



Council for Responsible Nutrition

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March 14, 2018

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition from ViGuard Health Inc. Docket No. FDA-2017-P-6245.

Dear Sir or Madam:

The Council for Responsible Nutrition (CRN), the leading trade association for makers and marketers of dietary ingredients, dietary supplements and functional foods,¹ respectfully submits these comments in support of the Citizen Petition submitted by ViGuard Health (the petitioner) on October 23, 2017.² In its Citizen Petition, ViGuard Health requests the following actions:

1. ViGuard Health requests that the FDA issue a regulation declaring pyridoxamine is no longer an article authorized for investigation as a new drug, and therefore is not excluded from the definition of dietary supplement under 21 U.S.C. §321(ff)(3)(B)(ii).

¹ The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing more than 150 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.

² Citizen Petition from ViGuard Health Inc. (Oct. 23, 2017). <https://www.regulations.gov/document?D=FDA-2017-P-6245-0001>.

CRN Comments on Pyridoxamine

March 14, 2018

Page 2

2. If the FDA denies Action(1), ViGuard Health requests the FDA uses its discretionary authority under 21 U.S.C. §321(ff)(3)(B)(ii) to create an exception to the statute, issuing a regulation authorizing pyridoxamine to be marketed as a dietary supplement.
3. ViGuard Health requests that the FDA affirm pyridoxamine is a vitamin and therefore a dietary supplement under 21 U.S.C. §321(ff)(1)(A).

CRN urges FDA to reassess the regulatory status of pyridoxamine in light of new information regarding the status of investigational new drug applications (INDs) for which pyridoxamine is the subject. CRN maintains that pyridoxamine was marketed in dietary supplements prior to the effective date (September 1, 1999) of the IND for Pyridorin (pyridoxamine dihydrochloride). We provided evidence of prior marketing of pyridoxamine in dietary supplements in our comments to the Biostratum Citizen Petition dated July 29, 2005. However, the central issue in the current petition is of broad interest to the dietary supplement industry and we appreciate the opportunity to provide further comments. The issue is whether an article that was once the subject of an IND is permanently excluded from the dietary supplement definition under the “prior marketing clause” in 21 U.S.C. §321(ff)(3)(B)(ii). CRN urges that it is not.

CRN agrees with the petitioner that the prior marketing clause was intended to create fairness for pharmaceutical companies that intend to bring an article to market as a new drug and have invested in substantial clinical investigations in the process and that this protection should only be necessary and appropriate so long as the article is still in the drug development process. Under certain circumstances, this prior marketing clause should no longer apply, such as when all INDs for the article have been permanently terminated, and thus, no longer in effect. And without any IND in effect, an article is not authorized for investigation as a new drug under 21 U.S.C. §321(ff)(3)(B)(ii) and cannot be excluded from the dietary supplement definition under this section.

If such an article meets the definition of a dietary supplement under 21 U.S.C. §321(ff) and all other requirements of the statute, including, as applicable, requirement for notification of new

CRN Comments on Pyridoxamine

March 14, 2018

Page 3

dietary ingredients to FDA, then it should be allowed on the market in or as a dietary supplement. Such is the case with pyridoxamine.

In FDA's recently issued Revised NDI Draft Guidance, the agency states in Section IV.D.11 that "withdrawal of the IND and cessation of clinical trials of the ingredient's use as a new drug make no difference in whether the ingredient may be used in a dietary supplement" and that "Authorized for investigation" in 21 U.S.C. §321(ff)(3)(B)(ii) means that "the article is the subject of an IND that has gone into effect (see 21 CFR 312.40)."³ FDA's interpretation of "authorized for investigation" in the Revised NDI Draft Guidance is permissible for the purpose of determining a reference date that is inherently required to interpret the portion of 21 U.S.C. §321(ff)(3)(B)(ii) which permits the continued sale of dietary supplements containing an article that was marketed as a dietary supplement or as a food prior to the article's authorization for investigation as a drug. Under 21 CFR 312.40, an investigational new drug may not be used in a clinical investigation before the effective date of the IND, which is 30 days after FDA receives the IND unless investigations are placed on a clinical hold.⁴ Thus, the effective date of the IND serves to prompt the sponsor when it may begin to use an investigational new drug in a clinical trial. The effective date of an IND is the authorization date of an article for investigation as a new drug.

However, "authorized for investigation" within the meaning 21 U.S.C. §321(ff)(3)(B)(ii) cannot be construed as "permanently" authorized for investigations, or that once given an effective date, an IND always remains in effect. FDA's interpretation in the Revised NDI Draft Guidance is contrary to the FDCA provisions governing the use of investigational new drugs as well as FDA's own policy regarding the discontinuation of INDs.⁵ The fact that FDA has the authority to

³ Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues [NDI Draft Guidance], FDA (Aug. 2016), <https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf>.

⁴ 21 CFR 312.40(b).

⁵ Food and Drug Administration, Center for Biologics Evaluation and Research. SOPP 8206: Discontinuing Investigational and Related Applications (IRAs). Available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM586345.pdf>

CRN Comments on Pyridoxamine

March 14, 2018

Page 4

terminate INDs under 21 CFR 312.44 to effectively require the sponsor to end all clinical investigations conducted under the IND means that such authorization can be rescinded. Under the statute, FDA may terminate an IND on various grounds, including when the sponsor fails to submit an accurate annual report of the investigations in accordance with 21 CFR 312.33 or when the IND has been on inactive status for five years or more.⁶ According to FDA's own policy written in SOPP 8206, IND terminations are permanent and clinical studies may be resumed only upon submission of a new IND. The one exception is when an IND is terminated by FDA under 21 CFR 312.44(d), in which case the IND may be reinstated by the agency. It follows that once permanently terminated, an IND is no longer in effect. At the time when all INDs involving the article cease to be in effect, the article is no longer an article authorized for investigation as a new drug and should not be excluded from the dietary supplement definition under 21 U.S.C. §321(ff)(3)(B)(ii).

Under 21 CFR 312.38, a sponsor may withdraw an effective IND for any reason. If an IND is withdrawn, FDA is notified and all clinical investigations conducted under the IND shall be ended.⁷ It follows that withdrawn INDs ultimately become permanently terminated under 21 CFR 312(b)(viii) for failure to submit annual reports in accordance with CFR 312.33.

Further, FDA has procedures in place to determine an IND as "no longer effective" and terminate it. In accordance with SOPP 8206, the agency regards an IND "no longer in effect/approved" if a sponsor of an active IND dies. SOPP 8206 states, "if it is determined that no studies have continued after the sponsor's death, the IND should be **Terminated** for failure to submit progress reports...." In accordance with the statute and FDA policy, termination of an IND is a permanent and final action—with one exception provided in 21 CFR 312.44(d)—that effectively rescinds the authorization of the IND, making it no longer effective; thus, the article that is the subject of a terminated IND is no longer "authorized for investigation" as a new drug under 21 U.S.C. §321(ff)(3)(B)(ii).

⁶ 21 CFR 312.44(x).

⁷ 21 CFR 312.38(b).

CRN Comments on Pyridoxamine

March 14, 2018

Page 5

Pyridoxamine became the subject of an effective IND on September 1, 1999. On October 23, 2017, the petitioner provided information demonstrating that all INDs in which pyridoxamine was the subject have been withdrawn and that clinical investigations have ceased. If all such withdrawn INDs is determined to be permanently terminated, pyridoxamine would not be an article authorized for investigation as a new drug under 21 U.S.C. §321(ff)(3)(B)(ii). Moreover, so long as pyridoxamine meets all requirements under the statute, it should be lawfully marketed in or as a dietary supplement in the United States. CRN persists in its position, espoused in its 2005 comments (FDA-2005-P-0259), that pyridoxamine was indeed marketed as a dietary supplement prior to 1999, and indeed, even prior to October 15, 1994, making it an “old dietary ingredient,” which would not be subject to the requirements of new dietary ingredients in 21 U.S.C. §350b. However, even if that was not the case, pyridoxamine should not now be encumbered by the limitations of 21 U.S.C. §321(ff)(3)(B)(ii) whether by FDA’s proper interpretation of that provision, or by regulation issued by the Secretary as permitted by that provision. Any marketer willing to meet the requirements of 21 U.S.C. §350b and to demonstrate the ingredient is reasonably expected to be safe should be permitted to bring pyridoxamine to market as a dietary supplement.

Finally, FDA’s position in its Revised NDI Draft Guidance is not well-supported by law. 21 U.S.C. §321(ff)(3)(B)(ii) is warranted to prevent firms from misusing the protections afforded to pharmaceutical firms. The provision was enshrined in law and the discretion afforded to the Secretary to issue a regulation finding the article to be a lawful dietary supplement to assure that a substance that otherwise meets the definition of a dietary ingredient in 21 U.S.C. §321(ff)(1) is not unfairly snatched from consumer access by firms that would begin new drug investigations of the substance only to prevent its marketing as a supplement but never commercialize those outcomes. Without that protection, the intent of the Dietary Supplement Health & Education Act (DSHEA) to provide consumer access to a wide range of dietary ingredients could be limited by firms looking to prevent promising dietary ingredients from getting to market as dietary supplements.

CRN Comments on Pyridoxamine

March 14, 2018

Page 6

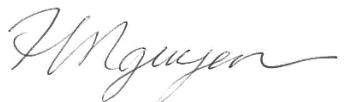
CRN thanks FDA for the opportunity to provide our views on this important issue and urges FDA to act swiftly to affirm ViGuard Health's requests to begin marketing pyridoxamine as a dietary supplement.

Sincerely,

A handwritten signature in black ink, appearing to read "Steve Mister".

Steve Mister

President and CEO

A handwritten signature in black ink, appearing to read "Haiuyen Nguyen".

Haiuyen Nguyen

Sr. Director, Scientific & Regulatory Affairs