METROBIOTECH

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Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Citizen Petition from Natural Products Association and Alliance for Natural Health USA / Citizen Petition from the Council for Responsible Nutrition

To Whom it May Concern:

Metro International Biotech ("Metro") is a privately-owned clinical-stage pharmaceutical company that has established the most comprehensive portfolio of nicotinamide adenine dinucleotide ("NAD+") precursors in the world. As a pioneer of NAD+ related products, Metro has serious concerns over the Citizen Petitions submitted by Natural Products Association and Alliance for Natural Health USA (the "NPA/ANH Petition") (Docket ID FDA-2023-P-0872-0001) and the Council for Responsible Nutrition (Docket ID FDA-2023-P-1867-0001) (the "CRN Petition") (collectively the "Petitions").

The NPA/ANH Petition asks the Food & Drug Administration ("FDA") to allow products containing nicotinamide mononucleotide ("NMN") to be marketed as dietary supplements either by revisiting FDA's correct interpretation of the "drug exclusion clause" of the Federal Food, Drug, and Cosmetic Act ("FDCA")[1] or by committing to an enforcement discretion policy under which FDA would permit the unlawful sale of NMN-containing dietary supplements while it crafted regulations to end-run around the drug exclusion. Similarly, the CRN Petition seeks to have FDA reconsider its interpretation of the drug exclusion clause and to adopt a much narrower (and in Metro's view legally unsupportable) interpretation of that statutory provision instead.[2]

Metro agrees with FDA that NMN is rightly excluded from marketing as a dietary supplement under the drug exclusion clause of the FDCA. FDA should not permit NMN products to be sold as a dietary supplement—which would be in violation of the drug exclusion clause and without sufficient demonstration of safety, adequate directions for use, or compliance with good manufacturing practices. Metro thanks FDA for the opportunity to submit this public comment to the Petitions.

I. BACKGROUND

The Petitions assert that NMN products were offered for sale as dietary supplements prior to FDA's authorization—and Metro's initiation and publication of—clinical studies for NMN as

[1] 21 U.S.C. § 321(ff)(3)(B).
[2] According to the CRN Petition, it is seeking broader relief than that requested by the NPA/AHN Petition with respect to NMN. The CRN Petition is "not limited to the facts of the NMN case," but instead to FDA's interpretation of the drug exclusion clause more broadly. These arguments are coextensive from Metro's perspective.

a drug ingredient. In particular, the Petitions state that NMN dietary supplement products were sold in Japan as early as 2015 and by Nutraland in 2018 and by Cellmark in 2020. The Petitions also argue that FDA acknowledged an NDIN filed by SyncoZymes (Shanghai) Co., Ltd. in May 2022. But the petitions fail to acknowledge that FDA had rejected all NDINs for NMN products submitted prior to that time, and that any NMN products previously sold as dietary supplements in the United States were unlawful.

Regardless, as Metro has publicly stated, it is studying NMN as a new drug and has commenced substantial clinical investigations under an Investigational New Drug ("IND") application for NMN intended to treat Alzheimer's, Friedreich Ataxia, kidney disease, and more. Indeed, Metro's substantial clinical investigations of NMN were authorized by FDA and made public years ago, well before any NMN-containing products had been (or could have been) lawfully marketed as dietary supplements. As such, FDA is correct that marketing of NMN as a dietary supplement is precluded by the drug exclusion provision of the FDCA.

A. Metro's Well-Publicized Substantial Clinical Development of NMN as a Drug

Metro's proprietary form of beta-nicotinamide mononucleotide (β-NMN), MIB-626, has been authorized for investigation as a new drug, and substantial clinical investigations have been instituted and are ongoing. This includes several three phase 2 trials that Metro publicly listed on clinicaltrials.gov:

- Metro's Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia was posted on March 25, 2021 and commenced on May 17, 2021[3]
- Metro's Phase 2a Study of MIB-626 in Adults With COVID-19 Infection and Early Acute Kidney Injury was posted on September 9, 2021 and commenced on October 26, 2021[4]
- Metro's Phase 1/2 Proof of Concept Trial of a Sirtuin-NAD Activator in Alzheimer's Disease was posted on September 10, 2021 and commenced on December 1, 2021.[5]

The earliest of these postings, which occurred on March 25, 2021 when Metro posted on clinicaltrials.gov its Phase 2a study of NAD+ precursor supplementation in Friedreich's Ataxia, as well as Metro's study of NMN as a drug ingredient, were widely publicized when on December 1, 2021 Metro submitted a letter to Docket No. FDA-2021-P-0938, responding to a citizen petition from the Natural Products Association regarding N-acetyl-L-cysteine (NAC) requesting that FDA change its position with respect to applicability of the drug exclusion clause to NAC. In that letter, Metro clearly stated:

> Metro is the sole source of MIB-626, Metro's proprietary form of beta-nicotinamide mononucleotide (β-NMN) which is authorized for investigation as a new drug and for which substantial clinical investigations have been instituted. As a company that

[3] *NAD+ Precursor Supplementation in Friedreich's Ataxia*, CLINICALTRIALS.GOV, NCT04817111.
[4] *Phase 2a MIB-626 vs. Placebo COVID-19*, CLINICALTRIALS.GOV, NCT05038488
[5] *A Proof of Concept Trial of a Sirtuin-NAD Activator in Alzheimer's Disease*, CLINICALTRIALS.GOV, NCT05040321.

has instituted publicly available clinical trials on β-NMN, we request that FDA take the preclusion provision of Section 201(ff) of the Federal, Food, Drug, and Cosmetic Act seriously 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.[6]

On December 6, 2021, the widely read trade news quoted Metro's comment, noting that "[t]he 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" and that it "has instituted publicly available clinical trials with [NMN]."[7] At that time, as reported in the trade press, Metro "suggest[ed] 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.'"[8]

B. FDA Rejected Several Earlier NDINs

FDA rejected two NDINs for NMN in the years preceding FDA's determination that NMN is excluded from the statutory definition of a dietary supplement because it was authorized for investigation under an effective IND before being lawfully marketed as a dietary supplement or food in the United States. In 2020 and 2021, FDA rejected these NMN NDINs because, among other things, FDA found the safety data provided by the companies to be insufficient, as detailed in Table 1, below.

Table 1: Overview of NMN NDINs Rejected In 2020-2021

NDIN #	Date of Submission	Submission	Date of FDA Response	FDA Response	Date Response Was Posted
1174	8/25/2020	FDA receives NDIN # 1174 from Willy Chemicals, Inc	11/2/2020	The product did not meet the definition of a dietary supplement because it was intended to be "taken under the tongue or in the buccal area," and not "intended for ingestion" (21 U.S.C. § 321(ff)).[9]	1/8/2021

[6] *Comment from Metro International Biotech*, REGULATIONS.GOV (Dec. 1, 2021), https://www.regulations.gov/comment/FDA-2021-P-0938-0006; *see also* M. Spicer, *In NAC Docket, NAD+ Drug Firm Suggests US FDA Get Serious About Dietary Ingredient Regulations*, HBW INSIGHT (Dec. 6. 2021), https://hbw.pharmaintelligence.informa.com/RS152012/In-NAC-Docket-NAD-Drug-Firm-Suggests-US-FDA-Get-Serious-About-Dietary-Ingredient-Regulations (an example of media coverage of Metro's comment letter discussing its ongoing NAD clinical investigations).

[7] Malcolm Spicer, *In NAC Docket, NAD+ Drug Firm Suggests US FDA Get Serious About Dietary Ingredient Regulations*, HBW PHARMA INTELLIGENCE (Dec. 6, 2021).

[8] *Id*.

[9] *Letter from FDA CFSAN to Willy Chemicals, Inc regarding NDI 1174 - Reju-Me,* REGULATIONS.GOV (Jan. 8, 2021), https://www.regulations.gov/document/FDA-2020-S-0023-0103.

1189	12/3/2020	FDA receives NDIN #1189 by Willy Chemicals, Inc	2/11/2021 11/4/2022 (supplemental)	The Agency was unable to establish the safety of the dietary supplement containing NMN based on the "vague history of use" provided and "significant concerns" over the safety data on which the company relied.[10]	4/9/2021
1234	11/15/2021	FDA receives NDIN #1234 by Willy Nutra, Inc.	1/18/2021 11/4/2022 (supplemental)	The agency was unable to establish the safety of the dietary supplement containing NMN due to "significant concerns" about the safety data on which the company relied.[11]	6/13/2022

C. FDA Rejected Additional NDINs

On March 25, 2021, Metro's Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia was posted in clinicaltrials.gov. In early December of the same year, Metro filed a letter to the NAC citizen petition docket stating that its NMN drug has been authorized for investigation as a new drug and for which substantial clinical investigations have been instituted. As mentioned, that letter was reported in the trade press. Indeed, by then it was publicly known that substantial clinical research had commenced for NMN as a drug under an IND—such that any NDIN filers knew or should have known that substantial clinical investigations were underway.

Subsequently, FDA began denying NMN NDINs *both* because the Agency was unable to establish the safety of these products, and because NMN had been "authorized for investigation as a new drug" and, as such, was excluded from the dietary supplement definition under 21 U.S.C. § 321(ff).

Table 2: Overview of NMN NDINs Rejected In 2021-2022

NDIN #	Date of Submission	Submission	Date of FDA Response	FDA Response	Date Response Was Posted
1240	12/27/2021	FDA receives NDIN #1240 by SyncoZymes (Shanghai) Co., Ltd.	2/24/2022 11/4/2022 (supplemental)	The agency was unable to establish the safety of the dietary supplement containing NMN due to "significant concerns"	6/13/2022

[10] *Letter from FDA CFSAN to NDI 1189 - Reju-Me from Willy Chemicals, Inc*, REGULATIONS.GOV (Feb. 11, 2021), https://www.regulations.gov/document/FDA-2021-S-0023-0017.

[11] *Letter from FDA CFSAN to Willy Nutra, Inc. regarding NDI 1234 - Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Jan. 18, 2021), https://www.regulations.gov/document/FDA-2022-S-0023-0001.

				about the safety data on which the company relied.[12]	
1247	3/21/2022	FDA receives NDIN #1247 by SyncoZymes (Shanghai) Co., Ltd.	5/16/2022 11/4/2022 (supplemental)	FDA initially acknowledged receipt[13] and subsequently issued a supplemental response explaining that, "[b]ased on new information that came to light" while reviewing a different application, "NMN is excluded from the dietary supplement definition under 21 U.S.C. § 32l(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement."[14]	7/29/2022
1259	7/28/2022	FDA receives NDIN #1259 by Inner Mongolia Kingdomway Pharmaceutical Limited	10/11/2022	FDA explained that "[b]ased on new information that came to light" while reviewing a different application, "NMN is excluded from the dietary supplement definition under 21 U.S.C. § 32l(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement."[15]	11/08/2022

Both Petitions devote considerable energy to the idea that FDA acknowledged without objection the NDIN (#1247) submitted by SyncoZymes (Shanghai) Co., Ltd. in May 2022. We note that by the time of FDA's rejection, Metro's substantial clinical investigation of NMN was authorized, publicized, and well underway. In any case, FDA first acknowledged receipt of NDIN #1247 without objections and reminded the company that "acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. § 342."[16] However, shortly thereafter, on November 4, 2022, FDA wrote SyncoZymes that "[b]ased 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

[12] *Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1240 - beta-nicotinamide mononucleotide (β-NMN)*, REGULATIONS.GOV (Feb. 24, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0013.

[13] *Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (B-NMN)*, REGULATIONS.GOV (May 16, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0027.

[14] *Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[15] *Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Oct. 11, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[16] *Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (B-NMN)* (May 16, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0027.

excluded from the definition of a dietary supplement."[17] FDA also sent supplemental responses to the other NDINs that were previously rejected due to the insufficiency of safety data provided and where NMN's exclusion from the definition of a dietary supplement was erroneously not addressed.[18]

Notably, FDA did not post its acknowledgement without objection to NDIN 1247 until July 29, 2022—after Inner Mongolia Kingdomway Pharmaceutical Limited had submitted NDIN 1259. In other words, there was no reliance on FDA's acknowledgement of NDIN 1247 before FDA realized that the drug exclusion clause applied and sent both a supplemental response to NDIN 1247 and an objection to NDIN 1259. It cannot be—as the CRN Petition alleges—that FDA's initial acknowledgement resulted in companies "mov[ing] forward with investments…completing the NDIN process, and committing funding to marketing and advertising,"[19] because that initial acknowledgement was not posted until *after* the last of the NMN NDINs was submitted. A full timeline of key events is provided in Appendix A.

II. FDA IS CORRECT THAT NMN IS PROPERLY EXCLUDED FROM THE DEFINITION OF DIETARY SUPPLEMENT

Under section 201(ff)(3)(B) of the Federal Food, Drug & Cosmetic Act ("FDCA"), if an article has been (1) "authorized for investigation" as a new drug, (2) substantial clinical investigations have been instituted, and (3) the existence of such investigations have been made public, products containing that article are outside the definition of a dietary supplement. In addition, there are two possible exceptions to this exclusionary clause: if the article was lawfully marketed as a dietary supplement or as a food before such approval or authorization; or if FDA issues a regulation establishing that the article would be lawful under the FDCA.

The Petitioners nevertheless ask FDA to determine that NMN is not excluded from the definition of a dietary supplement, claiming that the Agency has "misconstrued and misapplied" that drug exclusion clause to NMN.[20] In particular, the NPA/AHN Petition claims (without offering any alternative definition) that the FDA permitting an IND to go into effect is not "authorization" for investigation and that clinical investigations cannot be considered to have been made public in the absence of "a database or list of current articles that are the subject of an IND." The NPA/AHN Petition also claims that a policy under which dietary supplements and drugs are in a "regulatory race-to-market" is contrary to Congressional intent.[21] Finally, the NPA/AHN

[17] *Supplemental Response Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (B-NMN)* (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0027. FDA also sent supplemental responses to the other NDINs that had been previously rejected due to the insufficiency of safety data provided, and where NMN's exclusion from the definition of a dietary supplement was not properly acknowledged.

[18] *Supplemental Response Letter from FDA CFSAN to NDI 1189 - Reju-Me from Willy Chemicals, Inc* (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2021-S-0023-0017; *Supplemental Response Letter from FDA CFSAN to Willy Nutra, Inc. regarding NDI 1234 - Nicotinamide Mononucleotide (NMN)* (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0013.

[19] CRN Citizen Petition at 6.

[20] NPA/AHN Citizen Petition at 8.

[21] NPA/AHN Citizen Petition at 6.

Petition argues that NMN capsules having been sold in Japan, and unlawfully in the United States, the drug exclusionary clause cannot apply.[22]

The CRN Petition makes similar claims. That Petition would also have FDA find that:

- The date on which drug preclusion is effective is "the date the existence of substantial clinical trials are made public, not the non-public date on which an investigational new drug (IND) application goes into effect."[23]

- "Marketing" as used in the FDCA is not limited to marketing in the United States, nor is it limited to lawful marketing. In other words, CRN claims that even unlawful marketing outside of the United States can trigger the exceptions to the drug exclusion from the dietary supplement definition.[24]

- "Substantial clinical investigations" in section 201(ff)(3)(B) of the FDCA does not include Phase 1 clinical studies.

- FDA's compliance with the exclusion clause is improper unless and until FDA issues guidance regarding the exceptions to the drug exclusion clause

As explained below, NMN-containing articles are clearly excluded from the dietary supplement definition, and neither exception applies. Neither petitioner's arguments to the contrary change this fundamental fact. FDA has properly excluded NMN-containing articles and should deny the Petitions in their entirety.

A. NMN-Containing Articles Are Properly Excluded Because Metro's Clinical Studies Are Authorized and Public

Both petitions argue that FDA's interpretation and application of the statutory drug preclusion language in 21 U.S.C. § 321(ff)(3) is incorrect, because "INDs are not authorized by FDA" and there is "no public access to a list of current articles that are the subject of an IND." Petitioners also take issue with FDA's determination that Congress intended the phrase an "article authorized for investigation" to mean an article that is the subject of an IND that has gone into effect, because, they assert, IND effective dates are not made public by FDA in the ordinary course.[25]

1. A Cleared IND Is An FDA Authorization

Neither Citizen Petition provides any evidence or legal analysis to support the idea that an IND is not an "authorization" by FDA. In fact, FDA's interpretation of the drug exclusion provision is entirely reasonable in light of both the language and structure of the relevant

[22] NPA/AHN Citizen Petition at 8-9 ("There is nothing in the plain language of the statute that requires the prior marketing of the article to only have occurred in the United States.")
[23] CRN Citizen Petition at 2.
[24] CRN Citizen Petition at 2.
[25] *Dietary Supplements: Dietary Ingredients Notifications and Related Issues: Guidance for Industry* at 44, U.S. FOOD & DRUG ADMIN. (Oct. 2016), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues.

provisions. The FDCA provides that an article is not a "dietary supplement" if that article has been "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."[26] "[A] drug maker must gain authorization to conduct clinical trials (tests on humans) by submitting an investigational new drug application" that contains specific information.[27] Stated differently, a cleared IND is, in fact, FDA's authorization to conduct clinical trials, just as an approved new drug application ("NDA") is FDA's authorization to market a new drug.[28] Indeed, FDA's regulations require that an IND be in effect before initiation of a clinical investigation;[29] until such time as an IND is in effect, a drug sponsor may not ship or distribute an investigational new drug across state lines nor administer such a drug to human subjects.[30] Petitioners proffer no other interpretation of the drug exclusion clause's use of "authorization," and in fact, none is needed.

The CRN Citizen Petition also asserts that FDA cannot interpret the drug exclusion clause to preclude dietary supplement marketing beginning on the date of IND authorization, but rather that such preclusion can begin only on the date on which the investigations are publicized. But FDA reasonably considers an IND effective date to be the date on which an article is authorized for investigation. It is at that time—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—that clinical investigations described in the IND are authorized to proceed.[31] As FDA has explained, this interpretation is commanded by the other dietary supplement exclusion,[32] under which the approved drug exclusion provisions take effect on the date of approval of a new drug. In order for these parallel provisions to operate in harmony, the IND drug exclusion provision must, therefore, take effect on the date of clearance of the IND.

2. Regardless of the Cleared IND for NMN, Metro's Substantial Clinical Investigations Were Made Public

In any case, an IND effective date does not need to be public in a particular way (*e.g.*, the petitioners' proposed "database") for FDA's interpretation of the statute to be reasonable. It is true that FDA's regulations prohibit the Agency from disclosing the existence of an IND, including an effective date of an IND.[33] The Citizen Petition insists that the drug preclusion is tied to a "secret date,"[34] but it fails to acknowledge that Metro publicized its clinical investigations entirely separately and apart from the IND effective date. There is no dispute that, one way or another, the industry was on sufficient notice of the clinical investigations *before* FDA issued its drug preclusion determination.

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[26] 21 U.S.C. § 201(ff)(3)(B) (emphasis added).
[27] *Utts v. Bristol-Myers Squibb Co*., 226 F. Supp. 3d 166, 176 (S.D.N.Y. 2016) (citing See 21 U.S.C. § 355(i); 21 C.F.R. § 312.20–312.21); see generally .
[28] *See* 21 U.S.C. § 355(i); 21 C.F.R. § 312.
[29] 21 C.F.R. § 312.20.
[30] 21 C.F.R. § 312.40.
[31] 21 C.F.R. § 312.40(b).
[32] 21 U.S.C. § 321 (ff)(3)(B)(i).
[33] 21 C.F.R. § 312.130.
[34] CRN Citizen Petition at 9.

Critically, neither Citizen Petition addresses the fact that *even if* a cleared IND did not constitute authorization because FDA would not typically make such approval public, *in this case* the drug sponsor and the media publicized the initiation of substantial clinical investigations. As described in detail above, both the effective date of Metro's IND for MIB-626 and the publicization of clinical studies conducted thereunder clearly predate any lawful dietary supplement marketing. There was publicly available information posted on clinicaltrials.gov as of March 25, 2021, submitted to the public docket by Metro on December 1, 2021, and reported in the trade press on December 6, 2021.[35] In short, well before —which again, was before a submission of an NDIN to which FDA lodged no objection. In particular, Metro already had publicly disclosed its substantial clinical investigations *before* the NDIN submissions petitioners cite from SyncoZymes (NDIN #1247) and Inner Mongolia Kingdomway (NDIN #1259).

B. Unlawful and International Marketing of NMN Products Are Irrelevant

The Petitions argue that FDA should construe the drug exclusion clause in the definition of dietary supplement as not applying to an article that was marketed either (1) unlawfully or (2) outside of the U.S. These arguments are baseless and have already been thoroughly rejected by FDA.[36]

1. Unlawful Marketing Does not Exempt an Article From the Drug Exclusion Clause

FDA has explained clearly that if an article was not "marketed as a dietary supplement, except unlawfully without an NDI notification" before FDA authorized it for investigation as a new drug, the article may not be marketed as or in a dietary supplement.[37] Indeed, FDA correctly rejected the very same arguments that the petitioners make now:

> [The NDIN] 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.[38]

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[35] The CRN Petition argues that Metro's clinicaltrials.gov entries referenced only "MIB-626" and not "NMN." CRN Citizen Petition at 6. But Metro's docket submission and subsequent media coverage clearly stated that Metro's clinical investigations pertained to NMN.

[36] Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN), REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[37] Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN), REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051 (emphasis added).

[38] *Id.*

Thus, FDA explained, "[e]vidence that NMN was unlawfully marketed as a dietary supplement in the United States is irrelevant under section 201(ff)(3)(B)(ii)."[39] This makes sense as a matter of both law and policy. Congress would not have authorized or expected FDA to create exceptions to statutory definitions based on illegal sales—nor to create a policy under which illegal marketing is rewarded by allowing continued marketing of the illegally marketed (and hence adulterated) article[40] while evidence generation on safe and effective use through the drug pathway takes the back seat.

The NPA/AHN Citizen Petition points to three purported examples of "lawful marketing" of NMN prior to commencement of clinical investigations: (1) Japanese products sold in 2015; (2) self-affirmation as GRAS by Nutraland and Cellmark; and (3) FDA's acknowledgement without objection of NDIN #1247 filed by SyncoZymes (Shanghai) Co., Ltd.[41] None of these examples carry any weight. First, as discussed below, sales outside f the U.S. have no bearing on the analysis of regulatory preclusion of dietary supplement products within the U.S. Second, a self-affirmation that a food additive is generally recognized as safe ("GRAS") equally has no bearing on the drug exclusion clause. To the extent that Nutraland and Cellmark asserted that their NMN products were food additives, and hence that they were able to self-affirm GRAS status, that would have been an incorrect assertion given that these NMN products were actually dietary supplements. As FDA has explained, "[i]nterpreting '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."[42] Finally, as explained above, the FDA's non-objection to NDIN #1247 happened incorrectly *after* FDA had authorized (and Metro had publicized) clinical drug investigations. At most, these examples illustrate only the "vague history of use" for NMN that FDA found insufficient in 2020 during its rejection of NDIN #1189 by Willy Chemicals, Inc.[43]

2. Non-U.S. Marketing Does not Exempt an Article From the Drug Exclusion Clause

Petitioners assert that sales of NMN products in Japan also constitute prior dietary supplement sales that nullify the drug exclusion clause. But the Petitions fail to acknowledge that FDA already rejected this same evidence in its prior assessment of NMN NDINs. In response to NDIN #1259 by Inner Mongolia Kingdomway, FDA found that "[e]vidence 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"[44] FDA explained:

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[39] Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN), REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051 (emphasis added).
[40] *See* 21 U.S.C. § 350b.
[41] NPA/AHN Citizen Petition at 7-8.
[42] *Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.
[43] *Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.
[44] *Id.*

> 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. The petitioners' reading of the statute ignored 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.[45]

To be clear, the context of § 321(ff)(3)(A) is plainly U.S.-specific. When Congress and FDA have wanted to involve countries outside of the U.S. in its regulatory scheme they have done so explicitly. For example, in FDA's guidance on Periodic Benefit-Risk Evaluation Reports ("PBRERs"), FDA defines the scope of a PBRER as starting on the "international birthdate" or "the date of the first marketing approval in any country in the world."[46] There is no similar language used in the dietary supplement space or relating to the drug preclusion rule. FDA has clearly and reasonably taken the position that NMN is excluded because it was authorized for investigation before being marketed as a dietary supplement in the *United States*.[47]

III. PETITIONERS' POLICY ARGUMENTS ARE MISPLACED

The Petitions are informed by both petitioners' misperception of the drug exclusion provisions as setting up a fictional "race" between drug and dietary supplement manufacturers in which the dietary supplement manufacturers need access to the IND effective dates. This race does not exist and is not the balance that Congress struck in including the exclusion provisions in the Dietary Supplement Health and Education Act ("DSHEA") of 1994.

The Petitioners agree that there is at least one important policy consideration behind 21 U.S.C. § 321(ff)(3)(B), which is to preserve financial incentives to bring innovative dietary ingredients to market and to conduct research on new drugs. Indeed, companies that spend significant time and resources to develop new drug products should be protected, as the development of clinical data is vital for advancements in innovation and ultimately public health and safety. The exclusion provision codified by DSHEA is intended to do exactly that—to ensure the drug development incentives by protecting the rights of companies that have spent significant time and research to develop drugs products against competition from dietary supplements that are clearly new dietary ingredients but that did not timely file new dietary ingredient notifications. This is particularly helpful for ingredients, like NMN, where evidence of efficacy and safety had not been clearly established at the time of unlawful marketing. Allowing for NMN to be sold as a

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[45] *Id.*

[46] *E2C(R2) Periodic Benefit Risk Evaluation Report (PBRER):* Guidance for Industry at 6, FOOD & DRUG ADMIN. (July 2016), .fda.gov/media/83371/download.

[47] *Dietary Supplements: Dietary Ingredients Notifications and Related Issues: Guidance for Industry* at 44, U.S. FOOD & DRUG ADMIN. (Oct. 2016), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues.

dietary supplement would permit companies to sell NMN without fully understanding its potential benefits and risks.

IV. FDA RULEMAKING OR ENCORCEMENT DISCRETION WOULD BE INAPPROPRIATE AND CONTRARY TO STATUTE

The NPA/AHN Petitioners ask FDA to commit to exercise enforcement discretion in connection with the marketing and selling of NMN in or as a dietary supplement; and/or issue a regulation, after notice and comment, such that NMN would be lawful in or as a dietary supplement. The CRN Petitioners also seek FDA to "reconsider its positions" with respect to the drug exclusion clause, and to "immediately issue guidance" implementing the exceptions to that clause to "allow marketing of certain ingredients as dietary supplements even when they might otherwise be prohibited by the express reading of the section."[48]

FDA should decline to change its position, and likewise should decline to exercise enforcement discretion or otherwise stretch the boundaries of the exclusion provisions' exceptions to accommodate dietary supplement sales of articles containing NMN. While Petitioners appear to be trying to piggyback on FDA's recent enforcement discretion provided to NAC, the circumstances are much different here. For NAC,[49] as described by FDA, it had a "long-standing" policy that NAC-containing products could be dietary supplement given the approval of Mucomyst (acetylcysteine) on September 14, 1963. However, Mucomyst was discontinued prior to the citizen petitions at issue there, which presented a unique situation that cannot (and should not) be replicated to the NMN-context and other dietary ingredients that include active clinical investigations and pharmaceutical development.

V. CONCLUSION

Metro agrees that NMN is rightly excluded from marketing as a dietary supplement under the "drug exclusion clause" of the FDCA. The FDA should not permit NMN products to be sold as a dietary supplement, which would be in violation of the drug exclusion clause and without sufficient demonstration of safety, adequate directions for use, or compliance with good manufacturing practices. Metro thanks the Food & Drug Administration for the opportunity to submit this public comment to the Petitions.

Sincerely,

Metro International Biotech, LLC

[48] CRN Citizen Petition at 2.

[49] *Guidance for Industry: Policy Regarding N-acetyl-L-cysteine*, U.S. FOOD & DRUG ADMIN. (Aug. 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-policy-regarding-n-acetyl-l-cysteine.

APPENDIX A: TIMELINE OF KEY EVENTS

8/25/2020	FDA receives NDIN #1174 by Willy Chemicals, Inc
11/2/2020	FDA responds to NDIN #1174 by Willy Chemicals, Inc and states that the product did not meet the definition of a dietary supplement because it was intended to be "taken under the tongue or in the buccal area," and not "intended for ingestion" as required by the dietary supplement definition (generally, in tablet, capsule, powder, softgel, gelcap, or liquid form (21 U.S.C. § 321(ff)).[50]
12/3/2020	FDA receives NDIN #1189 by Willy Chemicals, Inc
2/11/2021	FDA responds to NDIN #1189 by Willy Chemicals, Inc and states that the agency was unable to establish the safety of the dietary supplement containing NMN based on the "vague history of use" provided and "significant concerns" over the safety data on which the company relied.[51]
3/25/2021	Metro's Phase 2a Study of NAD+ Precursor Supplementation in Friedreich's Ataxia, is posted in clinicaltrials.gov
11/15/2021	FDA receives NDIN #1234 by Willy Nutra, Inc.
12/1/2021	Metro files a letter to the NAC citizen petition docket stating that its NMN drug has been authorized for investigation as a new drug and for which substantial clinical investigations have been instituted
12/27/2021	FDA receives NDA #1240 by SyncoZymes (Shanghai) Co., Ltd
1/18/2022	FDA responds to NDIN #1234 by Willy Nutra, Inc and states that the agency was unable to establish the safety of the dietary supplement containing NMN due to "significant concerns" about the safety data on which the company relied.[52]
2/24/2022	FDA responds to NDA #1240 SyncoZymes (Shanghai) Co., Ltd and states that the agency was unable to establish the safety of the dietary supplement containing NMN due to "significant concerns" about the safety data on which the company relied.[53]
3/21/2022	FDA receives NDA #1247 by SyncoZymes (Shanghai) Co., Ltd
5/16/2022	FDA responds to NDA #1247 by SyncoZymes (Shanghai) Co., Ltd and acknowledged receipt without objections and reminded the company that "acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. § 342."[54]

[50] *Letter from FDA CFSAN to Willy Chemicals, Inc regarding NDI 1174 - Reju-Me,* REGULATIONS.GOV (Jan. 8, 2021), https://www.regulations.gov/document/FDA-2020-S-0023-0103.

[51] *Letter from FDA CFSAN to NDI 1189 - Reju-Me from Willy Chemicals, Inc*, REGULATIONS.GOV (Feb. 11, 2021), https://www.regulations.gov/document/FDA-2021-S-0023-0017.

[52] *Letter from FDA CFSAN to Willy Nutra, Inc. regarding NDI 1234 - Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Jan. 18, 2021), https://www.regulations.gov/document/FDA-2022-S-0023-0001.

[53] *Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1240 - beta-nicotinamide mononucleotide (β-NMN)*, REGULATIONS.GOV (Feb. 24, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0013.

[54] *Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (B-NMN)*, REGULATIONS.GOV (May 16, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0027.

7/28/2022	FDA receives NDIN #1259 by Inner Mongolia Kingdomway Pharmaceutical Limited
10/11/2022	FDA responds to NDIN #1259 by Inner Mongolia Kingdomway Pharmaceutical Limited and concludes that "conclude that NMN is excluded from the dietary supplement definition under 21 U.S.C. § 32l(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement."[55]
11/4/2022	FDA issues supplemental response to NDIN #1259 by Inner Mongolia Kingdomway Pharmaceutical Limited finding that, "[b]ased on new information that came to light" while reviewing a different application, "NMN is excluded from the dietary supplement definition under 21 U.S.C. § 32l(ff)(3)(B)(ii) and may not be marketed as or in a dietary supplement."[56] FDA also sends supplemental responses to the other NDINs that were previously rejected due to the insufficiency of safety data provided and where NMN's exclusion from the definition of a dietary supplement was erroneously not addressed.[57]

[55] *Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Oct. 11, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[56] *Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - B-Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[57] *Supplemental Response Letter from FDA CFSAN to NDI 1189 - Reju-Me from Willy Chemicals, Inc*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2021-S-0023-0017; *Supplemental Response Letter from FDA CFSAN to Willy Nutra, Inc. regarding NDI 1234 - Nicotinamide Mononucleotide (NMN)*, REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0013; *Supplemental Response Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (B-NMN),* REGULATIONS.GOV (Nov. 4, 2022), https://www.regulations.gov/document/FDA-2022-S-0023-0027.