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CITIZEN PETITION

May 9, 2023

Via Electronic Submission

Division of Dockets Management
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Re: Citizen Petition Requesting FDA Reconsider Its Position with Respect to the Application of Section 201(ff)(3)(B) of the Food, Drug, and Cosmetic Act; Acknowledge That Agency Prior Statements and Actions Cannot be Reversed on Drug Preclusion Grounds; and Clarify Its Position on Rulemaking

Dear Sir or Madam:

The Council for Responsible Nutrition (CRN)[1] submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 requesting that the Food and Drug Administration ("FDA" or "the Agency") reconsider its positions with respect to section 201(ff)(3)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), as these interpretations of the statute were recently stated with regard to the legality of beta-nicotinamide mononucleotide (NMN); acknowledge that agency prior statements and actions affirming the legal use of an ingredient as a dietary supplement cannot be reversed on the grounds of drug preclusion; and issue guidance clarifying the agency's rulemaking authority. FDA's tentative positions with regard to various aspects of the so-called "drug preclusion" provision found in section 201(ff)(3)(B) (codified at 21 U.S.C. § 321(ff)(3)(B)), as have been discussed in various FDA documents and guidance, such as those related to NAC, NMN, and new dietary ingredients, have the effect of diminishing the purpose of that provision, and the careful balance Congress intended between drug and dietary supplement interests, as well as the plain

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 180 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

reading of the words. These positions have the potential to inject significant uncertainty and inequities into the supplement marketplace and to upend the intended balance in the law between pharmaceutical and dietary supplement interests. The totality of FDA's various viewpoints on the application of the statute – with respect to pyridoxamine, vinpocetine, NAC, other ingredients, and now NMN – unfairly promotes pharmaceutical research at the expense of dietary supplements, consumer access, and public health.

Action Requested

CRN requests that FDA reconsider its positions with respect to section 201(ff)(3)(B), as these perspectives were recently stated with regard to the legality of NMN. Specifically, we ask FDA:

- To determine that the preclusion date referenced in the statute (*i.e.*, the date on which the "race to market" between a drug and a supplement is adjudicated) 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;
- To determine that "marketing" as used in section 201(ff)(3)(B) is not limited to marketing in the United States, nor does it require "legal" marketing of the ingredient;
- To determine that evidence of marketing as a food or dietary supplement should be dispositive, unless FDA has met its statutory burden of demonstrating that the marketing was unlawful;
- To determine that "substantial clinical investigations" as used in section 201(ff)(3)(B) refers only to clinical trials that are adequately designed and powered to support approval of a drug, and does not refer to Phase I clinical trials; and
- To determine that the agency's prior affirmative statements recognizing the legal status of a particular article as a legal dietary ingredient prevents FDA from subsequently reversing that decision on the grounds of drug preclusion.

Further, CRN requests that FDA immediately issue guidance indicating how it will utilize the discretion conferred upon the Agency in section 201(ff)(3)(B) to create regulatory exceptions to drug preclusion that may arise under the statute through notice and comment rulemaking. Such guidance should provide clear criteria by which the Agency would determine that an article "would be lawful under this [Act]"and provide a framework for companies to petition for such rulemaking. By its inclusion in the express language of the statute, Congress clearly intended that FDA would effectualize this process and allow for marketing of certain ingredients as dietary supplements even when they might otherwise be prohibited by the express reading of the section. FDA should make that a reality.

CRN emphasizes that this petition differs from a citizen petition recently submitted by another trade association seeking simply the reversal of the FDA's position regarding NMN and the return of NMN to the market. CRN's petition is not limited to the facts of the NMN case, but rather FDA's misapplication of the law with the potential to impact other ingredients and create uncertainty and unpredictability in the supplement marketplace. This petition addresses the legally unsound

reasoning on which FDA's NMN decision was predicated and the faulty premises on which that decision, as well as future actions using that reasoning, might be based. CRN asks the Agency to clarify the application of section 201(ff)(3)(B) with respect to any ingredient. We do not ask for an exercise of enforcement discretion with respect to NMN as such a contingency only serves to "kick the can down the road" and to avoid addressing critical questions with respect to the interpretation of section 201(ff)(3)(B). Any actions requested in other citizen petitions that specifically reference an outcome for NMN should be considered separately by FDA and CRN requests that a response to this petition not be delayed by a response to other petitions. Such delay in providing clarity to industry about the application of section 201(ff)(3)(B) creates continued unpredictability for the supplement industry, dissuades innovation, and limits consumer access.

Statement of Grounds

A. Background - Congressional Purpose for Drug Preclusion

The Dietary Supplement Health and Education Act (DSHEA), which amended the FDCA in 1994, created dietary supplements as a newly defined product category regulated by FDA while preserving consumer access to these products as important tools to support public health and nutrition. DSHEA included language defining the type of ingredients that can be included in dietary supplements. As part of the definition for dietary supplement, Congress included exclusion language removing certain dietary supplement ingredients from consideration where that ingredient was the same ingredient as a drug ingredient and the drug use was "first-to-the-market." This language (called "drug preclusion" for purposes of this petition) was intended to provide limited protection for "bona fide new drug ingredients as well as research investment into natural ingredients for use as new drugs."[2]

Specifically, the drug preclusion section of DSHEA provides that a dietary supplement does –

> *(B) not include —*
> *(i) an article that is approved as a new drug under section 355 of this title, certified as an antibiotic under section 357 of this title, or licensed as a biologic under section 262 of title 42, or*
> *(ii) an article authorized for investigation as a new drug, antibiotic, or biologic 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] . . .* [3]

[2] I. Scott Bass & Anthony L. Young, *The Dietary Supplement Health and Education Act: A Legislative History and Analysis* (1996) at 36.
[3] Food, Drug, and Cosmetic Act (FDCA) § 201(ff)(3)(B) (codified at 21 U.S.C. § 321(ff)(3)(B)).

The drug preclusion provision of section 201(ff) was added as a late in-the-process amendment to the DSHEA legislation to help assuage fears from some members of Congress that "manufacturers or importers of drugs could avoid the drug approval process by marketing drug products as dietary supplements."[4] When offering the amendment, the drafters emphasized this fact, noting that "[a]lthough current authorities should be adequate to deal with such potential problems, the committee is sensitive to those concerns."[5] The drafters further recognized the different purposes of drugs, versus dietary supplements, when allowing pre-existing dietary ingredients to remain on the market as supplements despite a subsequent drug approval, specifically noting that substances approved as a drug "would be drugs because they would be promoted with drug claims. They would and should have no effect on the food status of a properly labeled dietary supplement."[6] Drug preclusion language was simply offered as a limited check to help prevent nefarious behavior where a bad actor might bring to the dietary supplement market, a substance, once approved as a drug or substantially investigated as a drug, under the guise of a dietary supplement without going through the appropriate approval process.

B. FDA's Recent Application of Drug Preclusion

CRN has expressed repeated concerns over the last few years with FDA's overly broad interpretations of section 201(ff)(3)(B). What was intended by Congress for a limited use has been increasingly cited by FDA to block consumer access to numerous safe and beneficial dietary supplement ingredients. FDA's latest actions related to drug preclusion for NMN further expand the section's scope, threaten to severely limit all new dietary ingredient innovation moving forward, and block consumer access to ingredients that in no way threaten to compromise the drug approval process or disincentivize drug research investment. FDA's overly broad expansion of drug preclusion unfairly favors drug innovation at the expense of a robust, innovative dietary supplement marketplace.

Previously, CRN raised concerns with FDA that its interpretation of section 201(ff)(3)(B) was legally invalid because it: (1) failed to acknowledge that different forms of an ingredient and route of administration are relevant to determining if ingredients are the same "article"; and (2) violated the well-established presumption against statutory retroactivity.[7] FDA's latest drug preclusion action raises additional concerns as summarized below.

CRN also has pointed out repeatedly that, despite a determination that an ingredient is precluded, Congress gave FDA the authority to promulgate regulations allowing consumer access

[4] S. Rep. 103-410 (1994), at V § 3.
[5] *Id.*
[6] *Id.*
[7] CRN Citizen Petition Requesting FDA Allow N-acetyl-L-cysteine (NAC) to be Marketed as a Dietary Supplement (June 1, 2021) ("CRN NAC Citizen Petition").

to the ingredient as a dietary supplement. FDA still has never used this authority.[8] If FDA insists on taking such an expansive view of the express statutory language, then it must immediately begin to use the discretion also afforded by the statute to create a pathway for granting exceptions when the equities involved demand it. All concerns, including those raised in CRN's previous NAC citizen petition and here, should be addressed in a forthcoming guidance clarifying FDA's position and addressing how FDA will use its rulemaking authority.

In May 2022, FDA accepted a new dietary ingredient notification (NDIN) for NMN without objection.[9] Prior to this no-objection letter, FDA reviewed NDINs[10] and structure/function claim notifications[11] for other companies' NMN dietary supplement products, and never indicated that NMN might be subject to drug preclusion. This reversal was similar to FDA's actions regarding two other dietary ingredients: 1) n-acetyl-L-cysteine (NAC), the subject of the above cited citizen petition—where FDA reviewed industry notifications regarding the ingredient's use in dietary supplements and food for decades and never objected to this use based on drug preclusion—until a sudden reversal of this policy in June 2020;[12] and 2) vinpocetine, for which the agency received NDI notification letters from four different manufacturers, issued no-objection letters prior to 2000,[13] and then issued a Request for Comment on the Status of Vinpocetine in 2016 that called into question the status of the ingredient under drug preclusion.[14] Each of these cases creates compelling inequities by signaling to a company that the article is a legitimate dietary ingredient, only to reverse course after business decisions have been made in reliance on FDA's statements.

With NMN, in November 2022, FDA reversed its determination related to NMN's legality as a dietary ingredient "[b]ased on new information that came to light when we were reviewing another notification."[15] This new information was a statement by Metro International Biotech, LLC ("MetroBiotech"), a drug company, alleging that an ingredient being studied by that company

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[8] FDA, Policy Regarding N-acetyl-L-cysteine: Guidance for Industry (August 2022) (stating that "FDA intends to exercise enforcement discretion until either of the following occurs: we complete notice-and-comment rulemaking to allow the use of NAC in or as a dietary supplement . . . or we deny the NPA citizen petition's request for rulemaking"). This same guidance indicates that FDA would move forward with rulemaking unless the agency identified any safety-related concerns for NAC. NAC has been sold safely for decades as a dietary supplement, with no safety issues raised by FDA. Further companies provided FDA with NAC safety data, at FDA's request, in January 2022. Over a year later, FDA has neither identified any safety-related concerns, nor moved forward with rulemaking.

[9] *See* Letter from FDA CFSAN to SyncoZymes Co., Ltd., Regarding NDIN 1247 (May 16, 2022).

[10] *See* Letter from FDA CFSAN to Willy Chemicals, Inc., Regarding NDIN 1174 (Nov. 2, 2020); Letter from FDA CFSAN to Willy Chemicals, Inc. Regarding NDIN 1189 (Feb. 11, 2021); Letter from FDA CFSAN to Willy Nutra, Inc. Regarding NDIN 1234 (Jan. 18, 2022).

[11] *See e.g.,* SFC 2020-000700, Yiling Pharmaceutical, Inc. – NMN Nicotinamide Mononucleotide Dietary Supplement-30 Vegetarian Capsules (June 26, 2020); SFC 2020-001267, Seneque-Elevant (Dec. 2, 2020).

[12] *See* CRN NAC Citizen Petition (June 2021).

[13] *See* NDI notifications from Amrion Inc., Leiner Health Products, General Nutrition Corporation, and Pharmavite Corporation, compiled at https://www.fda.gov/media/160660/download.

[14] FDA Request for Comment on the Status of Vinpocetine (Sept. 7, 2016).

[15] Letter from FDA CFSAN to SyncoZymes Co., Ltd Regarding NDIN 1240 and 1247 (Nov. 4, 2022).

was the same "article" as NMN.[16] This ingredient appears only to be referenced as MIB-626 in public information regarding clinical trials for the ingredient, making it impossible for a supplement company to determine that MIB-626 and NMN are the same article. Further, clinical trials for MIB-626 appear to be in the preliminary phase, not likely meeting the threshold for substantial clinical investigation. FDA has taken the position that the existence of a non-public investigational new drug (IND) application that has gone into effect for MIB-626, and the preliminary studies cited by MetroBiotech, preclude NMN supplement use.

The actions of the agency are particularly egregious here where FDA permitted companies to move forward with investments in safety research, completing the NDIN process, and committing funding to marketing and advertising, without objecting to the ingredient's use under drug preclusion. The agency has confirmed the safety of NMN through the NDIN process and is now blocking supplement use based on confidential data. When FDA staff at the Center for Food Safety and Applied Nutrition (CFSAN) acknowledged the May 2022 NDIN with no objection, it appears that FDA staff was not even aware of the purported IND for NMN, demonstrating the danger and unfairness of using non-public data to trigger drug preclusion protection—if FDA staff are not even able to discern whether drug preclusion protection attaches to an ingredient, how could dietary supplement companies make this determination and make informed decisions about the commercial success of such new ingredients?

C. DSHEA's Purpose is Clear – Preserve Public Access to Dietary Supplements; FDA's Interpretation of Drug Preclusion Reduces Access.

By enacting DSHEA, Congress aimed to preserve public access to dietary supplements as the statute explicitly states:

> It is the purpose of this Act to . . . improve the health status of the people of the United States and help constrain runaway health care spending by ensuring that the Federal Government erects no regulatory barriers that impede the ability of consumers to improve their nutrition through the free choice of safe dietary supplements.[17]

Contrary to that stated purpose, FDA has increasingly interpreted section 201(ff)(3)(B) over nearly three decades in a manner that overly advantages drugs at the expense of dietary supplements. The continued reading of the drug preclusion provision in deference to drug company interests runs contrary to the statute's text, structure, history, and purpose. Because the statute lacks ambiguity, under settled statutory interpretation principles, FDA's contrary interpretation is not entitled to deference.[18] Further, the agency's interpretations are

[16] Letter from Metro International Biotech, LLC to FDA (Dec. 1, 2021).
[17] Congressional Record, H1173, Oct. 6, 1994 (House Passage of S. 784).
[18] *See, e.g., SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1358 (2018) ("[W]e owe an agency's interpretation of the law no deference unless, after 'employing traditional tools of statutory construction,' we find ourselves unable to discern Congress's meaning.").

inconsistent and favor providing the broadest protections to drug interests. FDA's only consistent interpretation of drug preclusion has been to adopt the broadest possible reading to further the interest of drug companies at any cost—to the detriment of supplement companies and consumers. A court is unlikely to uphold such a strangled interpretation of the statute.[19]

D. FDA's Approach to Interpreting Drug Preclusion Statutory Language is Inconsistent, Ignores Important Statutory Construction Principles, and Negates the Purpose of DSHEA

1. The preclusion date is the date the existence of substantial clinical trials are made public, not a non-public IND authorization date, or any other date which does not provide a clear starting point for prospective marketers

Under section 201(ff)(3)(B)(ii), an article is precluded from the supplement definition if three criteria are met: (1) the article is authorized for investigation as a new drug; (2) substantial clinical investigations have been instituted; **and** (3) the existence of such investigations has been made public. FDA has taken the position that for an article to avoid preclusion it must have been marketed as a dietary supplement or food before the date the article was authorized for investigation (element #1),[20] even though the statute indicates that an ingredient is only precluded if all three elements are met. According to FDA, "[t]he 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 . . . ."[21] There is no set date when an IND goes into effect and is dependent upon confidential communications from FDA to the IND holder.[22] FDA is prohibited from disclosing even the existence of an IND, let alone the effective date. In the case of NMN, the effective date is still not known to dietary supplement companies.[23]

To interpret other provisions of the drug preclusion language, FDA relies heavily on the principle that "[u]nder cannons of statutory interpretation, the text of a statute must be read as a whole and in accordance with the statute's structure and purpose."[24] The agency has referred to this as the "whole act" principle of statutory interpretation.[25] FDA's interpretation of the IND preclusion

[19] In the one court case analyzing the legal validity of how FDA interprets drug preclusion (involving the meaning of the term "article"), which FDA heavily relies upon in support of its interpretations involving other drug preclusion language, the court found FDA's interpretation valid because it "comport[ed] with common sense and the overall purpose of the [FD&C Act]". *Pharmanex v. Shalala,* 221 F. 3d 1151, 1159-60 (10th Cir. 2000). The interpretations challenged by CRN do not comport with common sense and the overall purpose of the statute; but rather create non-sensical outcomes, are inconsistent in their use of statutory interpretation tools, and overly favor drug interests in conflict with DSHEA's purpose to preserve supplement access.

[20] FDA, Draft Guidance for Industry: New Dietary Ingredient Notifications and Related Issues, at 43- 44 (Oct. 2016).

[21] Letter from FDA CFSAN to Inner Mongolia Kingdomway Pharmaceutical Limited, Regarding NDIN 1259 (Nov. 4, 2022) at 2 ("FDA Letter to Kingdomway").

[22] 21 C.F.R. § 312.40(b).

[23] 21 C.F.R. § 312.130(a).

[24] FDA Letter to Kingdomway (Nov. 4, 2022) at 4, citing 2A Norman J. Singer & J.D. Shambie Singer, *Sutherland Statutes and Statutory Construction* § 46.5 (7th ed., Nov. 2021).

[25] FDA Letter to Kingdomway at 7.

date as the first element of a multi-pronged list that must be satisfied for a drug to preclude supplement use appears to violate all of these principles.

Congress' purpose when enacting the IND provision of drug preclusion is confirmed by a compilation of and commentaries upon the legislative history written by attorneys who participated in DSHEA's drafting. FDA relies on these same experts and the same legislative history to support the agency's interpretation of other DSHEA provisions. Specifically, these experts identified publicizing the existence of substantial clinical investigations as the key element of preclusion under section 201(ff)(3)(B)(ii).

> "This provision added investigational new drugs for which substantial investigations had been completed *and publicized* to the mix of ingredients that presumptively are not dietary ingredients. In the legislative history, for this section, the term "substantial clinical investigations" was explained as not including "compassionate investigational new drug applications or an [IND] submitted by a physician for a single patient." Thus, sporadic investigation by clinics, independent physician trials, or other secret drug investigations into dietary ingredients cannot form the basis for presumptive exclusion as dietary ingredients. If a drug researcher seeks the protection of this provision, the researcher must publicize the data. Making an investigation public protects dietary supplement manufacturers from having their product franchises removed by secret investigations."[26]

Reading the IND effective date as the preclusion date in the manner advanced by FDA completely nullifies section 201(ff)(3)(B)(ii)'s purpose and renders the term "public" meaningless. The legislative history cited above makes clear that the "public" element of this section is key to both the attachment of benefits for drug companies and the protection of dietary supplement companies. If a company is able to backdate the protection to a time before data is publicly available, drug companies are being afforded the preclusion protections well before an article meets the defined preclusion criteria, and supplement companies can have "their product franchises removed by non-public, secret investigations."

Further, because IND effective dates are not public, this interpretation creates a non-sensical scenario where supplement companies will have no way to know if a substance was marketed as a food or dietary supplement before the IND trigger date. Why would Congress require a drug company to publicize the existence of substantial clinical investigations if the trigger date for preclusion was meant to be the non-public IND authorization date? Under FDA's interpretation, publication becomes meaningless for dietary supplement company interests because they have no way to assess whether an ingredient was marketed as a food or supplement before the IND trigger date. Supplement companies are stripped of the protection that publicizing data afforded them in their determination of whether FDA would consider an ingredient precluded. Any

[26] I. Scott Bass & Anthony L. Young, *The Dietary Supplement Health and Education Act: A Legislative History and Analysis* (1996) at 36.

ingredient for which an IND has been submitted to FDA has the potential now to block supplement use regardless of when studies were made public, or the ingredient was first marketed in a dietary supplement or food.[27]

This scenario is exactly what has happened with NMN—drug preclusion protections have been attached to a dietary ingredient using a secret date, well before any date that it could be argued that substantial clinical investigations were made public. Dietary supplement companies have been told by FDA to remove their NMN supplements from the market because non-public, secret investigations were underway before NMN was marketed as a supplement or food. Evidence demonstrating when NMN may have first been marketed as a food or dietary supplement is meaningless to these companies because the IND preclusion date is secret.

The structure of the rest of the drug preclusion language in section 201(ff)(3)(B) further underscores the invalidity of FDA's interpretation. The marketing date trigger clause includes other actions that can preclude supplement use if supplement or food marketing does not occur first. The full text of this phrase reads "which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food." The words "approval," "certification," and "licensing" refer back to clauses included within section 201(ff)(3)(B)(i) and that are all qualified by other language; just as the term "authorization" refers back to a clause included within section 201(ff)(3)(B)(ii) and is qualified by other language. It is clear by this structure that the phrase "such approval, certification, licensing, or authorization" refers back to the preceding sections and their qualifying language. To not have to repeat the lengthy phrases relevant to each preclusion condition, Congress simply used the first term in each phrase as shorthand to refer to the entire qualifying phrase.

Finally, FDA's interpretation removes important fairness policy protections for dietary supplement companies that Congress acknowledged by ensuring that an ingredient would not be precluded until the substantial clinical investigations were made public. By including this language, dietary supplement companies would be put on notice that FDA could consider an ingredient precluded. Based on FDA's interpretation, however, and the exact situation we saw unfold with NMN, a dietary supplement company can unknowingly invest significant resources researching and developing a dietary ingredient, only to have it removed from the marketplace.

[27] In addition to the fact that supplement companies have no way to determine compliance, an IND can remain in effect secretly for many years—and sometimes indefinitely. As long as Phase 1 studies are ongoing, an IND can remain in effect endlessly and without public disclosure. This creates an obscure, protracted, and potentially boundless period before the other two triggers could be met, precluding supplements from the market. FDA can terminate an IND, but only after many years and after certain conditions are met. For example, if an IND has been on clinical hold for at least 1 year or no subjects have been entered into clinical studies for at least 2 years, FDA may place the IND on inactive status. FDA may terminate—but is not required to terminate—an IND that has been inactive for at least 5 years. 21 C.F.R. § 312.45(e) ("An IND that remains on inactive status for 5 years or more ***may*** be terminated . . ." (emphasis added)). Thus, an IND—whether active or inactive—could persist covertly for many years, creating a real risk that any new dietary ingredient a supplement company markets could be pulled from the market at any point after which a drug company moves forward with clinical trials under that IND and makes the studies public.

If the triggering date is not made public, how is a supplement company to know whether it can market an ingredient as a supplement. This is a fundamental aspect of fairness. Drug companies, according to FDA's interpretation, get the benefit of drug preclusion at the beginning of their investment period, whereas dietary supplement companies must engage in significant investment to lawfully bring an ingredient to market, such as by conducting safety studies and submitting an NDIN to FDA, before any protections allowing the ingredient to remain on the market as a dietary supplement take effect.

2. "Marketing" as used in section 201(ff)(3)(B) is not limited to marketing in the United States

Where FDA attempts to interpret the statute narrowly for the IND preclusion date in a manner that ignores the statute's structure and purpose and is detrimental to supplement interests, the agency relies on this "whole act" principle of statutory interpretation referenced above to broadly interpret other sections in favor of drug interests. In response to FDA's determination that NMN was subject to drug preclusion because it was not marketed before the IND went into effect, one company provided evidence that NMN had been sold as a dietary supplement as early as 2016. FDA has taken the position that this evidence is irrelevant because "marketing" in section 201(ff)(3)(B) refers to "marketing in the United States."[28]

In making this determination based on the "whole act" principle, FDA ignores other key rules of statutory interpretation. Specifically, 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."[29] Section 201(ff)(3)(B) does not use the term "in the United States" anywhere in that section. Other sections of DSHEA, however, do. FDA has found this dispositive in other situations in which it has had to interpret the meaning of section 201(ff)(3)(B). For example, in response to CRN's citizen etition regarding the legality of NAC, FDA relied on Congress' inclusion of specific text in one section of DSHEA, but not others, as support for the proposition that Congress intended section 201(ff)(3)(B) to apply retroactively.[30]

With regard to retroactive application, FDA stated that "when Congress wanted DSHEA to set different requirements for products first marketed before DSHEA's enactment and those first marketed after it, it did so clearly in the statutory text."[31] Section 413 of the FDCA, added by DSHEA, defines 'new dietary ingredient' as 'a dietary ingredient that was not marketed in the

[28] FDA Letter to Kingdomway (Nov. 4, 2022) at 7.
[29] *Russello v. United States*, 464 U.S. 16, 23 (1983) (citations omitted).
[30] Letter from FDA CFSAN to CRN and the Natural Products Association (NPA) (March 31, 2022) at 11 ("FDA Letter to CRN and NPA"). CRN had argued that the presumption against statutory retroactivity and drug preclusion's purpose made it clear that drug preclusion should not be interpreted to remove dietary ingredients from the market that had existed as both a food or dietary supplement and a drug (or had been substantially studied as a drug) prior to DSHEA's enactment regardless of which use was first.
[31] *Id.*

United States before October 15, 1994.'"[32] FDA cited section 413 in response to the CRN NAC Citizen Petition as evidence that had Congress meant to limit the drug preclusion scope to post-DSHEA enactment (*i.e.*, that it would not apply "before October 15, 1994") they would have specifically stated this, just as they did in other DSHEA sections.

Section 413 also is relevant to the current issue—that FDA believes "marketing" when used in 201(ff)(3)(B) refers to "marketing in the United States." Section 413 uses the term "in the United States" – clearly imposing a geographical limitation within the definition of new dietary ingredient and demonstrating that when Congress wanted DSHEA provisions to be limited to the United States, it did so clearly in the statutory text. The use of phrases in one section of DSHEA, but not others, was dispositive for FDA in determining drug preclusion's retroactive application. The agency went as far as to note that this inclusion of language in one section but not the other removed any ambiguity in statutory interpretation and made "FDA's interpretation . . . the only possible reading of the statutory text."[33] It should be dispositive here as well. Conversely, if FDA finds that language used in one section of DSHEA but not others is not dispositive here (*i.e.*, "marketing in the United States"), then it should not hold that the language omission has a bearing on Congress' retroactive application of the drug preclusion clause ("before October 15, 1994").[34]

In adding a geographic limitation to the scope of marketing in the drug preclusion clause, FDA indicates that it must look at the "the physical and logical relation of [DSHEA's] many parts."[35] FDA goes on to argue that the preclusion conditions listed in section 201(ff)(3)(B) were drafted in the context of U.S. law and the U.S. marketplace and the statute directs FDA to compare the date these U.S. drug conditions were met to the date that a substance is "first marketed as a dietary supplement or as a food" for the purposes of the preclusion date. According to FDA, this context "indicates that Congress intended 'marketing as a dietary supplement or as a food' to be

[32] *Id.*
[33] *Id.*
[34] CRN also wants to take this opportunity to point out that FDA appears to have misunderstood CRN's position on "retroactive application" of the preclusion clause as raised in our citizen petition on NAC. CRN takes the position that the preclusion clause should not remove dietary supplements from the market that coexisted as both a food or supplement and a drug prior to DSHEA's passage. In its response, FDA raises concerns about supplement companies marketing an article post-DSHEA that is the same article as a drug approved or IND authorized pre-DSHEA. They point to lovastatin, the same article in the prescription drug Mevacor, which FDA approved in 1987 (pre-DSHEA). Standardized lovastatin levels (which was FDA's concern with lovastatin preclusion), according to FDA, were not used in dietary supplements until post-DSHEA. FDA Letter to CRN and NPA (March 31, 2022) at 15. This is not CRN's position – acknowledging that drug preclusion should not have a retroactive effect to remove pre-DSHEA grandfathered supplements from the market is not the same as pre-DSHEA drug approvals blocking new dietary ingredients from entering the market post-DSHEA. NAC as a supplement and a drug co-existed prior to DSHEA passage – nothing in the drug preclusion language or Congress's purpose in enacting this language suggests that grandfathered supplements should be removed from the market Lovastatin is not the same as NAC – the use of standardized levels of lovastatin, based on FDA's determination, did not co-exist with Mevacor prior to DSHEA's passage.
[35] FDA Letter to Kingdomway (Nov. 4, 2022) at 7.

evaluated in the context of U.S. law and the U.S. marketplace."[36] Congress, however, had a reason to draft the drug preclusion conditions in the context of U.S. law without that language being relevant to where a food or supplement was marketed. Congress was concerned with protecting the U.S. drug approval process and research investments intended to support U.S. drug approval. A substance's status as a drug or research investments for approval as a drug in another country have no bearing on whether a company could usurp U.S. drug approval requirements by offering a substance in the U.S. as a dietary supplement or disincentivize U.S. drug research and development. Congress could have explicitly used the term "in the United States" to qualify the scope of "marketing" if that was their intention, as they did for the definition of new dietary ingredient, but they did not. And while marketing, or even publicly investigating, an ingredient as a drug somewhere else in the world should not give drug manufacturers in the U.S. monopoly status over that ingredient, the reverse is not true: marketing the ingredient in food or supplements anywhere in the world *should be* sufficient to alert drug manufacturers that their unique molecule is not so novel, and thus, not deserving of drug preclusion and the permanent prohibition on marketing the ingredient in a dietary supplement.

FDA also argues that the date of first marketing should be determined by U.S. marketing because other countries many define regulatory categories like foods and dietary supplements differently than they are defined in the U.S. Not being precluded from the definition of dietary supplement under 201(ff)(3)(B), however, is not the same as FDA permitting a substance to be distributed in the U.S. as a legal dietary supplement – it just means the substance is still eligible to be a supplement if it meets all the other U.S. dietary supplement criteria.

3. "Marketing" as used in section 201(ff)(3)(B) is not limited to "legal" marketing as espoused by FDA; evidence of marketing as a food or dietary supplement should be dispositive, unless FDA has met its statutory burden of demonstrating that the marketing was unlawful

The requirement of dietary supplement marketing here is intended only to serve as a marker to drug companies to put them on notice that a dietary supplement already exists that includes the ingredient, and thus, they proceed with expensive drug development of that same article at the own risk. The considerable research investment they incur going forward may, or may not, be lucrative or recoupable. Legal marketing is not necessary to provide notice that the article may already be available to consumers as a supplement or as a food.[37] Like with adding the term

[36] *Id.*

[37] For NMN, it appears that MetroBiotech – the drug company now objecting to NMN's use as a supplement – was aware of supplement marketing. MetroBiotech founder David Sinclair, as early as 2018, talks about his use of NMN in response to consumer questions about what supplements they should be taking. *See e.g.,* June 25, 2018 Twitter article by Dr. Sinclair, available at https://www.linkedin.com/pulse/advice-article-david-sinclair/ (last visited May 9, 2023). He also talks extensively about NMN supplement use in his 2019 book, acknowledging that he uses NMN as a supplement, as does his father and colleagues' families. D. Sinclair, *Lifespan: Why We Age and Why We Don't Have To*, Atria Books (2019) at 138, 142 (noting that NMN is "available as a supplement"), and 304. *See also,*

"United States" to the marketing requirement, FDA reads the word "legal" into the statute where it does not exist or need to exist to serve the law's purpose. Further, at a minimum, marketing should be presumed legal, for purposes of this section, unless FDA has met its statutory burden that the marketing was unlawful.

With regard to precluding NMN, FDA dismissed evidence of NMN marketing as a food or dietary supplement in the United States as irrelevant because, according to FDA, the marketing was unlawful. FDA supports this determination by pointing to the requirements for drug approval and IND authorization included as part of the preclusion trigger. This is a false equivalence between the drug approval/IND authorization process and food and dietary supplement legality in the U.S. Drug approval and IND authorization require an FDA action before a substance is deemed legal to be used in the manner described in the drug preclusion clause. Food and dietary supplements are not subject to such pre-approval processes.

In the case of NMN, FDA challenged the evidence of NMN's marketing prior to the IND authorization because "the companies in question did not submit NDI notifications for their NMN products." FDA goes on to note that "dietary supplements that are marketed without a required NDI notification are adulterated under section 413(a) of the FD&C Act." Section 413 directs that a supplement is adulterated only if certain conditions are not met as dictated by section 402(f). Section 402(f) places the burden of establishing that these conditions are not meet on FDA and requires that "[i]n any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis." [38] With regard to NMN, FDA has not met this burden.

Not only has FDA not meet its burden, but most of FDA's drug preclusion interpretations remain difficult if not impossible to challenge because FDA makes these interpretations in warning letters and through other mechanisms that are not considered final agency action. Because of their informal status, there is generally no way for parties who disagree with these actions to challenge them in court, and indeed, courts have rejected such challenges as not ripe for judicial review.[39] If a party tries to challenge FDA's NMN NDIN no-objection reversals, it's likely that FDA will argue that these determinations are not final agency actions. Without a final agency action and opportunity for affected companies to seek judicial review, companies are left in limbo to determine if conduct would actually be deemed violative of the FDCA.

Harvard Medical School, The Sinclair Lab, David A. Sinclair's Affiliations, available at https://sinclair.hms.harvard.edu/david-sinclairs-affiliations (last visited May 9, 2023) (listing his affiliations with MetroBiotech (2015 – present) as a founder, investor, equity, advisor/consultant, board of directors, and inventor on licensed patents).

[38] I. Scott Bass & Anthony L. Young, *The Dietary Supplement Health and Education Act: A Legislative History and Analysis* (1996) at 42, n. 18 (These experts also make the case that "[a]rguably, the failure to notify the FDA under section 413 does *not* make out a *prima facie* case of adulteration because it is not a separate cause of adulteration under section402(f)").

[39] *See e.g.,* Memo from Covington & Burling LLP to CRN, July 28, 2021 (available to the public and FDA and linked in this citizen petition).

To make an equivalence argument that marketing must be lawful in a manner that drug approval and IND authorization make drug use lawful, FDA should be required to demonstrate that it has met its statutory burden of establishing that the supplement or food marketing in question was in fact not lawful. Otherwise, drug companies are provided clear preclusion criteria based on a specific FDA action and supplement companies are left vulnerable to market removal based on tentative FDA decisions.

4. "Substantial clinical investigations" refers only to clinical trials that are adequately designed and powered to support drug approval and does not refer to Phase I clinical trials

Section 201(ff)(3)(B) excludes from the dietary supplement definition only articles for which "*substantial* clinical investigations" have been instituted. The statute does not define "substantial clinical investigations," thus creating significant uncertainty for stakeholders in both the pharmaceutical and dietary supplement industries who seek to understand the scope of section 201(ff)(3)(B). That said, both fundamental principles of statutory interpretation and relevant public policy considerations indicate that this term should be read to refer only to clinical trials that are adequately designed and powered to support drug approval, which, at minimum, should exclude Phase I clinical trials.[40] CRN requests that FDA affirm this conclusion, and that FDA provide clear guidance on when a clinical investigation constitutes a "substantial clinical investigation" for purposes of section 201(ff)(3)(B).

Congress's use of the word "substantial" in "substantial clinical investigations" conveys that it intended for this phrase to encompass more than mere "clinical investigations"—otherwise, Congress would have simply used the term "clinical investigations" without qualifying that these investigations need to be "substantial." FDA defines "clinical investigations" as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."[41] So, if "clinical investigations" refers broadly to all human clinical investigations (*i.e.*, Phase I-IV trials), then the statutory phrase "substantial clinical investigations" must refer only to a narrower, more robust subset of such investigations.

Under the "whole act" principle of statutory interpretation—which FDA has invoked elsewhere when interpreting section 201(ff)(3)(B) and we discuss in this petition [42]—FDA should determine what "substantial" means by looking to how related provisions of the FDCA define that term. The most relevant comparator is section 505(d) of the FDCA, which states that drug approvals must be supported by "*substantial* evidence" of effectiveness. The statute defines "substantial evidence" as follows:

[40] We incorporate by reference FDA's definitions of Phase I-III trials at 21 C.F.R. § 312.21(a).
[41] 21 C.F.R. § 312.3(b).
[42] FDA Letter to Kingdomway (Nov. 4, 2022) at 7.

> 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.[43]

Applying a similar definition of "substantial" here, "substantial clinical investigations" should be read to encompass only investigations capable of producing "substantial evidence" of effectiveness (*i.e.*, only investigations from which "it could fairly and responsibly be concluded by [qualified scientific] 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"). This, at minimum, means that Phase I investigations should not be considered "substantial clinical investigations" under section 201(ff)(3)(B), and could be read to suggest that only "adequate and well-controlled" studies (as that term is defined by FDA[44]) should trigger preclusion under section 201(ff)(3)(B).

This interpretation is consistent with the statutory requirement for registering clinical studies for publication on clinicaltrials.gov, which applies only to "applicable drug clinical trials." The Public Health Service Act (PHSA) defines "applicable drug clinical trials" as "controlled clinical investigation[s], *other than phase 1 clinical investigation[s]*, of a drug [or biologic]."[45] The fact that Congress did not consider Phase I trials to be "applicable" trials for purposes of this requirement—*i.e.*, the fact that Congress chose not to require that information about such trials be published in the primary database through which stakeholders can identify authorized drug trials—provides further evidence that "substantial" trials under section 201(ff)(3)(B) do not include Phase I trials.

Finally, from a policy standpoint, interpreting "substantial clinical investigations" to refer only to clinical trials that are adequately designed and powered to support approval of a drug—and to specifically exclude Phase I trials—strikes an appropriate balance between Congress's overarching policy aims in passing DSHEA (*i.e.*, to facilitate consumers' access to healthy and innovative dietary supplements) and the policy aims behind section 201(ff)(3)(B) in particular (*i.e.*, to protect the pharmaceutical industry's research and development investments and prevent entities from subverting the drug approval process). This interpretation continues to provide robust protections for pharmaceutical companies by ensuring that when companies invest in progressing products beyond the early-stage clinical phase, those investments will be protected. At the same time, it ensures that section 201(ff)(3)(B) will not preclude consumers from accessing the broad range of products that never proceed beyond the early-stage clinical

[43] FDCA § 505(d) (emphasis added).
[44] 21 C.F.R. § 314.126.
[45] *See* 42 U.S.C. § 282(j); 42 C.F.R. §§ 11.10, 11.22 (emphasis added).

phases.[46] Thus, by adopting this interpretation and offering clear guidance on the meaning of "substantial clinical investigations," FDA can provide stakeholders in both the pharmaceutical and dietary supplement industries with the certainty needed to foster crucial investments and innovation across product categories.

E. The agency's prior affirmative statements recognizing the legal status of a particular article as a legal dietary ingredient prevents FDA from subsequently reversing that decision on the grounds of drug preclusion

As has been argued throughout this petition, FDA's determinations about the lawfulness of an ingredient have substantial consequences for dietary supplement manufacturers and marketers and for consumers. The factual circumstances of each case vary, but ingredients like pyridoxamine, vinpocetine, NAC, and NMN were each marketed as dietary supplements either with FDA's express allowance or without FDA objection, only to have drug preclusion invoked by FDA later to remove the ingredients from the supplement marketplace. During that time, and in reliance on FDA's action or inaction, consumers have come to rely on these products to promote their good health and well-being, just as DSHEA intended. Manufacturers made considerable investments to source the ingredients, develop innovative delivery forms, and scale up production. Marketers devoted considerable resources to promote the availability of the ingredients as supplements and advertise their health benefits.

And each time, FDA pulled the rug out from under consumers and these companies with its post hoc reversal. In attempting to remove these ingredients from the market, FDA is denying consumers access to products that otherwise meet the definition of a dietary ingredient for reasons other than their safety. That directly contravenes the intent of DSHEA to ensure consumer access to safe and beneficial products. FDA should recognize the gross inequities of these decisions and immediately move to recognize these articles "would be lawful under this Act."

F. Conclusion

It strains credibility to suggest that Congress would have intended to create a scenario in which innovative supplement manufacturers could discover a novel health-related use for an ingredient, scour the publicly available literature and find no indication that it was being used in substantial clinical investigations as a drug, then develop their own safety and efficacy research, and invest in marketing the ingredient in a supplement, to then have the ingredient precluded from supplement use based on limited clinical study of an ingredient and non-public,

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[46] *See* FDA, The Drug Development Process - Step 3: Clinical Research, https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#:~:text=In%20Phase%202%20studies%2C%20researchers,the%20drug%20will%20be%20beneficial (indicating that while approximately 70% of drugs move past Phase I, only approximately 33% of drugs subject to phase II trials progress beyond that stage, and only approximately 25-30% move of those drugs move beyond Phase III).

undiscoverable information that is only available to certain FDA offices. Yet that scenario is precisely what the collection of FDA interpretations of this section have effectively created. As we have demonstrated in this petition, FDA's approach to drug preclusion language interpretation has served one purpose – to favor drug interests over supplements in a manner that is inconsistent, ignores important statutory construction principles, and negates the purpose of DSHEA.

The public health benefits from robust innovation in both the supplement and pharmaceutical categories, ensuring consumers have access to a wide array of safe and beneficial ingredients for a number of purposes. Drugs occupy an important lane allowing ingredients to be to be studied and used to treat disease under very specific conditions and often at higher doses than can be found in supplements; while supplement use preserves access to ingredients for general non-disease uses, ensuring consumers are not unnecessarily barred from using safe and beneficial ingredients. The demands to appropriately balance these interests are clear based on Congress' purpose in enacting DSHEA and what we ask FDA to do here. Reversing the agency's position as we have requested here and providing guidance for the discretionary use of rulemaking under drug preclusion help ensure DSHEA is read consistently and fairly to the benefit of public health.

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Environmental Impact Statement

CRN maintains that the actions requested in this petition are exempt from the requirement to provide an environmental impact statement pursuant to 21 C.F.R. § 25.30(h).

Economic Impact

Information on the economic impact of this proposal can be provided if requested.

Certification

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

Sincerely,

Steve Mister
President & CEO

Megan Olsen
Senior Vice President & General Counsel