U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

September 29, 2029

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Sent via email to: daniel.fabricant@npanational.org and gretchen@anh-usa.org

Re: Docket Number FDA-2023-P-0872

Dear Dr. Fabricant and Ms. DuBeau:

This letter responds to your citizen petition regarding the regulatory status of Beta (β) Nicotinamide Mononucleotide (NMN).[1] Your petition, as amended, requests that the Food and Drug Administration (FDA or we) take the following actions:

1) Revoke or amend our determination that NMN is excluded from the definition of a dietary supplement under section 201(ff)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 321(ff)(3),[2] and issue a determination that NMN is not excluded from the definition of a dietary supplement.
2) In reaching FDA's determination, take action and provide the following:
    a. FDA's interpretation of the date that the agency uses to determine when an article is excluded from the definition of a dietary supplement under section 201(ff)(3)(B)(ii) (e.g., if an article is authorized for investigation as a new drug, antibiotic or biological in 2021, but existence of such investigation is not made public until 2023, identify the date FDA would use).
    b. FDA's interpretation of how the agency determines whether a clinical investigation is "substantial" within the meaning of section 201(ff)(3)(B)(ii), including "how FDA determined the date as to which any clinical investigations relating to NMN was [sic] 'substantial' and what those dates were determined to be."

[1] Citizen Petition from Natural Products Association and Alliance for Natural Health USA, submitted to the Division of Dockets Management, Food and Drug Administration, dated March 7, 2023, as amended by petition dated December 24, 2024, titled "Amended Citizen Petition Regarding Regulatory Status of β-Nicotinamide Mononucleotide" (Petition).

[2] For purposes of this citizen petition response, "section 201(ff)(3)" refers to section 201(ff)(3) of the FD&C Act.

c. FDA's interpretation of whether "substantial," as used in section 201(ff)(3)(B)(ii), "relates to efficacy."
d. FDA's interpretation of how the agency determines whether a dietary supplement was "lawfully" marketed.
e. The basis for FDA's interpretation of "marketing" in section 201(ff)(3)(B) as referring to marketing only in the United States.
f. The date FDA relied on in determining under section 201(ff)(3)(B) that NMN had been approved as a new drug or had been authorized for investigation as a new drug for which substantial clinical investigations had been instituted and for which the existence of such investigations was made public.
g. The clinical investigations instituted and made public that FDA relied on in finding that NMN was excluded from the definition of a dietary supplement and the dates each clinical investigation was deemed "substantial" and "made public" under section 201(ff)(3)(B).
h. The basis for the authority FDA relied on to support the agency's ability to revoke or withdraw its "issued acknowledgement of a New Dietary Ingredient Notification."

3) To the extent that FDA does not revoke or amend its position regarding NMN, (a) exercise enforcement discretion with respect to products labeled as dietary supplements that contain NMN and would be lawfully marketed dietary supplements if NMN were not excluded from the definition of dietary supplement or, alternatively, (b) recommend that the Secretary of Health and Human Services (Secretary) initiate rulemaking stating that NMN is not excluded from the definition of a dietary supplement and would be lawful in or as a dietary supplement under the FD&C Act.

(Petition at 1-3).

We have carefully considered your petition, its attachments, and the comments submitted to the docket. In accordance with 21 CFR 10.30(e)(3), and for the reasons stated below, we are granting your petition in part and denying it in part. Specifically, we are granting your petition insofar as it requests that we "amend" our determination that NMN is excluded from the definition of a dietary supplement and explain our thinking on certain topics. We are denying your petition insofar as it requests details on topics that we are prohibited from disclosing and requests actions that are now moot.

I. Background

A. Statutory Language and Legislative History of Section 201(ff)(3)(B)

The Dietary Supplement Health and Education Act of 1994 (DSHEA), Pub. L. No. 103-417, 108 Stat. 4325, amended the FD&C Act to define the term "dietary supplement" in section 201(ff) and establish requirements specific to dietary supplements. Paragraphs (1), (2)(A), and (2)(C) of the definition identify specific inclusion criteria for a product to fall within the scope of the dietary supplement definition (sections 201(ff)(1), (2)(A), and (2)(C) of the FD&C Act). That is, the product must have the characteristics articulated in the statute to be a dietary supplement.

Paragraphs (3)(A) and (B)(i) of section 201(ff) specify circumstances when a substance is excluded from the dietary supplement definition. The drafters of DSHEA added those provisions as a compromise to address concerns expressed by some members of Congress that the bill's initial definition of dietary supplement was too broad and would enable manufacturers to escape appropriate safety and efficacy review and FDA oversight for drugs by classifying those products as dietary supplements.[3] The language in paragraphs (3)(A) and (B)(i) and the inclusion of paragraph (B)(ii) (which, together, constitute section 201(ff)(3)[4]) establish a race to market between drugs and dietary supplements that contain the same ingredient.

Section 201(ff)(3)(A) provides that a product that otherwise meets the definition of a dietary supplement *does not lose* its status as a dietary supplement if it includes an article that is approved as a new drug or licensed as a biologic, provided that the article was marketed as either a dietary supplement or as a food before it was approved as a new drug or licensed as a biologic. Congress included a mirror image of that provision in section 201(ff)(3)(B)(i), which provides that a product that would otherwise meet the definition of a dietary supplement *loses* its status as a dietary supplement if the product includes an article that was approved as a new drug, certified as an antibiotic,[5] or licensed as a biologic before it was "marketed as a dietary supplement or as a

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[3] See, e.g., 140 Cong. Rec. S22413 (Aug. 13, 1994) (statement of Sen. Kennedy ("There continue to be differences among us as to how to achieve these goals most effectively. For example, the Hatch legislation offers a definition of dietary supplements that many feel is too broad. It will allow certain products which are treated as prescription drugs in other countries, or as unapproved drugs in this country, to be treated as dietary supplements and therefore subjected to inadequate safeguards.")); 140 Cong. Rec. S12104 (Aug. 18, 1994) (statement of Sen. Harkin ("[T]he [Hatch-Harkin] compromise assures that prescription drugs cannot escape appropriate review and oversight by being classified as dietary supplements. This concern was raised by a number of Senators and the legislation before us addresses it in a sensible manner.")).

[4] Section 201(ff)(3) states that the definition of "dietary supplement" does:

> (A) include an article that is approved as a new drug under section 505 or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless the Secretary has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f); and
>
> (B) not include—
>
> (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, or
>
> (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,
>
> 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.

[5] Pub. L. No. 105-115, § 125(b)(1) (1997) repealed then-section 507 of the FD&C Act. In addition, Pub. L. No. 105-115, § 125(d)(1) states: "An application that was approved by the Secretary of Health and Human Services before the date of the enactment of this Act for the marketing of an antibiotic drug under section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357), as in effect on the day before the date of the enactment of this Act, shall,

food." Put differently, section 201(ff)(3)(B)(i) provides that a dietary supplement *cannot include* an article that was approved as a new drug, certified as an antibiotic, or licensed as a biologic before it was "marketed as a dietary supplement or as a food." (Both sections 201(ff)(3)(A) and (B) authorize the Secretary—and, by delegation, FDA—to make exceptions via notice-and-comment rulemaking.)

Congress included a separate provision addressing investigational new drugs, antibiotics, and biologics. Section 201(ff)(3)(B)(ii) provides that a dietary supplement *cannot include* 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," unless the article was "marketed as a dietary supplement or as a food" "before such . . . authorization." Congress's extension of the drug exclusion provision beyond approved new drugs, certified antibiotics, and licensed biologics, which are covered by sections 201(ff)(3)(A) and (B)(i), reflects Congress's intent to protect the incentives for developing investigational new drugs, antibiotics, and biologics that are not yet approved, certified, or licensed. In other words, one of the overarching purposes of section 201(ff)(3)(B)(ii) is to protect the incentives for new drug development, as your petition acknowledges (Petition at 5).

Section 201(ff)(3)(B) consists of the following four clauses:

- *The new drug approval/biologic licensing clause (referred to as the "NDA clause" in this response)*: "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";

- *The investigational new drug (IND)/biological clause (referred to as the "IND clause" in this response)*: "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";

- *The "race-to-market clause"*: "which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food"; and

- *The "rulemaking clause"*: "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."

B. The New Dietary Ingredient Notification (NDIN) Requirement

A new dietary ingredient (NDI) is defined in section 413(d) of the FD&C Act (21 U.S.C. 350b(d)) as a dietary ingredient that was not marketed in the United States before October 15, 1994. Under section 413(a)(2) of the FD&C Act, the manufacturer or distributor of an NDI, or

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on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of such Act (21 U.S.C. 355(b)) and approved for safety and effectiveness under section 505(c) of such Act (21 U.S.C. 355(c)), except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of such Act (21 U.S.C. 355(j))."

of the dietary supplement that contains the NDI, must submit a premarket notification to FDA at least 75 days before introducing the product into interstate commerce or delivering it for introduction into interstate commerce, unless the NDI and any other dietary ingredients in the dietary supplement "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." Dietary ingredients marketed in the United States before October 15, 1994, are not NDIs and, therefore, do not require an NDIN.

An NDIN must contain the information, including any citation to published articles, that provides the basis on which the manufacturer or distributor of the NDI or dietary supplement (the notifier) has concluded that the dietary supplement containing the NDI "will reasonably be expected to be safe" (section 413(a)(2) of the FD&C Act). If the required premarket notification is not submitted to FDA, section 413(a) of the FD&C Act provides that the dietary supplement containing the NDI is deemed to be adulterated under section 402(f) of the FD&C Act (21 U.S.C. 342(f)). Even if the notification is submitted as required, the dietary supplement containing the NDI is deemed to be adulterated under section 402(f) of the FD&C Act unless there is 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 (section 413(a) of the FD&C Act).

To help industry comply with the FD&C Act's premarket notification requirements for dietary supplements that contain an NDI, FDA issued a regulation regarding NDINs (21 CFR 190.6). This regulation specifies the information the manufacturer or distributor must include in its premarket NDIN (see 21 CFR 190.6(b)). In addition to the requirements for the content of NDINs, the regulation establishes the administrative procedures for NDINs. Among other things, the regulation provides that FDA's failure to respond to an NDIN does not constitute a finding by us that the NDI or the dietary supplement containing the NDI is safe or is not adulterated under section 402 of the FD&C Act (see 21 CFR 190.6(f)).

C. Background and Relevant Regulatory History of β-Nicotinamide Mononucleotide

NMN is an intermediate in nicotinamide adenine dinucleotide (NAD+) biosynthesis produced from nicotinamide.[6] NMN is a dietary ingredient under section 201(ff)(1)(E) and was not marketed as a dietary ingredient in the United States before October 15, 1994. Therefore, NMN is an NDI under section 413(d) of the FD&C Act.

Over the last several years, FDA has received and responded to several NDINs related to NMN in dietary supplements. On November 2, 2020, FDA responded to an NDIN for NMN filed by Willy Chemicals, Inc.[7] In our letter, we explained that the company's product is not a dietary

[6] Mills, K. F., Yoshida, S., Stein, L. R., Grozio, A., Kubota, S., Sasaki, Y., Redpath, P., Migaud, M. E., Apte, R. S., Uchida, K., Yoshino, J., & Imai, S. I. (2016). Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice. *Cell metabolism*, 24(6), 795–806. https://doi.org/10.1016/j.cmet.2016.09.013.

[7] Letter from FDA Center for Food Safety and Applied Nutrition (CFSAN (now the Human Foods Program)) to Willy Chemicals, Inc. regarding NDI 1174 - beta-nicotinamide mononucleotide (β-NMN), available at https://www.regulations.gov/document/FDA-2020-S-0023-0103.

supplement within the meaning of section 201(ff)(2)(A)(i), which states: "[a dietary supplement] is intended for ingestion in a form described in section 411(c)(1)(B)(i)" of the FD&C Act. Because the product is not a dietary supplement, we wrote, "we are providing no response with respect to whether there is an adequate basis of safety for your product of commerce under" section 413(a)(2) of the FD&C Act. The company subsequently filed a second notification for the same ingredient (NMN) in a product intended for ingestion.[8] In our response, we found that the company did "not provide an adequate basis to conclude that [its] dietary supplement containing 'NMN', when used under the conditions recommended or suggested in the labeling … will reasonably be expected to be safe."[9]

On May 16, 2022, FDA acknowledged an NDIN for NMN filed by SyncoZymes (Shanghai) Co., Ltd. (SyncoZymes).[10] In our letter, we wrote, "[A]cceptance 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."[11]

We received an NDIN concerning NMN submitted on behalf of Inner Mongolia Kingdomway Pharmaceutical Limited (Inner Mongolia Kingdomway) and filed it on July 28, 2022.[12] On October 11, 2022, we sent a letter to Inner Mongolia Kingdomway stating that NMN is excluded from the definition of a dietary supplement under section 201(ff).[13] The letter noted that FDA reviewed information that Inner Mongolia Kingdomway had provided relating to NMN, along with other sources, including our own records.[14] Based on that review, we determined 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."[15] We sent similar letters to all firms that had submitted NDINs for NMN.[16]

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[8] New Dietary Ingredient (NDI) Safety Information from Willy Chemicals, Inc. regarding NDI 1189 - beta-nicotinamide mononucleotide (β-NMN), available at https://www.regulations.gov/document/FDA-2021-S-0023-0018.

[9] Letter from FDA CFSAN to Willy Chemicals, Inc. regarding NDI 1189 - beta-nicotinamide mononucleotide (β-NMN), available at https://www.regulations.gov/document/FDA-2021-S-0023-0017. FDA responses to subsequent NMN NDINs also include the same findings, available at https://www.regulations.gov/document/FDA-2022-S-0023-0001 and https://www.regulations.gov/document/FDA-2022-S-0023-0013.

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

[11] Id.

[12] See Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - β-Nicotinamide Mononucleotide (NMN), available at https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[13] Id.

[14] Id. at 2.

[15] Id.

[16] See, e.g., Supplemental response letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (β-NMN), available at https://www.regulations.gov/document/FDA-2022-S-0023-0027.

We elaborated on our reasoning in a supplemental letter to Inner Mongolia Kingdomway dated November 4, 2022 (November 2022 supplemental response).[17] The November 2022 supplemental response explained that we could not disclose certain facts, including the date on which NMN was first authorized for investigation as a new drug, due to legal prohibitions on disclosure of information concerning investigational new drugs.[18] Among other things, we explained that evidence of marketing of NMN as a dietary supplement in Japan did not exempt NMN from the U.S. requirement to submit an NDIN because dietary supplements are not part of the "food supply" under section 413(a)(1) of the FD&C Act.[19]

II. Discussion

A. Section 201(ff)(3)

1. The Relevant Date for the Race-to-Market Clause Is the Authorization Date

Your petition requests that FDA provide its interpretation of the date that FDA uses to determine when an article is excluded from the definition of a dietary supplement under section 201(ff)(3)(B)(ii) (e.g., "if an article is authorized for investigation as a new drug, antibiotic or biological in 2021, but existence of such investigation is not made public until 2023, identify the date FDA would use") (Petition at 2). FDA's position is that, if an article has been authorized for investigation as a new drug, antibiotic, or biological and substantial clinical investigations of that article have been instituted and made public, the relevant date for purposes of the race-to-market clause in section 201(ff)(3)(B) is the date the article in question was authorized for investigation as a new drug, antibiotic, or biological.[20] The relevant date is not the date that substantial clinical investigations were instituted or the date that the existence of such investigations was made public.

FDA's interpretation is based on a straightforward reading of the statute. Of the three criteria in the IND clause, the first ("an article authorized for investigation as a new drug") is the only one that uses the word "authorized." Thus, following a grammatical reading of the two clauses, "such . . . authorization" refers to the last mention of "authorization"—the date on which the article was "authorized for investigation as a new drug." FDA does not expressly "authorize" INDs. (Indeed, unless FDA informs the investigator that the investigations described in the IND are subject to a clinical hold, INDs simply go into effect, as set forth in 21 CFR 312.40(b)(1).) Therefore, FDA interprets "such . . . authorization" as referring solely to the date the IND went into effect, rather than to the other criteria listed in the IND clause (i.e., "instituted" and "made public").

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[17] Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - β-Nicotinamide Mononucleotide (NMN), available at https://www.regulations.gov/document/FDA-2022-S-0023-0051.

[18] Id.

[19] Id.

[20] For general background on the investigational new drug application process and its relationship to clinical trials, please see FDA's website, "Investigational New Drug (IND) Application," available at https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application.

Your petition appears to argue that "such . . . authorization" in the race-to-market clause refers to the entirety of the IND clause, meaning "such authorization" refers to all three criteria listed in the IND clause (i.e., the date all three criteria were met) as opposed to only the IND authorization criterion (i.e., the date the IND went into effect) (Petition at 6-8). Your argument appears to assume, among other things, that "authorization" is the subject of the IND clause (that is, the subject of section 201(ff)(3)(B)(ii)). Such a construction would not be consistent with the plain meaning. Under a plain-meaning reading, the term "article"—and not "authorization"—is the subject of the IND clause. Thus, the language in the clause related to substantial clinical investigations having been made public modifies the term "article," and does not inform the meaning of "such . . . authorization."

Moreover, the structure of section 201(ff)(3)(B) does not suggest that Congress meant the phrase "such approval, certification, licensing, or authorization" to refer back to the full text of the preceding sections (e.g., "such . . . authorization" refers back to the entirety of section 201(ff)(3)(B)(ii)). Such a reading would suggest that Congress intended a meaning that is not consistent with the grammatical reading of the text.[21]

Further, FDA has consistently interpreted the phrase "such . . . authorization" in the race-to-market clause as referring to the IND authorization date. For example, both the August 2016 and April 2024 versions of the *Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* state:

> **May I use an ingredient in a dietary supplement if it has been clinically tested as a drug but has not been approved as a drug in the U.S.?**

[21] In addition, FDA's interpretation is consistent with the structure of section 301(ll) of the FD&C Act. Section 301(ll) of the FD&C Act was enacted 13 years after section 201(ff)(3)(B) and prohibits, in relevant part, "[t]he introduction or delivery for introduction into interstate commerce of any food to which has been added . . . a drug or a biological product for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public" unless "such drug or such biological product was marketed in food . . . before any substantial clinical investigations involving the drug or the biological product have been instituted" or another exception applies.

Thus, in both sections 201(ff)(3)(B)(ii) and 301(ll) of the FD&C Act, Congress created a system where the article must meet multiple criteria to be excluded or prohibited in the first instance, but also established an exception that is tied to the date the article satisfied the first criterion. Moreover, section 301(ll) of the FD&C Act is unambiguous that the relevant date is the date the article satisfied the first criterion: there is no other way to interpret "before any substantial clinical investigations involving the drug or the biological product have been instituted."

In sum, FDA is not persuaded by your argument that because the plain language of section 201(ff)(3)(B)(ii) requires three criteria to be met for the ingredient to be excluded in the first instance, basic canons of statutory interpretation require the operative date to be the date the substantial clinical trial is made public (i.e., the date the third criterion is satisfied) (Petition at 7-8).

We likewise are unpersuaded by your argument that reading the IND effective date as the relevant date is incorrect because it renders the terms "substantial" and "public" in section 201(ff)(3)(B)(ii) meaningless (id.). As noted above, to trigger the "race-to-market" clause, the article must also be the subject of substantial clinical investigations that have been instituted and made public. However, the statute is clear that the relevant date is the authorization date of the underlying IND, not the date that any substantial clinical investigations were instituted or the date that the existence of such investigations was made public.

> It depends on whether the ingredient was authorized for investigation in clinical trials under an investigational new drug application (IND), *whether the date the IND went into effect was before or after the date the ingredient was first marketed as a food or as a dietary supplement*, whether the clinical trials were "substantial clinical investigations," and whether their existence was made public. The general rule is that an article that was authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public . . . .

(emphasis added).

In your petition, you assert, "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" (Petition at 8). While we are sympathetic to these concerns, the textual analysis disfavors an interpretation of the statute different from that which we have described above. Moreover, even if the considerations you cite—as they apply to the dietary supplement industry—might favor your interpretation, Congress may have decided to make the IND "authorization" date the operative date because it is a clear, definitive date that FDA can easily determine, whereas it could be difficult to pinpoint the precise date substantial clinical investigations were made public. Further, FDA's IND regulations, which restrict our ability to disclose information about a particular IND (e.g., 21 CFR 20.61, 312.130, 314.430), were in effect at the time DSHEA was enacted. Thus, at the time of DSHEA's enactment, Congress chose a non-public date to be the relevant date. Given the above considerations, we continue to believe that the interpretation set forth above (i.e., if an article has been authorized for investigation as a new drug, antibiotic, or biological and substantial clinical investigations of that article have been instituted and made public, the relevant date for purposes of the race-to-market clause is the date the article in question was authorized for investigation as a new drug, antibiotic, or biological) is the best reading of the statutory text.

2. Which IND Authorization Date Is the Relevant Date

Our November 2022 supplemental response included the following statements:

- "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."

- "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."

- "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."[22]

For clarification, when we stated, "the date an article is first authorized for investigation as a new drug," we were referring to the authorization date of the first IND that is associated with a substantial clinical investigation that was instituted and made public. That is the most natural reading of the phrase "such . . . authorization," is consistent with the statutory purpose of section 201(ff)(3)(B)(ii), and parallels the reading of the phrase "marketed as a dietary supplement or as a food" as referring to the first such marketing.

As background, it is not uncommon for multiple clinical investigations to be conducted under a single IND. When multiple study protocols are included under a single IND, they have a single authorization date—the original date the IND was authorized to proceed. Likewise, a sponsor may add a new protocol for a clinical investigation that is not covered under an IND to an existing IND through an amendment and need not obtain a new authorization for a later clinical investigation, so long as that later clinical investigation was properly added to an existing IND through the amendment process (21 CFR 312.30).[23] Thus, the "authorization" date for all clinical investigations covered under one IND would be the original date the IND was authorized to proceed, regardless of when the clinical investigations were conducted.

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[22] Supplemental Response Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited regarding NDI 1259 - β-Nicotinamide Mononucleotide (NMN), available at https://www.regulations.gov/document/FDA-2022-S-0023-0051 (citing 21 CFR 312.40(b)).

[23] Under FDA's regulations, an amendment to an IND to add a new protocol for a new clinical investigation "should build logically on previous submissions and should be supported by additional information" (21 CFR 312.22(c)).

Given the way IND authorization operates under 21 CFR part 312, which was in effect at the time of DSHEA's enactment, it is logical to look to the authorization date of the *first* IND that is associated with a substantial clinical investigation that was instituted and made public as the relevant date for purposes of the race-to-market clause. Using the date of the first authorized IND that is associated with a substantial clinical investigation that was instituted and made public as the relevant authorization date is also appropriate when substantial clinical investigations that have been instituted and made public are conducted under separate INDs (i.e., the first IND is associated with only one substantial clinical investigation that is instituted and made public and a subsequent IND is associated with a substantial clinical investigation that is instituted and made public).

A different interpretation could lead to arbitrary outcomes and, at least theoretically, to IND sponsors manipulating their IND applications. For example, one might consider interpreting "such . . . authorization" (i.e., the relevant date) to be the authorization date for the IND that is associated with the second substantial clinical investigation that was instituted and made public. The rationale for this interpretation would be that section 201(ff)(3)(B)(ii) requires that "substantial clinical investigations have been instituted and . . . made public" and thus the criteria of section 201(ff)(3)(B)(ii) are not satisfied until a second substantial clinical investigation is instituted and made public. However, if the relevant date were the authorization date for the IND that is associated with the second substantial clinical investigation that was instituted and made public, this could create a scenario where the relevant IND authorization date depends on whether the first two substantial clinical investigations of an article that were instituted and made public happened to be conducted under the same IND (in which case there would be a single IND authorization date that applies to both substantial clinical investigations) or under different INDs (in which case there would be different IND authorization dates that apply to each substantial clinical investigation). There is nothing to indicate that Congress intended for the relevant date to hinge on whether the first two substantial clinical investigations that were instituted and made public happened to be conducted under the same IND or under different INDs. Further, when the relevant date is the authorization date of the first IND that is associated with a substantial clinical investigation that was instituted and made public, this avoids the potential for arbitrary outcomes. Accordingly, the best reading of "such . . . authorization" is that it refers to the authorization date of the first IND that is associated with a substantial clinical investigation that was instituted and made public.

3. Meaning of the Term "Substantial Clinical Investigations"

As noted above, your petition requests that FDA provide its interpretation of how the agency determines whether a clinical investigation is "substantial" within the meaning of section 201(ff)(3)(B)(ii), including whether "substantial," as used in that clause, "relates to efficacy" (Petition at 2).

As noted above, section 201(ff)(3)(B)(ii) provides that a dietary supplement cannot include "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," unless certain criteria are met. This clause extends the scope of the drug exclusion provision beyond approved new drugs, certified antibiotics, and licensed biologics,

which are covered by sections 201(ff)(3)(A) and (B)(i). Accordingly, as discussed above, Congress's inclusion of this provision in addition to sections 201(ff)(3)(A) and (B)(i) demonstrates that Congress sought to protect investigational new drugs, antibiotics, and biologics that are not yet approved, certified, or licensed. In other words, one of the overarching purposes of section 201(ff)(3)(B)(ii) is to protect the incentives for new drug[24] development.

"Substantial clinical investigations" is not defined in section 201(ff)(3)(B)(ii) or elsewhere in the FD&C Act. FDA regulations that set forth the requirements governing the use of investigational new drugs, which were in effect at the time DSHEA was passed, define "clinical investigation," in relevant part, as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."[25]

In section 201(ff)(3)(B)(ii), the term "substantial" modifies the term "clinical investigations." "Substantial," as the Supreme Court has noted, is an ambiguous term and, as it is commonly understood, "may refer either to qualitative importance or to quantitatively large size."[26] Clinical investigations conducted to support new drug development vary in size, based on a number of factors, and a large number of study subjects does not, by itself, ensure that a study will produce reliable data about the safety or efficacy of a drug. Thus, we do not interpret "substantial clinical investigations" to mean "quantitatively large in size," although, as discussed below, size may be a consideration. The context of section 201(ff)(3)(B)(ii) suggests that "substantial" means clinical investigations that are of qualitative importance in the context of new drug development.[27]

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[24] For purposes of this response, the terms new drug, investigational new drug, and drug refer to both human drugs and biological drug products.

[25] See 21 CFR 312.3.

[26] *Life Techs. Corp. v. Promega Corp*., 580 U.S. 140, 146 (2017) (citing Webster's Third New International Dictionary 2280 (defs. 1c, 2c) (1981) (Webster's Third) ("important, essential," or "considerable in amount, value, or worth"); 17 Oxford English Dictionary 67 (defs. 5a, 9) (2d ed. 1989) ("That is, constitutes, or involves an essential part, point, or feature; essential, material," or "Of ample or considerable amount, quantity, or dimensions").

[27] To be clear, the term "substantial clinical investigations" in section 201(ff)(3)(B)(ii) does not mean "substantial evidence" as defined in section 505(d) of the FD&C Act (21 U.S.C. 355(d) (defining "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."). The substantial evidence standard of effectiveness in section 505(d) of the FD&C Act is used by FDA as a basis for approval of new drugs and is a very high bar. At the time that DSHEA was enacted in 1994, the "substantial evidence" standard for drug approval existed in the FD&C Act, as did the term "adequate and well-controlled investigations" (see Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1938, Public Law 87-781 (Oct. 10, 1962)). Had Congress intended "substantial clinical investigations" to have the same meaning as "substantial evidence," it could have used the same term or the term "adequate and well-controlled investigations" (see *Barnhart v. Sigmon Coal Co*., 534 U.S. 438, 452 (2002) ("It is a general principle of statutory construction that when Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.") (internal citations omitted)). It did not. Thus, it is clear that Congress intended the term "substantial clinical investigations" to mean something different than "substantial evidence" or "adequate and well-controlled investigations."

Our interpretation is supported by a Statement of Agreement the chief sponsors of DSHEA included in the legislative record, which states, "the term 'substantial clinical investigations' does not include compassionate investigational new drug applications or an investigational new drug application submitted by a physician for a single patient."[28] A single patient is clearly not a large size. If "substantial clinical investigations" meant clinical investigations that are of quantitatively large size, there would be no need to clarify that an IND application for a single patient is not a substantial clinical investigation. Further, in general, the purpose of an IND for a single patient is to provide the patient with access to an investigational drug; a single patient IND is not intended to further new drug development and is unlikely to do so. Thus, the chief sponsors' express exclusion of an IND application for a single patient suggests that they did not intend for "substantial clinical investigations" to limit clinical investigations to those that are of quantitatively large size, but rather to refer to clinical investigations that are of qualitative importance for new drug development, for which size is one (not dispositive) consideration.

Moreover, "compassionate use" or "expanded access" is the use of an investigational drug outside of a clinical trial to treat patients with a serious or immediately life-threatening disease or condition when there are no comparable or satisfactory alternative treatment options.[29] The primary purpose for a "compassionate use" or "expanded access" IND is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about a drug that is generally derived from a clinical trial.[30] Among the requirements for use of an investigational drug under a "compassionate use" or "expanded access" IND is that the requested use "will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use."[31] In other words, the primary purpose for a "compassionate use" or "expanded access" IND is not to generate data to support new drug development. Thus, the chief sponsors' express exclusion of compassionate IND applications provides further evidence that section 201(ff)(3)(B)(ii) is best read as protecting the incentives for new drug development and that the term "substantial clinical investigations" means clinical investigations that are of qualitative importance for new drug development.

There are many considerations—requiring application of scientific expertise—that may contribute to the assessment of whether a clinical investigation is "substantial," and thus a one-size-fits-all definition is not appropriate. In determining whether a clinical trial is "substantial," we consider the article (drug) under investigation and the purpose of the study (e.g., assessing the article's effect on a disease or condition or on the structure/function of the body, or to evaluate the safety of the article), which inform appropriate trial design. Characteristics of the article that

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[28] See Statement of Agreement, 140 Cong Rec H 28668 (Oct. 6, 1994).

[29] See FDA's website, "IND Applications for Clinical Treatment (Expanded Access): Overview," available at https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-applications-clinical-treatment-expanded-access-overview.

[30] See, e.g., FDA's guidance for industry *Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (June 2016), available at https://www.fda.gov/media/85675/download; FDA's draft guidance for industry*: Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers* (November 2022), available at https://www.fda.gov/media/162793/download.

[31] 21 CFR 312.305(a)(3).

would influence trial design can include, for example, the toxicity profile, pharmacological effects, and interactions with other drugs or substances.[32] Characteristics of the study that can be relevant considerations in determining appropriate trial features can include, for example, whether a study is intended to demonstrate safety, effectiveness, or both, and the therapeutic context in which the article will be used in the study (e.g., indication and the nature and severity of the disease condition).

With the context described above in mind, FDA can evaluate a clinical investigation to determine whether it is substantial for purposes of making our determination under section 201(ff)(3)(B)(ii). For a trial to be substantial, it must be qualitatively important for new drug development. Safety studies, efficacy studies, and studies of both efficacy and safety can be qualitatively important for new drug development. For example, some types of early studies may be considered "substantial" due to their impact and ability to directly inform drug development by providing critical information that otherwise could not be obtained.[33]

Moreover, for a trial to further new drug development, the overall trial design should be of high quality (though, for avoidance of doubt, this does not mean that every high-quality study will further new drug development and be considered a "substantial clinical investigation"). Such high quality trial designs should describe appropriate trial objectives and endpoints, identify appropriate trial participants with distinct inclusion and exclusion criteria, identify the appropriate size for the study population, and include an appropriate comparator (i.e., control) to meet the objectives of the trial protocol in support of the safety and/or effectiveness of the drug product.[34] Because each article and study present a unique set of circumstances, FDA may find that certain features of a trial design are appropriate for one article with a specific study purpose but not for a different article and study purpose.

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[32] For example, an article may have certain properties that could influence the trial design, such as the choice of control. A traditional placebo control may not be the optimal comparator in a clinical trial of an article with psychoactive effects because it may be apparent to the study subject whether they received the test product or the placebo. To facilitate blinding in these studies, investigators may consider use of alternatives to inert placebo such as lower doses of the psychedelic drug or other psychoactive drugs that mimic some aspects of the psychedelic experience (see FDA's draft guidance for industry *Psychedelic Drugs: Considerations for Clinical Investigations* (June 2023), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/psychedelic-drugs-considerations-clinical-investigations. As another example, a clinical trial of an article with a high toxicity profile may need to be monitored for unacceptable toxicity limits or include a mechanism to reduce dose, which may not be necessary for a different trial of a different drug that does not have the same or similar toxicity profile. Finally, if the article is known or suspected of having an interaction to a drug or other substance, the trial design may need to include further studies to assess those interactions.

[33] Some examples may include drug-drug interaction (DDI) or ascending dose studies, that often provide pertinent pharmacokinetics, safety and/or efficacy information on the drug proposed for use. These studies may be considered more informative to drug developers than other types of early studies due to their design elements and the safety outcomes ascertained from the study.

[34] Although a trial that is of sufficient quality to be considered a "substantial clinical investigation" will frequently share the attributes of an "adequate and well controlled" trial, see generally 21 CFR 314.126, FDA does not equate "substantial clinical investigation" with a clinical investigation that is capable of producing substantial evidence of effectiveness as defined by section 505(d) of the FD&C Act (see discussion in footnote 27 above).

As noted above, because appropriate trial design depends on the context of the article and purpose of the study, the trial design for a serious or life-threatening condition or one for which there are no available therapies may not include all of the trial design features described above; nevertheless, FDA may still find that it is substantial because FDA recognizes that certain aspects of drug development that are feasible for common diseases or conditions may not be feasible for rare ones and that development challenges are often greater with increasing rarity of the disease or condition. As such, FDA will apply flexibility in these situations to address particular challenges posed by each disease or condition.[35] Additionally, FDA is generally more likely to find that a clinical investigation is "substantial" if the trial is appropriately sized to meet the objectives of the study and is capable of producing meaningful data.[36] Typically, the larger the study population, the more reliable the study results due to findings with smaller margins of error. However, "larger" is a relative term and is dependent on the specific circumstances of the trial.[37]

These are generalizations and common characteristics of studies we have evaluated for purposes of exclusion determinations. That said, as emphasized previously, each article and study purpose present a unique set of circumstances, and thus, we evaluate each exclusion determination on a case-by-case basis.

4. *The Meaning of the Phrase "Marketed as a Dietary Supplement or as a Food"*

Your petition asserts two errors in FDA's interpretation of the phrase "marketed as a dietary supplement or as a food." First, you contend that FDA reads the phrase "in the United States" into the statute where it does not exist (Petition at 11-12). Second, you state that FDA "erred when it found that it would not consider evidence of marketing for a product on which no NDIN had been submitted" (Petition at 12). We address these two distinct interpretation questions separately below.

a. *Whether "Marketing" Must be in the United States*

Your petition requests that FDA explain the basis for its interpretation of "marketing" in section 201(ff)(3)(B) as referring to marketing only in the United States (Petition at 2). In addition, your petition states that "FDA contends that [21 U.S.C.] section 321(ff)(3)(B) … requires that the

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[35] 21 CFR part 312, subpart E; see also FDA's guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics.

[36] That said, clinical trials with "small" population sizes may produce safety findings that are not statistically significant but are clinically important enough to halt drug development. Further, it is possible for a clinical study to have a "large" population size that can produce statistically significant results but with effect sizes so small that they are clinically meaningless.

[37] For example, a large number of study participants cannot always be recruited for a trial involving an orphan drug or when the indication being studied impacts only specific subpopulations (e.g., pregnant women or pediatric subjects). In such cases, the study population may be small in comparison to other drug development programs, but the study may still be considered "substantial."

article be 'marketed as a dietary supplement or as a food' in the United States" and argues that "nothing in the plain language of the statute requires prior marketing of the article to **only** have occurred in the **United States**" (Petition at 11 (emphasis in original)). Your petition also contrasts the absence of the words "in the United States" in section 201(ff)(3)(B) with the definition of new dietary ingredient in section 413(d) of the FD&C Act (i.e., "those 'not marketed in the United States before October 15, 1994'") and contends the omission in section 201(ff)(3)(B) "was intentional" (Petition at 11). Your petition also notes that FDA considers marketing outside of the United States when reviewing NDINs (i.e., when reviewing an NDIN, FDA would consider food use outside of the United States as capable of providing evidence of safety of the NDI) (Petition at 12).

FDA continues to believe that the best reading of the statute is that the phrase "marketed as a dietary supplement or as a food" in the race-to-market clause in section 201(ff)(3)(B) refers to marketing as a dietary supplement or as a food *in the United States*. The statutory structure, text, and legislative history support this as the best reading of the statute.

Although it is true that when "Congress includes particular language in one section of a statute but omits it in another section of the same," it is "generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion," the inquiry does not end there (*Russello v. United States*, 464 U.S. 16, 23 (1983) (citations omitted) (comparing language in two consecutive subsections of the Racketeer Influenced and Corrupt Organizations Act)). Courts also apply other tools of statutory interpretation, including looking to the evolution of the statutory provisions (id. at 23-24). A statute must be construed as a whole, and individual sections must be read in light of the statute's structure, object, and purpose (*United States v. Kozeny*, 541 F.3d 166, 171 (2d Cir. 2008)), including "the physical and logical relation of its many parts." (Antonin Scalia & Bryan A. Garner, *Reading Law: The Interpretation of Statutory Texts* § 24, at 167 (2012)); see also *Dolan v. United States Postal Serv*., 546 U.S. 481, 486 (2006) ("Interpretation of a word or phrase depends upon reading the whole statutory text, considering the purpose and context of the statute, and consulting any precedents or authorities that inform the analysis."). "Context counts, and it is sometimes difficult to read much into the absence of a word that is present elsewhere in a statute." *Bartenwerfer v. Buckley*, 598 U.S. 69, 78 (2023) (internal citations omitted). Here, the context clearly shows that Congress intended the race-to-market clause to refer to marketing as a dietary supplement or as a food in the United States.

It is evident that section 201(ff)(3)(B)—both the medical product portion and the dietary supplement/food portion—was drafted in the context of U.S. law and the U.S marketplace, even though the phrase "in the United States" does not appear in section 201(ff)(3)(B). The medical product portion refers to the U.S. drug regulatory framework (e.g., "approved as a new drug under section 505 [of the FD&C Act]") and uses terms defined in the FD&C Act, such as "new drug." Similarly, the dietary supplement/food portion of section 201(ff)(3)(B) uses the term "dietary supplement," a term defined in the FD&C Act and not necessarily used in other countries. For example, Canada does not have a direct equivalent to the U.S. dietary supplement category. Although there is some overlap, Canada's "natural health products" category is considerably broader than the U.S. dietary supplement category. Moreover, Canada's "natural

health products" category includes some products (e.g., homeopathic medicines) that are drugs under U.S. law.[38]

Moreover, if your logic were applied consistently throughout section 201(ff)(3)(B), the comparison under section 201(ff)(3)(B)(ii) would be between (1) an article that is authorized for investigation as a new drug, antibiotic, or biological *anywhere in the world* and for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public and (2) an article marketed as a dietary supplement or as a food *anywhere in the world*. Put differently, applying your logic, the universe of investigational medical products that trigger exclusion under the IND clause would expand to investigational medical products authorized for investigation by any regulatory entity anywhere in the world, because the statute does not expressly state "by the Secretary," "by the U.S. Food and Drug Administration," or "in the United States."[39] However, this would not be the best reading of the statute, just as reading "marketed as a dietary supplement or as a food" as geographically unlimited is not the best reading of the statute, because it is clear that section 201(ff)(3) as a whole was drafted in the context of the U.S. law and the U.S. marketplace.

In addition, the purpose of the race-to-market clause supports interpreting that clause as referring to marketing as a dietary supplement or as a food in the United States. Congress's purpose in enacting the race-to-market clause was to ensure that the relevant dietary supplements and food that were already on the market before the corresponding approval, certification, licensing, or authorization could continue to be dietary supplements (or food) (see S. Rep. No. 103-410 (1994) at V § 3). Because Congress has the authority to regulate U.S. commerce, it makes sense that Congress would have thought of this protection as limited to U.S.-marketed dietary supplements and food rather than as extending to dietary supplements and food marketed outside of the United States. Further, the language of the Senate Report suggests that Congress intended the race-to-market clause to be a U.S.-focused inquiry (see S. Rep. No. 103-410 (1994) at V § 3 ("For example, if ever FDA should eventually approve Vitamin C as a drug to treat cancer, Vitamin C properly would also *continue to be available* as a dietary supplement (food) product, so long as it is promoted as a dietary supplement without disease prevention claims." (emphasis added))). Congress cannot dictate what "continue[s] to be available as a dietary supplement" in other countries.

Additional evidence also supports the conclusion that Congress omitted an express reference to "in the United States" in the race-to-market clause not because Congress wanted the geographic scope to be unlimited, but because Congress thought it was already clear from the context of section 201(ff)(3)(B) that the race-to-market clause is limited to the United States. In particular, DSHEA-predecessor bills included earlier versions of what is now section 201(ff)(3) ("the drug inclusion / exclusion paragraph"). In these earlier versions, it was clear that Congress was setting up a comparison of drug and food marketing within the United States. For example, a

[38] See Natural Health Products Regulations (SOR/2003-196), last amended by SOR/2022-143 (June 21, 2022) (definition of "natural health product").

[39] Moreover, the phrase "authorized for investigation" does not inherently restrict the scope of section 201(ff)(3)(B)(ii) to the United States. In fact, as noted above, FDA does not affirmatively "authorize" investigations; rather, an IND goes into effect unless FDA places it on hold (see 21 CFR 312.40(b)(1)).

Senate bill from August 11, 1994 (S. 784, 103d Cong. § 3 (as engrossed in Senate, Aug. 11, 1994)), would have amended the drug definition in section 201(g) of the FD&C Act to include the following paragraph:

> (3) The term "drug" does not include a dietary supplement as defined in paragraph (ff), except that—
>
> (A) an article that is approved as a new drug, certified as an antibiotic (under section 355 or 357), or licensed as a biologic (under section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.)) and was, prior to such approval, certification or license, marketed as a dietary supplement or as a food, *may continue to be offered for sale as a dietary supplement* unless the Secretary has issued a regulation, after notice and comment, finding that the article when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f);
>
> (B) an article that is approved as a new drug, certified as an antibiotic (under section 355 or 357), or licensed as a biologic (under section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.)) and was not prior thereto marketed as a dietary supplement or as a food, may not be considered as a dietary ingredient or dietary supplement unless the Secretary has issued a regulation, after notice and comment, finding that the article would be lawful under section 402(f) under the conditions of use and dosages set forth in the recommended labeling for such article.

(emphasis added). This earlier version of the statutory language that eventually became section 201(ff)(3) also does not include "in the United States," but the phrase "may continue to be offered for sale as a dietary supplement" makes clear that Congress intended to set up a comparison of drug and food marketing within the United States. As noted above, Congress cannot dictate what "continue[s] to be offered for sale as a dietary supplement" in other countries. The statutory language that was ultimately enacted through DSHEA placed the drug inclusion / exclusion paragraph in the dietary supplement definition rather than in the drug definition where it was in predecessor bills, which also changed the structure and precise language of the drug inclusion / exclusion paragraph but not its overarching purpose. In addition, as noted above, similar "continue to be" available language also appears in the explanation of the race-to-market clause in the Senate Report.

Thus, the legislative history of section 201(ff)(3) provides further evidence that Congress did not intend for the geographic scope of the race-to-market clause to be unlimited; rather, Congress thought it was already clear from the context that the race-to-market clause was limited to the United States. By contrast, the definition of "new dietary ingredient" in section 413(d) of the FD&C Act does not involve a comparison to drug marketing within the United States, and thus, if Congress had not included the phrase "in the United States" in the definition of "new dietary ingredient," it might not have been clear from the context of section 413(d) of the FD&C Act that Congress intended the term to be geographically limited. Accordingly, we do not agree that the reference to "in the United States" in section 413(d) of the FD&C Act suggests that its absence in section 201(ff)(3)(B) "was intentional" (see Petition at 11).

Finally, it is true that FDA limits "market[ing] as a dietary supplement or as a food" to marketing in the United States for purposes of the race-to-market clause in section 201(ff)(3)(B) but considers global food use when evaluating the safety of an ingredient in reviewing an NDIN under section 413(a) of the FD&C Act. There are good reasons for this difference. The provisions use different phrases and have different purposes. In particular, section 413(a) is about safety, so it makes sense that evidence that an ingredient was used in food in another country could inform the evaluation of the safety of that ingredient for use in the United States. By contrast, the race-to-market clause in section 201(ff)(3)(B) is about providing that dietary supplements and foods that were already on the market may continue to be dietary supplements and foods; thus, as discussed above, it is not logical to extend that category continuity to products that were on the market only outside of the United States.

b. Whether the Marketing Must Be Lawful Marketing

Your petition states that FDA "erred when it found that it would not consider evidence of marketing for a product on which no NDIN had been submitted" when comparing the date of marketing as a dietary supplement or food with the date of IND authorization (Petition at 12). You also state, "FDA concedes [in the November 2022 NMN supplemental response letter] that the [FD&C] Act does not contain that language" (id.). In addition, you request that FDA "[r]evoke or amend" our determination that NMN is excluded under section 201(ff)(3)(B)(ii) and that, in doing so, we explain "FDA's interpretation on how it determines whether a dietary supplement was 'lawfully' marketed" (Petition at 1-2). Taken together, we understand your petition to request that FDA reconsider our interpretation that the phrase "marketed as a dietary supplement or as a food" in the race-to-market clause refers only to products that were *lawfully* marketed as a dietary supplement or as a food. After careful consideration, we maintain that the best reading of that phrase is that the marketed product must be a dietary supplement or a food, but we agree it need not have been lawfully marketed.

Although it is true that the phrase "marketed as a dietary supplement or as a food" in section 201(ff)(3)(B) does not contain the word "lawful," the inquiry does not end there. We must also look to the context in which the reference to "marketed as a dietary supplement or as a food" appears and the structure and purpose of DSHEA (see, e.g., *Bartenwerfer*, 598 U.S. at 78 ("Context counts, and it is sometimes difficult to read much into the absence of a word that is present elsewhere in a statute.")). Upon further consideration, we believe that it is not sufficiently clear from the context that Congress intended for FDA to consider the lawfulness of a dietary supplement or a food when assessing when an article was first marketed as a dietary supplement or as a food for purposes of the race-to-market clause.

As an initial matter, as you allude to, there are many ways to interpret what it means for a dietary supplement (or a food) to be "lawfully marketed" for purposes of the race-to-market clause. For example, one could interpret "lawfully marketed" to mean a product that complies with every applicable legal requirement. As another example, "lawfully marketed" could mean a product that has satisfied all applicable premarket requirements (e.g., the NDIN requirement for certain NDIs). Satisfying all applicable premarket requirements before marketing a dietary supplement or a food would parallel satisfying the applicable drug premarket requirements that

are expressly stated in the NDA clause and the IND clause. However, upon further reflection, we do not believe it is sufficiently clear that Congress meant the phrase "marketed as a dietary supplement or as a food" to mean "marketed as a dietary supplement or as a food in compliance with *all* applicable legal requirements" or "marketed as a dietary supplement or as a food after satisfying all applicable *premarket* requirements." In short, it is not sufficiently clear that Congress intended FDA to assess any aspect of the lawfulness of a dietary supplement or a food when assessing when an article was first marketed as a dietary supplement or as a food for purposes of the race-to-market clause. This is particularly evident when comparing the support for the "lawful marketing" interpretation to the support for reading the phrase "marketed as a dietary supplement or as a food" as referring to marketing in the United States.

As discussed above, it is abundantly clear from the context that Congress intended the race-to-market clause to refer to marketing as a dietary supplement or as a food in the United States even though the phrase "in the United States" does not appear anywhere in section 201(ff)(3). The statutory structure, the U.S.-specific terms Congress used in the statutory text, the purpose of the race-to-market clause, and the legislative history (including the evolution of the statutory provisions) all support this as the best reading of the statute. By contrast, the context does not clearly indicate that Congress intended for FDA, as part of the agency's evaluation of which product category came first for purposes of the race-to-market clause, to examine whether a dietary supplement or a food satisfied all applicable premarket requirements (or any other applicable legal requirement).

Congress did not include language in section 201(ff)(3)(B) that expressly limited the geographic scope to the United States but used U.S.-specific terms in *both* the drug and dietary supplement/food portions of the subparagraph. By contrast, Congress was not evenhanded in expressly stating whether the drug and dietary supplement/food portions of the subparagraph must meet the applicable premarket requirements. Section 201(ff)(3)(B) expressly states that an article must meet the applicable new drug (or biologic) premarket requirements. Further, determining whether an article is approved as a new drug under section 505 of the FD&C Act, licensed as a biologic under section 351 of the Public Health Service Act, or authorized for investigation as a new drug, antibiotic, or biologic is a straightforward inquiry. There is a clear and easily obtainable answer.

By contrast, section 201(ff)(3)(B) does not expressly state that the article must meet all applicable premarket requirements to be "marketed as a dietary supplement or as a food" for purposes of the race-to-market clause. Moreover, there is not always a clear and easily obtainable answer to whether a dietary supplement or a food satisfied all applicable premarket requirements (let alone satisfied all applicable legal requirements). This is because FDA has to determine on a case-by-case basis whether the premarket requirements applied to that particular ingredient. Sometimes, FDA may not have reliable information to make this determination. For example, if a dietary supplement was first marketed in the United States 25 years ago, it may be very difficult for FDA to determine whether an NDIN was actually required under section 413(a) of the FD&C Act even though it is clear that the ingredient is an NDI. Section 413(a)(1) of the FD&C Act provides that an NDIN is not required if "[t]he dietary supplement contains 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," and it may be difficult for FDA to find

reliable information on an ingredient's presence in the food supply 25 years ago. Accordingly, where the context does not show a clear Congressional intent, we decline to presume that Congress intended the agency to take on this difficult task for every ingredient as part of the agency's evaluation of which product category came first for purposes of the race-to-market clause.

In light of the above, FDA believes that the best reading of the race-to-market clause is that Congress intended the sole focus to be the timing of specific events, such as the first approval of the article as a new drug under section 505 of the FD&C Act and the first marketing of the article as a dietary supplement or as a food in the United States. Congress did not intend for FDA to examine whether the first marketing of the article as a dietary supplement or as a food was lawful.[40] However, that does not mean there are no consequences if a manufacturer or distributor rushes to get its product to market first without complying with the applicable requirements of the FD&C Act, including the NDIN requirement of section 413(a) of the FD&C Act. Although the product would not automatically lose its eligibility to be a dietary supplement, in this same example it would be an adulterated dietary supplement under sections 413(a) and 402(f) of the FD&C Act. The Federal Government may take swift action to remove an adulterated dietary supplement from the market.[41]

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[40] A comment to the Docket states that the agency "cannot announce an interpretation" of the drug exclusion clause "that is contrary to statute in response to a request in a citizen petition" and asserts that "FDA has previously explained its long-standing interpretation" of that clause "in guidance, which is widely relied upon by manufacturers, drug sponsors, and other stakeholders interested in bringing innovative dietary ingredients to market or conducting research on new drugs" (Letter from MetroBiotech to the Docket dated Feb. 14, 2025 at 8 n.29, available at https://www.regulations.gov/comment/FDA-2023-P-0872-2752). The comment thus concludes that if FDA "consider[s] … modifying its interpretation of the drug exclusion clause" in response to the petition, any such change should be made through updated guidance (id). For the reasons discussed above, FDA's interpretation of "marketed as a dietary supplement or as a food" is not contrary to the statute. Moreover, neither the NDIN draft guidance cited by the commenter, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notifications-and-related-issues, nor the previous iterations of that draft guidance assert that the marketing of the dietary supplement or food must have been "lawful" for purposes of section 201(ff)(3). Indeed, the draft guidance's discussion of section 201(ff)(3) does not address whether "marketing as a dietary supplement or as a food" refers to "lawful marketing."

We are mindful that stakeholders may have relied on the discussion of "lawful marketing" in the agency's October 11, 2022 letter to Inner Mongolia Kingdomway and its November 2022 supplemental response, which were posted to the docket for NDI 1259, https://www.regulations.gov/document/FDA-2022-S-0023-0051, on November 8, 2022. Those statements are unlikely to have generated serious reliance interests, however, because they were promptly challenged in a citizen petition filed six months later (see Citizen Petition from the Council for Responsible Nutrition dated May 9, 2023, at 12-14, available at https://www.regulations.gov/document/FDA-2023-P-1867-0001). In any event, in response to that petition and the petition at issue in this response, we have reconsidered this issue of statutory interpretation and, for the reasons discussed above, we have concluded that the November 2022 supplemental response's interpretation of section 201(ff)(3) on this issue does not reflect the best reading of the statutory language.

[41] In our November 2022 supplemental response, we noted that the Congressional findings enacted as part of DSHEA state that "the Federal Government should take swift action against products that are unsafe or adulterated." Citing this Congressional finding, we asserted, "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." Upon further reflection, we believe this Congressional finding does not evince a clear intent by Congress for FDA to

Moreover, not every marketed product that is represented as a dietary supplement or as a food would be "marketed as a dietary supplement or as a food" for purposes of the race-to-market clause. A product is not "marketed as a dietary supplement" for purposes of the race-to-market clause if it is not actually a dietary supplement within the meaning of section 201(ff). For example, if a product is labeled as a dietary supplement but does not contain any dietary ingredients, the product would not be a dietary supplement (see section 201(ff)(1) of the FD&C Act). Thus, the sale of this product would not "count" for purposes of section 201(ff)(3)(B).

B. Status of NMN Under Section 201(ff)(3)(B)

In light of FDA's revised interpretation of the race-to-market clause in section 201(ff)(3)(B), we now conclude that NMN is not excluded from the definition of dietary supplement under section 201(ff)(3)(B). Specifically, although NMN was authorized for investigation as a new drug and substantial clinical investigations of NMN have been instituted and made public, NMN was marketed as a dietary supplement in the United States before such authorization.

For the reasons discussed above, we do not believe that our prior position that the dietary supplement or food must have been lawfully marketed for purposes of the race-to-market clause is the best reading of section 201(ff). Thus, although we continue to examine whether the evidence supports the conclusion that the product was marketed in the United States and is actually a dietary supplement or a food, we will no longer evaluate whether the dietary supplement or food was lawfully marketed when making a determination under the race-to-market clause.[42] FDA is aware of evidence that NMN was marketed as a dietary supplement in the United States as early as 2017.[43] This preceded the authorization of NMN for investigation as a new drug. Accordingly, we now conclude that NMN is not excluded from the dietary supplement definition under section 201(ff)(3)(B).[44]

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use the race-to-market clause to take swift action against products that are unsafe or otherwise adulterated. As with any unsafe or otherwise adulterated dietary supplement, if FDA finds that an ingredient that is also approved as a new drug (or otherwise described in the NDA clause or IND clause) is unlawful as a dietary supplement, FDA may always seek to use the tools available under the FD&C Act (including seizures and recalls) to remove an unsafe or otherwise adulterated dietary supplement from the market.

[42] Accordingly, we deny your request for FDA's interpretation of how the agency determines whether a dietary supplement was "lawfully" marketed for purposes of the race-to-market clause (Petition at 2), as this request is now moot.

[43] Because we are aware of evidence that NMN was marketed as a dietary supplement in the United States before NMN was authorized for investigation as a new drug, it is not necessary to address the examples you appear to present as evidence of NMN being marketed as a dietary supplement or as a food.

[44] Although we conclude that NMN is not excluded from the dietary supplement definition under section 201(ff)(3)(B), we disagree with your position that "NMN should be categorically treated as a dietary supplement" because NMN is a dietary ingredient and because "NMN has self-GRAS status and, according to FDA's own guidelines, does not require a NDIN to be sold as a dietary supplement" (Petition at 8-9). First, while we agree that NMN is a dietary ingredient, NMN's status as a dietary ingredient is not relevant with respect to whether it is excluded from the dietary supplement definition under section 201(ff)(3)(B) of the FD&C Act. Because the elements of the dietary supplement definition in sections 201(ff)(1), (2), and (3) are phrased conjunctively (separated

Your petition requests that we provide the specific date that we relied on in determining that NMN has been authorized for investigation as a new drug and that substantial clinical investigations of NMN have been instituted and made public (Petition at 2). As an initial matter, we no longer find that NMN is excluded under section 201(ff)(3)(B). In any event, we are limited in our ability to disclose information about particular INDs.[45] As we noted in our November 2022 supplemental response, "[A]lthough 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 …. Details about NMN's authorization [for investigation] as a new drug are documented in FDA's files."[46] This remains the case.[47]

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by "and"), a product qualifies as a dietary supplement only if it satisfies the criteria in all three of these paragraphs. Demonstrating that a product satisfies the requirement in section 201(ff)(1) to contain a dietary ingredient does not establish that the product meets the other criteria in sections 201(ff)(2) and (ff)(3). Second, it is true that an NDIN is not required for a dietary supplement that contains only dietary ingredients that "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" (section 413(a)(1) of the FD&C Act). However, this does not mean that an ingredient's "self-GRAS status" renders the NDIN requirement of section 413(a)(2) inapplicable. An ingredient's "self-GRAS status" is not, in itself, evidence that the ingredient 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.

Likewise, we disagree with your argument that because "NMN product has self-affirmed GRAS status," "there is no legitimate safety concern that should arise to justify FDA's exclusion of NMN from the definition of a dietary supplement" (Petition at 12). A product's safety profile does not determine whether it is "marketed as a dietary supplement or as a food" within the meaning of the race-to-market clause.

[45] E.g., 21 CFR 20.61, 312.130, 314.430.

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

[47] In addition, your petition requests that FDA provide the clinical investigations instituted and made public that FDA relied on in finding that NMN was excluded from the definition of a dietary supplement and the dates each clinical investigation was deemed "substantial" and "made public" under section 201(ff)(3)(B) (Petition at 3). We deny this request for two reasons. First, the request is now moot because we have determined that the first marketing of NMN as a dietary supplement in the United States preceded the authorization of NMN for investigation as a new drug. Second, for the reasons stated above, the dates a clinical investigation is deemed "substantial" and "made public" are irrelevant for purposes of the race-to-market clause and, thus, have no bearing on whether an ingredient is excluded under section 201(ff)(3)(B)(ii).

D. Other Issues Raised in the Citizen Petition and Comments

1. *FDA Acted Within Its Authority In Updating Its Responses to the NDINs for NMN*

In your petition, you request that FDA explain "the basis for the authority FDA relies upon to support its ability to revoke or withdraw its issued acknowledgement of a New Dietary Ingredient Notification" (Petition at 3). You further assert, "FDA did not cite the legal authority it has to object to or withdraw its acknowledgement of properly filed NDINs for NMN and summarily claim, without providing any evidence, that NMN is no longer included [in] the definition of a dietary supplement" (Petition at 11).

As FDA noted in our March 2024 *Dietary Supplements: New Dietary Ingredient Notification Procedures and Timeframes: Guidance for Industry*:[48]

> Note that receiving an acknowledgement letter without objection means that FDA's review of the NDIN did not find any reason to object to the notifier's basis for concluding that the NDI and the dietary supplement containing the NDI will reasonably be expected to be safe. However, such a letter does not constitute an independent finding by FDA that the NDI and the dietary supplement that contains the NDI are safe, or that they are not adulterated under section 402(f) of the FD&C Act. FDA is not precluded from taking action in the future against a dietary supplement containing your NDI if it is adulterated, misbranded, or if its distribution in interstate commerce otherwise violates the FD&C Act.

Our May 2022 acknowledgement letter to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 noted that the acceptance of the notification for filing was "a procedural matter" that did 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."[49] It also stated, "FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded" (id.). Thus, our acknowledgement letter itself made clear that our position could change based on additional information. As our November 2022 supplemental letter to SyncoZymes acknowledged, "[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 excluded from the definition of a dietary supplement."[50] Although this additional information (about the clinical investigations of MIB-626, i.e., NMN) was available at the time FDA sent our May 2022 acknowledgement letter,

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[48] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-new-dietary-ingredient-notification-procedures-and-timeframes-dietary-supplements.

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

[50] Supplemental Response Letter from FDA CFSAN to SyncoZymes (Shanghai) Co., Ltd. regarding NDI 1247 - beta-nicotinamide mononucleotide (β-NMN), Nov. 4, 2022, available at https://www.regulations.gov/document/FDA-2022-S-0023-0027.

it was not readily clear to the staff reviewing the NDIN that MIB-626 referred to NMN, and this information was overlooked in our searches for clinical investigations of NMN.

In any case, it is well-established that an agency, upon learning of a mistake, generally may correct it.[51] Here, as FDA explained in our November 2022 supplemental response, "[a]fter consulting our internal records, the clinical trials registry, and other relevant sources, we concluded that NMN is," in addition to being an article authorized for investigation as a new drug, "also an article for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public."[52] The supplemental response cited the clinical trials that we looked to in reaching that conclusion and explained our interpretation and application of the FD&C Act's provision relating to the drug exclusion clause.[53]

However, as discussed in this response, FDA has reconsidered its position that the dietary supplement or food marketing must be lawful to "count" for purposes of the race-to-market clause, and, in light of this change in interpretation, we have determined that NMN is not excluded from the dietary supplement definition.

2. *Your Requests that FDA Exercise Enforcement Discretion for NMN and Promulgate Rulemaking Finding that NMN Is Lawful Are Denied as Moot*

Your petition requests that FDA exercise enforcement discretion with regard to the "marketing and selling of NMN as a dietary supplement" (Petition at 3, 13, 15). You also request that FDA "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 Act . . . ." (Petition at 15-16; see also Petition at 13). Given our determination that NMN is not excluded from the definition of a dietary supplement, we deny these requests as moot.

[51] See, e.g., *Lannett Co., Inc. v. United States Food & Drug Admin.*, 300 F. Supp. 3d 34, 38 (D.D.C. 2017); *Ivy Sports Medicine, LLC v. Burwell,* 767 F.3d 81, 86 (D.C. Cir. 2014); *American Therapeutics, Inc. v. Sullivan*, 755 F. Supp. 1, 2 (D.D.C. 1990).

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

[53] Id. We note that NMN and MIB-626 have the same chemical structure, as confirmed by FDA's review of the relevant INDs, and, thus, are the same article.

III. Conclusion

For the reasons stated above, in accordance with 21 CFR 10.30(e)(3), your petition is granted in part and denied in part.

Sincerely

Donald A. Prater -S

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Donald Prater, DVM
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