading of section 201(ff)(3)(B)

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[15] Pub. L. No. 103-417, § 2(15)(B), 108 Stat. at 4326.
[16] Sometimes referred to as the "whole text" or "whole statute" principle of statutory interpretation.
[17] *United States v. Kozeny*, 541 F.3d 166, 171 (2d Cir. 2008); Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Statutory Texts* § 24, at 167 (2012)).
[18] Scalia & Bryan, *supra*.
[19] Section 201(p) of the FD&C Act (21 U.S.C. § 321(p).
[20] 21 U.S.C. § 355.
[21] Section 201(b)(1) of the FD&C Act (21 U.S.C. § 321(b)(1)).
[22] *See* Food and Drugs Act, Revised Statutes of Canada (R.S.C.), c. F-27, s. 2 (1985) (definitions of "food," "food for a special dietary purpose," "drug," "therapeutic product"); Natural Health Products Regulations (SOR/2003-196), last amended by SOR/2022-143 (6/21/2022).

requiring FDA to keep track of dietary supplement and food product launches all over the globe, research the law of the foreign country in which the article was being marketed, and try to figure out whether the product's regulatory category in the other country corresponded to the U.S. dietary supplement or food category would be entirely unworkable.

DSHEA includes a Congressional finding that "a rational Federal framework must be established to supersede the current ad hoc, patchwork regulatory policy on dietary supplements."[23] The existence of this finding demonstrates that Congress intended to enact an integrated, consistent framework for regulating dietary supplements, including the method for determining the date of first marketing as a dietary supplement or food under 201(ff)(3)(B), not a system of patchwork determinations based on monitoring activity in marketplaces around the globe and applying legal frameworks that differ from country to country.

3. Conclusions

After evidence that is irrelevant under section 201(ff)(3)(B) for the reasons discussed above has been eliminated, two possible dates of first marketing for NMN are left:

- February 16, 2021 – First date on which another notifier could have marketed its NMN-containing dietary supplement lawfully after submitting an NDI notification to FDA on December 3, 2020; however, it is unclear whether NMN was actually marketed on that date.

- September 2021 – Month during which Kingdomway first marketed Doctor's Best Instant Whey Protein Concentrate Plus NMN as a conventional food.

Both of these dates are after the first date on which NMN was authorized for investigation as a new drug.[24] Accordingly, we reaffirm our earlier conclusion that NMN is excluded from the dietary supplement definition under 21 U.S.C. § 321(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement. Today we are sending letters communicating this conclusion simultaneously to all firms that have submitted an NDI notification for NMN.

If you have any questions concerning this matter please contact Markeesa Scales, MPH, Division of Research and Evaluation, by email: NDITEAM@fda.hhs.gov.

Sincerely,

Philip Yeager -S

Digitally signed by Philip Yeager -S
Date: 2022.11.04 17:15:03 -04'00'

R. Philip Yeager, PhD, JD, DABT
Director
Division of Research and Evaluation
Office of Dietary Supplement Programs

[23] Pub. L. No. 103-417, § 2(15)(B), 108 Stat. at 4326.
[24] As discussed in subsection 1 of the Discussion and Conclusions section, FDA is prohibited from disclosing the date of authorization.

Center for Food Safety
and Applied Nutrition

Enclosure

1259 NDL
β-Nicotinamide Mor