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Citizen Petition

The undersigned submits this petition under 21 C.F.R. § 10.30 of the Federal Food, Drug, and Cosmetic Act (herein "the Act") to request the Commissioner of Food and Drugs (herein "the FDA" or "the Agency") to issue a regulation stating pyridoxamine is a dietary supplement as defined by the Dietary Supplement Health and Education Act of 1994 (herein DSHEA).

A. Actions Requested

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).
2. If the FDA denies Action (1), ViGuard Health requests that the FDA use 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).

B. Statement of Grounds

1. Summary

Pyridoxamine is one of the vitamers of the vitamin B6 family, which include pyridoxine, pyridoxal, and pyridoxamine. It has the same chemical structure as pyridoxine, the more common form of vitamin B_6, with the exception of an amino substituent at the 4' position which replaces a hydroxyl group. The combination of the phenolic hydroxyl at position 3 on the pyridine ring, and the aminomethyl group at position 4', endow pyridoxamine with a variety of chemical properties including the inhibition and scavenging of oxidative stress associated pathogenic chemistries including reactive oxygen species (ROS), reactive carbonyl species, and the binding of metal ions that catalyze post-Amadori oxidative reactions to form advanced glycation end-products (AGEs).

In July 1999, BioStratum Inc., a pharmaceutical company, filed an Investigational New Drug Application (IND) with the FDA to study pyridoxamine's potential use as a therapeutic agent to slow the progression of diabetic nephropathy. BioStratum sponsored several clinical studies of

pyridoxamine dihydrochloride under the trade name Pyridorin™, including two Phase 2a trials examining diabetic patients with moderate and advanced kidney disease. After the filing of the IND, BioStratum became aware that certain firms were marketing dietary supplements containing pyridoxamine. On July 29, 2005, BioStratum filed a citizen petition requesting the FDA:

> …(1) confirm in writing that dietary supplements that contain the drug pyridoxamine are adulterated under the Federal Good Drug and Cosmetic Act ("FFDCA or "the Act"); (2) exercise its enforcement authority under the FFDCA to remove dietary supplements containing the drug pyridoxamine from United States interstate commerce…[1]

On January 12, 2009, the FDA responded to BioStratum's petition, denying both requests. However, in their response, the FDA concluded that pyridoxamine was not a dietary supplement as defined in 12 U.S.C. § 321(ff). Specifically, they concluded, that pyridoxamine was excluded from being marketed as a dietary supplement under 12 U.S.C. § 321(ff)(3)(B), (herein the prior market clause). The prior market clause states that the term dietary supplement does not 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, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food."[2]

They concluded that there was no "verifiable, contemporaneous evidence documenting that pyridoxamine dihydrochloride or any other compound containing pyridoxamine as its active moiety was marketed as a dietary supplement or as a food prior to pyridoxamine's authorization for investigation as a new drug under an IND."[3] If such evidence existed, pyridoxamine would be classified as a dietary supplement under 12 U.S.C. § 321(ff)(3)(A).

On May 8, 2007, BioStratum licensed commercial rights for Pyridorin™ to NephroGenex Inc., who continued its clinical development. NephroGenex conducted and completed a Phase 2b study and initiated a Phase 3 study of Pyridorin™ as a treatment for diabetic nephropathy in patients with Type 2 diabetes. In February 24, 2016, NephroGenex was forced to pause the Phase 3 trial and ultimately terminate it later that year due to a lack of funding. The company subsequently filed for Chapter 11 bankruptcy on April 30, 2016.

NephroGenex shortly thereafter sought out a corporate partner for licensing or acquisition of Pyridorin™. The company retained the services of the investment banking firm Cassel Saltpeter and Co., LLC to secure a sale transaction for the Pyridorin™ asset. The firm identified 275 potential buyers and circulated 191 non-confidential presentations in their efforts to solicit an offer. In June, the company unblinded the truncated results of their Phase 3 study and shared it with prospective buyers. By September 2016, the firm had failed to consummate a transaction. NephroGenex then decided to sell all its assets, including Pyridorin™ through a bankruptcy

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[1] FDA Response to BioStratum Inc., Docket No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305). Page 1
[2] 21 U.S.C. 321 § 321(ff)(3)(B)(ii).
[3] FDA Response to BioStratum Inc., Docket No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305). Page 14

auction that was to be held on November 14th.[4] The company subsequently was forced to cancel the auction after it did not receive any qualifying bids. On December 16, 2016, the company filed a motion with the bankruptcy court, proposing a liquidation plan.

On August 24th, 2017, the Pyridorin™ IND #58,648 (filed July 30, 1999) for the prevention or slowing of the progression of diabetic nephropathy in type 1 and type 2 diabetic patients was formally withdrawn. Also on August 24th, 2017, IND #125,482 (filed November 11, 2015) to study an intravenous formulation of Pyridorin™ for the indication of patients at moderate to high risk for developing AKI following cardiac surgery, was also formally withdrawn. To the petitioner's knowledge, pyridoxamine is not the subject of any other active INDs.

Medpace, the Clinical Research Organization (CRO) that conducted the Pyridorin™ Phase 3 trial, proposed and received approval for a Plan Support Agreement which transferred ownership of NephroGenex to Medpace. The new NephroGenex, renamed Medpace Research Inc., has partnered with OxiPath Health Inc. to form the joint venture, ViGuard Health Inc., with the intention of marketing the oral formulation of pyridoxamine as a dietary supplement.

2. Argument

a. Pyridoxamine is not an Article Authorized for Investigation as a New Drug

Under the prior market clause, an article is excluded from the definition of dietary supplement if it is (1) authorized for investigation as a new drug, antibiotic, or biological; (2) for which substantial clinical investigations have been instituted; and (3) for which the existence of such investigations has been made public.[5] According to the FDA's Draft Guidance *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* published in August 2016 (herein draft guidance), an article authorized for investigation "means that the article is subject of an IND that has gone into effect."[6]

Pyridoxamine, the active pharmaceutical ingredient in Pyridorin™, was the subject of an IND for the prevention or slowing of the progression of diabetic nephropathy for 17 years, and another IND for the indication of patients at moderate to high risk for developing AKI following cardiac surgery for approximately 2 years. Both have been withdrawn. Since it is no longer the subject of an IND, pyridoxamine is no longer an article authorized for investigation, according to the definition given in the draft guidance. With the first element of the statute no longer satisfied, pyridoxamine should no longer be excluded from the definition of dietary supplement under the prior market clause.

The issue is whether the prior market clause should be interpreted to mean that an article that was authorized for investigation at one time is permanently excluded from the definition of a dietary supplement. To the petitioner's knowledge, the FDA has not addressed this specific issue

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[4] NephroGenex Inc., Case No. 16-11074-KG, DOC-147-1. U.S. Bankruptcy Court, Dist. Of Delaware.

[5] 21 U.S.C. 321 § 321(ff)(3)(B)(ii).

[6] U.S. Food and Drug Administration. (August 2016). *Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance For Industry*, Draft Guidance. Washington DC. Page 44.

in any guidance or administrative decision. Based on the language contained in the statute, the draft guidance, and the legislative intent behind the DSHEA, the exclusion is not permanent. By the definition provided in the draft guidance, an article authorized for investigation as a new drug "is subject of an IND that has gone into effect." The use of "is", the present indicative of be, means that the article must presently be the subject of an IND. If the IND is withdrawn or terminated,[7] the article is no longer the subject of an IND. Since INDs are not permanent in nature, an authorization for investigation is also not permanent.

The prior market clause ensures the DSHEA does not discourage drug companies from developing new drugs. It prohibits competing companies from marketing the same article without having to undergo the expensive drug approval process. In the Pharmanex Final Administration Decision (herein *Pharmanex*), the FDA found that the "DSHEA reflects Congress's determination that to allow such an article to be marketed as a dietary supplement would not be fair to the pharmaceutical company that brought, or intends to bring, the drug to market, and would serve as a disincentive to the substantial investment needed to gain FDA approval of new drugs."[8]

However, the prior market clause does not need to be applied as a permanent exclusion to fulfill its intended policy objective. Pharmaceutical companies require its protection so long as clinical investigations are ongoing on the article and there remains an intent to bring the drug to market. If clinical investigations have ceased and there exists no intent to continue its development, no company is harmed by finding the exclusion has lapsed.

In this case, the pharmaceutical company that intended to bring pyridoxamine to market is no longer pursuing its clinical development. In fact, the company intends to market it as a dietary supplement. Permitting its sale as a dietary supplement will not be unfair or undermine any drug development program. To the contrary, it suits the company's planned repositioning of pyridoxamine and gives consumers access to a new, safe, and beneficial dietary supplement.

Conversely, if the authorization for investigation element was interpreted to be permanent, it would be contrary to the legislative intent of the DSHEA. In enacting the law, Congress sought to encourage the development and marketing of new dietary ingredients. In Section 2 of the DSHEA, it states "Congress finds that although the Federal Government should take swift action against products that are unsafe or adulterated, the Federal Government should not take any actions to impose unreasonable regulatory barriers limiting or slowing the flow of safe products…"[9] Interpreting the prior market clause to be a permanent exclusion would impose an impassable regulatory barrier to new dietary ingredients with substantive clinical data establishing their safety and health benefits.

Since there are no known clinical investigations studying pyridoxamine as a drug, and the current owner of its commercial rights is seeking to market it as a dietary supplement, it is no

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[7] 21 C.F.R. 312.38, 21 C.F.R. 312.44.

[8] Pharmanex, Inc., Administrative Proceeding, Docket No. 97P-0441, at 4-5.

[9] Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (1994).

longer an article authorized for investigation as a new drug. Therefore, pyridoxamine should not be excluded from the definition of dietary supplement under the prior market clause.

b. An Exception Should be Granted Authorizing Pyridoxamine to be Marketed as a Dietary Supplement using the Discretion Granted to the FDA under 21 U.S.C. § 321(ff)(3)(B)(ii)

If the FDA finds that pyridoxamine should remain an article authorized for investigation as a new drug under the prior market clause, excluded from the definition of dietary supplement, the FDA should create an exception using the regulatory discretion granted in the clause.
An article authorized for investigation as a new drug is excluded from the definition of a dietary supplement unless "the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this chapter."[10] In addition, the draft guidance states the "FDA can create an exception to this prohibition by regulation, but only if the agency finds that the use of the article in dietary supplements would be lawful." If the article could be lawfully sold as a dietary supplement absent its exclusion under the prior market clause, then an exception is possible.

Pyridoxamine is a member of the vitamin B6 family, and thus fits under the definition of a dietary supplement under 21 U.S.C. § 321(ff)(1)(A). Therefore, its use in dietary supplements would be lawful absent its current exclusion under the prior market clause.

As explained above, there are no companies investigating therapeutic applications for pyridoxamine. NephroGenex terminated the last clinical investigation in 2016 and subsequently proposed a plan to liquidate under Chapter 11 of the Bankruptcy Code. Authorizing the sale of pyridoxamine as a dietary supplement would not harm the company, because it no longer is evaluating pyridoxamine as a drug.

In addition, no other pharmaceutical company has demonstrated any tangible interest in instituting new clinical investigations of pyridoxamine. NephroGenex actively sought out buyers for Pyridorin™ in the months after it was forced to terminate its Phase 3 trial. The company, through its engagement with the firm Cassel Saltpeter, identified 275 entities with possible interest in the asset and circulated 191 non-confidential presentations.[11] Despite these efforts, they were unable to execute a transaction. In the end, the company arranged a bankruptcy auction, which did not elicit a single qualifying offer.

Several factors may explain why the pharmaceutical industry was not interested in pursuing the development of pyridoxamine as a drug. First, after 17 years of clinical studies its patent life is significantly diminished, reducing the period it may be sold exclusively by the sponsor (aside from the 5-year market exclusivity granted by the FDA). Second, it has not demonstrated sufficient efficacy to convince companies or investors that it can obtain FDA approval. Third, it is difficult to obtain approval for the treatment of diabetic nephropathy, Pyridorin™'s intended

[10] 21 U.S.C. § 321(ff)(3)(B)(ii).
[11] NephroGenex Inc., Case No. 16-11074-KG, DOC-147-1. U.S. Bankruptcy Court, Dist. Of Delaware.

indication. To date, no new drug has obtained approval for the indication, although several previously approved blood pressure medications have received FDA approval for the indication.

Given these factors and recent events, it is reasonable to conclude that pyridoxamine is no longer a viable investigational drug candidate.

In addition, refusing to grant an exception in this case would be contrary to the intent of the DSHEA. In enacting the DSHEA, Congress recognized the benefits of dietary supplements to health promotion and disease prevention.[12] They found "there is a link between the ingestion of certain nutrients or dietary supplements and the prevention of chronic diseases such as cancer, heart disease, and osteoporosis."[13] Preventing disease would also reduce long-term health care expenditures, a serious problem facing the Federal Government today.

Pyridoxamine is a vitamer of the vitamin B6 family, and exists in our bodies at very low levels. It has been extensively studied and found to possess inhibitory activity against oxidative stress induced chemistries thought to promote disease processes. It's specificity and potency against these pathogenic chemistries are not present in established nutrient antioxidants. The other two vitamin B6 vitamers do not possess these unique inhibitory activities. In addition, pyridoxamine does not perturb metabolic or signaling pathways and consistently exhibits little or no toxicity in preclinical and clinical studies.

The petitioner acknowledges that the FDA may be concerned granting an exception for pyridoxamine will encourage other petitioners to seek exceptions for other previously investigated articles. This is unlikely. Pyridoxamine is a unique case because it is a vitamin, easily fitting under DSHEA's definition of a dietary supplement under 21 U.S.C. § 321(ff)(1). The vast majority of investigational drugs are unlikely to qualify as dietary supplements. Unless an article can be defined as a dietary supplement, a petition requesting an exception would be futile.

3. Conclusion

The prior market clause balances Congress's desire to encourage the sale and marketing of dietary supplements with its determination to be fair to the pharmaceutical industry. To achieve this balance, the clause should not be applied as a permanent exclusion. Where all clinical investigations have ceased and demonstrably no interest in resuming them, the pharmaceutical industry's interests are no longer at stake. It would be consistent with the intent of Congress to find the exclusion has lapsed and a previously investigated article may now be marketed as a dietary supplement.

If the FDA determines that the prior market clause is a permanent exclusion, it should use its discretion to grant an exception for pyridoxamine. It is a vitamin that has demonstrated potential

[12] Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, 108 Stat. 4325 (1994).
[13] Id.

significant health benefits and strong safety profile in numerous clinical studies. Granting an exception would give consumers access to a beneficial article.

C. Environmental Impact

The actions requested in this citizen petition are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22. Additionally, the actions requested in this petition are exempt from requirement of an environmental assessment pursuant to 21 C.F.R. § 25.24(a)(11).

(A) Claim for categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.)

D. Economic Impact

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

E. Certification

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

_____ (Signature)

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