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July 29, 2005

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, Maryland 20852

Re: **CITIZEN PETITION**

Dear Madam or Sir:

BioStratum, Inc. ("BioStratum") submits this petition pursuant to 21 C.F.R. § 10.30 to request that the Food and Drug Administration ("FDA" or "the Agency"): (1) confirm in writing that dietary supplements that contain the drug pyridoxamine are adulterated under the Federal Food, 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; and (3) not place this citizen petition in the Agency's docket for Premarket Notifications for New Dietary Ingredients (2004N-0454), because this document is specifically and narrowly focused on the legal, scientific, and public health issues presented by dietary supplements that contain the drug pyridoxamine.

I. Actions Requested

BioStratum requests that FDA take the actions noted above.

II. Statement of Grounds

A. Summary

BioStratum is the manufacturer of Pyridorin™ (pyridoxamine dihydrochloride) which is the subject of an Investigational New Drug Application ("IND") that was filed with FDA in July

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1999 for use as a potential therapeutic agent to slow or prevent the progression of diabetic nephropathy in patients with type 1 and type 2 diabetes. Diabetic nephropathy develops in 25-40% of patients with type 1 or type 2 diabetes, and almost one million diabetic patients have overt diabetic nephropathy in the United States. Despite the best available care, a majority of these patients will progress to end-stage renal disease ("ESRD"). Diabetes is the leading cause of ESRD in the United States, Europe, and Japan, and the number of patients with ESRD is expected to double over the next decade. The annual cost of managing ESRD in the United States alone is estimated to be \$23 billion per year.

Pyridorin™ was granted fast-track status in 2002 by FDA's Center for Drug Evaluation and Research, Division of Cardio-Renal Drug Products. In Phase II trials involving 224 patients, Pyridorin™ has been shown to slow the progression of diabetic nephropathy.^{1/} FDA has indicated that a successful single Phase III trial in patients with nephropathy due to type 2 diabetes would be sufficient to support a New Drug Application ("NDA") approval. As a result, a pivotal Phase III trial with approximately 1,200 subjects is currently being planned, which, upon completion in approximately three years, is expected to lead to approval of Pyridorin™ as a drug in the United States.

After filing the Pyridorin™ IND, and following release of data from Phase II clinical trials, BioStratum became aware that certain firms were engaged in marketing dietary supplements containing pyridoxamine. BioStratum was not aware of any of these products being marketed prior to the date on which it filed the Pyridorin™ IND, and no subsequent evidence has been uncovered to suggest pyridoxamine was marketed as a dietary supplement prior to the Pyridorin™ IND filing. Accordingly, dietary supplements that contain pyridoxamine are adulterated under the FFDCA because:

- Pyridoxamine is not a grandfathered dietary ingredient—
 - ◆ There is no evidence of pyridoxamine being marketed as a food or dietary supplement prior to passage of the Dietary Supplement Health and Education Act; and
 - ◆ Existing dietary ingredients must be chemically altered by synthetic processes to produce pyridoxamine, so pyridoxamine can not be considered a concentrate, metabolite, constituent, or extract of such dietary ingredients.
- Pyridoxamine has never been the subject of a 75-day new dietary ingredient notification ("75-day notification"), as required by 21 U.S.C. § 350b(a)(2) for all new dietary ingredients; and

^{1/} BioStratum, BioStratum Presents at the American Diabetes Association's 64th Scientific Sessions Meeting (2004), at <http://www.biostratum.com/060704.html>.

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- Prior to the marketing of pyridoxamine dietary supplements, this substance was 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.

FDA's legal interpretations and decisive enforcement approach in the case of *Pharmanex Inc. v. Shalala* established Agency precedent for the removal of illegal dietary supplements such as pyridoxamine from United States interstate commerce. As explained in more detailed below, consistent with the legal principles established in the *Pharmanex* case—which concerned the illegality of dietary supplements containing the active ingredient in Merck's cholesterol-lowering drug Mevacor—dietary supplements containing pyridoxamine are adulterated under the FFDCA and should be removed from the market.

Moreover, firms marketing pyridoxamine dietary supplements have engaged in making impermissible drug or disease claims that lack adequate substantiation, and samples from at least one of the illegal pyridoxamine dietary supplement products revealed a substantial impurity that raises serious concerns regarding the safety of these products.

FDA, therefore, properly should take the above requested actions consistent with the requirements of the FFDCA.

B. Argument

1. Legal Requirements for Dietary Ingredients

The FFDCA, as amended by the Dietary Supplement Health and Education Act (“DSHEA”), defines a dietary supplement as a product that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- a vitamin;
- a mineral;
- an herb or other botanical;
- an amino acid;
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- a concentrate, metabolite, constituent, extract, or combination of any ingredient described above.^{2/}

^{2/} 21 U.S.C. § 321(ff)(1).

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Dietary ingredients available in the United States prior to October 15, 1994 are considered “grandfathered,” and may legally be included in dietary supplements without any ingredient approval or notification process.^{3/} In contrast, a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient (i.e., a dietary ingredient that was not marketed in the United States before October 15, 1994) must submit a 75-day notification to FDA prior to introducing such a dietary supplement into interstate commerce, establishing that the dietary supplement will reasonably be expected to be safe.^{4/}

Importantly, however, under the FFDCA’s so-called “prior-market clause” set forth at 21 U.S.C. § 321(ff)(3)(B), a new dietary ingredient can not lawfully be included in a dietary supplement if it previously has been (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/} As FDA has acknowledged, Congress included this provision in DSHEA out of a concern about the unfairness of marketing as dietary supplements those articles that have “gained recognition in the marketplace as new drugs by either being approved or studied as new drugs.”^{6/} FDA has further explained that “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 often significant investment needed to gain FDA approval of new drugs.”^{7/}

^{3/} 21 U.S.C. § 350b.

^{4/} 21 U.S.C. § 350b(c); 21 C.F.R. § 190.6.

^{5/} 21 U.S.C. § 321(ff)(3)(B)(ii). Comments submitted by Senator Orrin Hatch, one of the chief sponsors of DSHEA, during administrative proceedings in the *Pharmanex* case, explained that that DSHEA should not be interpreted to “undermine the incentive of pharmaceutical manufacturers to develop and bring new drugs to market.” Letter from Orrin G. Hatch, United States Senator, to Dr. Michael A. Friedman, M.D., Lead Deputy Commissioner, U.S. Food and Drug Administration (Dec. 22, 1997) at 8, cited in Letter from William B. Shultz, Deputy Commissioner for Policy, U.S. Food and Drug Administration, to Stuart M. Pape, Counsel to Pharmanex, Inc. (May 20, 1998), *Pharmanex, Inc., Administrative Proceeding, Docket No. 97P-0441*, at 4-5 [hereinafter *Pharmanex Final Administrative Decision*].

^{6/} *Pharmanex Final Administrative Decision*, supra note 5, at 4-5.

^{7/} Id.

2. *Pyridoxamine is Not a "Grandfathered" Dietary Ingredient*

While pyridoxine (Vitamin B6) is a grandfathered dietary ingredient,^{8/} and is the starting material for the manufacture of pyridoxamine, pyridoxamine itself is not grandfathered under DSHEA for several reasons.

First, there is no evidence of pyridoxamine being marketed as a food or dietary supplement prior to October 15, 1994. A search of several medical/scientific databases including Medline and the International Bibliographic Information on Dietary Supplements, as well as a search of the trade press and a general Internet search, yielded no references to pyridoxamine having been marketed in the United States as a food or dietary supplement prior to July 1999 when BioStratum submitted its IND for PyridorinTM.^{9/} FDA has taken the position that "the relevant inquiry in determining whether a component present in a marketed product qualifies as an 'article marketed as a dietary supplement or as a food' within the meaning of [Section 201(ff)(3) of the FDCA] is whether, in marketing the product, a person was in actuality marketing the component as a food or as a dietary supplement."^{10/} There was no such marketing of pyridoxamine as a food or as a dietary supplement prior to 1994.

Second, while pyridoxine (Vitamin B6) is the starting material used to prepare pyridoxamine, there is no scientific evidence that pyridoxamine is naturally available in pyridoxine or that pyridoxamine can be isolated without chemical alterations to pyridoxine. The production of pyridoxamine from pyridoxine involves a sophisticated multi-step chemical synthesis. For example, the Japanese patent JP-09221473 describes a sequence involving (1) oxidation of pyridoxine to pyridoxal, (2) reaction of pyridoxal with hydroxylamine, (3) reduction of hydroxylamine with zinc metal, and (4) precipitation of the dihydrochloride with hydrochloric acid.^{11/} BioStratum's process, which is similarly complex, is the subject of a pending patent

^{8/} Pyridoxine is the dietary ingredient present in marketed dietary supplement versions of Vitamin B6. The United States Pharmacopoeia cross-references the entry for Vitamin B6 Tablets with pyridoxine in the dietary supplements monograph section, and pyridoxine is specifically listed under the various dietary supplement monographs for water-soluble vitamins. USP 28-NF 23, at 2136, 2142 (2005). Moreover, an extensive safety database has been compiled for pyridoxine in which the authors identify Vitamin B6 as pyridoxine. Cohen and Bendich, 1986. Cohen M, Bendich A. Safety of pyridoxine--a review of human and animal studies. Toxicol Lett. 34(2-3):129-39 (1986).

^{9/} Also of note, the European Union's Food Supplements Directive (2002/46/EC), which establishes a positive list of vitamins and minerals as well as the chemical forms in which they may be used as food supplements, does not list pyridoxamine. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the member states relating to the food supplements.

^{10/} Pharmanex Final Administrative Decision, *supra* note 5, at 23.

^{11/} Kissei Japanese patent JP-09221473 titled "Preparation of 3-hydroxy-4-methylpyridine derivatives as Maillard reaction inhibitors," by Ryo Iyobe et al.

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application. Accordingly, pyridoxamine can not be considered a concentrate, metabolite, constituent, or extract of pyridoxine (Vitamin B6).

Finally, the interpretation that pyridoxamine is not grandfathered is supported by the wording of the FFDCA itself, the legislative history of DSHEA, judicial decisions, and related commentary by FDA officials. The FFDCA defines a “new dietary ingredient” as “a dietary ingredient that was not marketed in the United States before October 15, 1994”^{12/} The Act goes on to provide that a dietary supplement that contains a new dietary ingredient is adulterated under section 402(f) of the FFDCA^{13/} unless it is the subject of a 75-day notification or “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.”^{14/} The legislative history of DSHEA explains that Congress intended the term “chemically altered” to mean processing beyond minor physical modifications such as dehydration and milling.^{15/} Specifically, in a Statement of Agreement, the chief sponsors of DSHEA expressed their intent that the term “chemically altered” does not include the following physical modifications: “minor loss of volatile components, dehydration, lyophilization [sic], milling, tincture or solution in water, slurry, powder, or solid in suspension.”^{16/} As noted, the production of pyridoxamine from pyridoxine requires chemical manipulation far exceeding these types of basic physical modifications.

Consistent with the statutory language and legislative history, FDA has previously taken enforcement action to prevent the marketing of chemically altered forms of grandfathered ingredients. In an analogous situation presented in *Pharmanex Inc. v. Shalala*, FDA asserted, and the courts agreed, that the red yeast rice contained in Pharmanex’s dietary supplement Cholestin was not grandfathered because it was chemically altered. Even though traditional red yeast rice had been consumed as a food in Asia prior to October 15, 1994, Cholestin was carefully manufactured to produce lovastatin, the active ingredient in Merck’s cholesterol-lowering drug Mevacor.^{17/} Pharmanex argued that lovastatin is present in red yeast rice, oyster mushrooms, and other foods that were marketed in the United States and East Asia prior to lovastatin’s approval as a new drug in 1987. As a result, Pharmanex asserted that lovastatin was “grandfathered” under DSHEA. In making this argument, Pharmanex asserted that “marketed

^{12/} 21 U.S.C. § 350b(c).

^{13/} 21 U.S.C. § 342(f).

^{14/} 21 U.S.C. § 350b(a)(1) emphasis added.

^{15/} STATEMENT OF AGREEMENT, 140 Cong. Rec. S14801, (Oct. 7, 1991), reprinted in 1994 U.S.C.C.A.N. 3523.

^{16/} Id.

^{17/} Pharmanex Inc. v. Shalala, Memorandum Decision and Order, 2001 U.S. Dist. LEXIS 4598 (D. Utah 2001) at 7.

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as” for purposes of Section 201(ff) of the FFDCFA meant “sold as” and thus, if an article was merely present in food, it was marketed as food.^{18/}

In response to Pharmanex’s interpretation of the meaning of “marketed as,” FDA asserted that, because this language was ambiguous, the Agency could interpret it to mean more than mere presence in food. As noted, FDA took the position that a component in a marketed product qualifies as an “article marketed as a dietary supplement or as a food” only if the component itself was actually marketed as a food or dietary supplement.^{19/} Otherwise stated, components in marketed food/dietary supplement products are not grandfathered unless they were actually marketed as a food/dietary supplement—their mere presence in food/dietary supplements does not alter the illegality of chemically-altered forms of grandfathered dietary ingredients.

Based on this interpretation of “marketed as,” FDA claimed that Pharmanex had failed to show that lovastatin as contained in red yeast rice was previously marketed as a food or dietary supplement, and therefore, Cholestin did not qualify as a dietary supplement.^{20/} Specifically, FDA determined that Cholestin was a “carefully manufactured, non-traditional product designed to contain specific levels of lovastatin, the active ingredient in the approved prescription drug Mevacor.”^{21/} The court found that FDA’s interpretation of the “marketed as” language was reasonable and should be afforded deference under principles of administrative law set forth in *Chevron*.^{22/}

Consistent with the foregoing statutory language, legislative history, and judicial precedent, if a component in a marketed food/dietary supplement product is not specifically marketed as a food/dietary supplement, or if a concentrate, extract, etc. of a grandfathered dietary ingredient is chemically different than the composition of the underlying grandfathered dietary ingredient, the component/substance would not be considered grandfathered and could only be legally marketed pursuant to an approved 75-day notification. Accordingly, pyridoxamine is not grandfathered because this substance (1) was not specifically marketed as a food/dietary supplement prior to October 15, 1994, and (2) is a chemically different and altered form of the grandfathered dietary ingredient pyridoxine (Vitamin B6).

3. *Pyridoxamine is Not a Legal New Dietary Ingredient*

Because pyridoxamine is not a grandfathered dietary ingredient, it legally could only be included in dietary supplements if it was (1) the subject of a 75-day new dietary ingredient notification and (2) not previously authorized for investigation as a new drug, antibiotic or biological for

^{18/} Id.

^{19/} Pharmanex Final Administrative Decision, supra note 5, at 23.

^{20/} Pharmanex Inc. v. Shalala, 2001 U.S. Dist. LEXIS 4598 at 10.

^{21/} Id.

^{22/} Id.

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which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public. These requirements for new dietary ingredients have not been met for pyridoxamine, as follows:

- BioStratum has been unable to identify any existing 75-day notifications for pyridoxamine;
- Prior to BioStratum's filing of its IND for Pyridorin™ in July 1999, pyridoxamine was not marketed as a dietary supplement or food;
- Substantial clinical investigations have been instituted for Pyridorin™ (e.g., Phase II trials involving 224 patients); and
- The existence of the clinical investigations of Pyridorin™ has been made public on BioStratum's Internet website and at many medical conferences.^{23/}

Accordingly, pyridoxamine is not a legal dietary ingredient, and all dietary supplements that contain this substance are adulterated under the FFDCFA.^{24/}

4. FDA's Prior Actions Concerning Cholestin Support the Removal of Dietary Supplements that Contain Pyridoxamine From the Market

FDA's exercise of its enforcement authority to remove illegal pyridoxamine dietary supplements from the market would be consistent with its diligent and persistent prior actions concerning Cholestin.

After initiating administrative proceedings in April 1997 following a complaint submitted to the Agency by a pharmacist, FDA issued a final decision in May 1998 stating that Cholestin was excluded from the definition of dietary supplement under 21 U.S.C. § 321(ff)(3).^{25/} The Agency determined that Cholestin contained lovastatin, a new drug that had not been marketed as a dietary supplement or food prior to the Agency's investigation and approval of lovastatin as a drug, and thus violated the Act's prior-market clause.^{26/} After FDA issued its final decision in the administrative proceeding, Pharmanex filed suit in district court appealing FDA's final decision and seeking a declaratory judgment that Cholestin was a dietary supplement within the meaning of 21 U.S.C. § 321(ff).^{27/} While the district court set aside FDA's decision and ruled

^{23/} See, e.g., BioStratum, BioStratum's Drug Pyridorin™ Enters Human Clinical Trials for Treatment of Diabetic Kidney Disease (1999), at <http://www.biostratum.com/090899.html>; BioStratum, BioStratum Presents at the American Diabetes Association's 64th Scientific Sessions Meeting (2004), at <http://www.biostratum.com/060704.html>.

^{24/} 21 U.S.C. § 342(f).

^{25/} See Pharmanex Final Administrative Decision, supra note 5

^{26/} Id.

^{27/} See Pharmanex, Inc. v. Shalala, 35 F. Supp. 1341 (D. Utah 1999).

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that Cholestin qualified as a dietary supplement under the Act,^{28/} FDA appealed to the U.S. Court of Appeals for the Tenth Circuit which reversed and remanded the district court's ruling.^{29/} The Tenth Circuit held that FDA's application of the prior-market clause to the dietary ingredient lovastatin rather than to the finished dietary supplement product Cholestin was reasonable and merited deference under *Chevron*.^{30/} The court explained that "to permit manufacturers to market dietary supplements with components identical to the active ingredients in prescription drugs would . . . contravene the incentive structures in place in the FDA for the development of orphan drugs and pediatric drugs."^{31/}

Consistent with this judicial and enforcement precedent, BioStratum respectfully requests that FDA take the same decisive action and exhibit the same conviction to remove illegal dietary supplement products that contain pyridoxamine from U.S. interstate commerce. Pyridorin™ is being investigated for an important and largely unmet medical need—to slow or prevent the progression of diabetic nephropathy in patients with Type 2 diabetes. The continued existence of illegal dietary supplements that contain pyridoxamine severely threaten (1) BioStratum's continued ability to sponsor and support these clinical investigations, (2) the potential approval of this important product, and (3) BioStratum's reasonable investment-backed expectations that its diligent adherence with the significant regulatory requirements for new drugs would not be made worthless by the overt availability of illegal dietary supplements containing its investigational drug. Moreover, uncontrolled and unsupervised consumption of pyridoxamine dietary supplements while the safety profile of this drug is being defined presents a significant public health issues.

5. *Illegal Pyridoxamine Dietary Supplements Bear Impermissible Drug and Disease Claims that Lack Adequate Substantiation*

In addition to the grounds set forth above demonstrating the illegality of pyridoxamine dietary supplements, impermissible drug and disease claims that lack adequate substantiation have been made for marketed products. These claims cause these products to be misbranded under the FFDCa and violative of the Federal Trade Commission's ("FTC's") truth-in-advertising law, and pose a safety risk to consumers.

As FDA is well aware, the FFDCa only permits limited types of claims to appear on dietary supplement labels and labeling, including health claims and structure/function claims. Health claims describe the relationship between a substance and reduction in the risk of disease or health-related condition, and must be specifically authorized by FDA prior to their use.^{32/}

^{28/} Id. at 1349.

^{29/} See Pharmanex, Inc. v. Shalala, 221 F.3d 1151 (10th Cir. 2000).

^{30/} Id. at 1159. See Chevron, U.S.A., Inc. v. NRDC, 467 U.S. 837, 842-44 (1984).

^{31/} See Pharmanex, 221 F.3d 1151 (10th Cir. 2000).

^{32/} See 21 C.F.R. § 101.14(a)(1).

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Structure/function claims describe the role of a nutrient or dietary ingredient in affecting the structure or function of the human body, or describe the documented mechanism by which the substance acts to maintain such structure or function, and must be the subject of a premarket notification to the Agency prior to their use.^{33/}

FTC, which has regulatory jurisdiction over dietary supplement advertising (i.e., print and broadcast advertisements, Internet marketing, catalogs, infomercials, and other direct marketing materials) requires that advertising be truthful and not misleading, and that advertisers have adequate substantiation for all objective product claims before the advertisement bearing the claim is disseminated.^{34/} Although Internet advertisements have traditionally been subject to FTC regulation, in January 2001, FDA began to exercise jurisdiction over “labeling” material appearing on the websites of FDA-regulated companies.^{35/} Moreover, in its October 2004 draft

^{33/} See 21 U.S.C. § 403(r)(6)(A). In January 2000, FDA issued its final rule defining the types of statements that will be considered structure/function claims and those that will be considered drug or health claims (i.e., statements that implicitly or explicitly claim a dietary supplement can diagnose, mitigate, cure, or prevent a specific disease or class of diseases). See 65 Fed. Reg. 1000 (Jan. 6, 2000). Among other things, the rule disallows the use of drug claims on dietary supplements labels. *Id.* The FFDCA also expressly prohibits the use of claims on dietary supplements that “diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases...” 21 U.S.C. § 343(r)(6). The inclusion of such claims on a product’s label or labeling can cause the Agency to view the product as a drug for purposes of the Act. The FFDCA defines “drug” as an article “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.” 21 U.S.C. § 321(g)(1)(B).

^{34/} See 5 U.S.C. § 45; FTC, *Dietary Supplements: An Advertising Guide for Industry* (1998).

^{35/} In January 2001, FDA took enforcement action against Ocean Spray for what the Agency characterized as unauthorized health claims and impermissible disease claims made for juice products on the company’s website. Letter from Gail T. Costello, District Director, New England District Office, U.S. Food and Drug Administration, to Robert Hawthorne, President, Ocean Spray Cranberries, Inc. (Jan. 19, 2001), available at <http://www.fda.gov/foi/warning.html> [hereinafter Ocean Spray Warning Letter]. FDA argued that material on the company’s website constituted labeling for purposes of the FFDCA.

In the Ocean Spray case, the company had included its website on their juice product labels, thus linking the impermissible web claims to the product labels. However, in subsequent enforcement action against a dietary supplement distributor regarding the eye disease treatment claims found on the company’s website, the company does not provide its website address on its product labels, and FDA based its objections solely on the labeling claims made on the company’s website. See Letter from John B. Foret, Jr., Director, Division of Compliance and Enforcement, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, to R. Scot Hunter, CEO, ScienceBased Health (Nov. 9, 2001), available at http://www.fda.gov/foi/warning_letters/g1936d.pdf.

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guidance on substantiation of dietary supplement claims, FDA has articulated standards for the amount, type, and quality of evidence necessary to substantiate dietary supplement labeling claims that are highly similar to the aforementioned FTC advertising standards.^{36/}

Internet websites marketing and selling pyridoxamine dietary supplement products have claimed that the use of pyridoxamine can alleviate various diabetic complications including nephropathy, which is the subject of BioStratum's clinical investigations under its IND. These claims are impermissible drug and disease claims because they go far beyond the scope of structure/function claims permitted by the Act, and FDA has not approved any health claim linking pyridoxamine or even Vitamin B6 to diabetes or its related health conditions. Moreover, the medical literature does not reveal any evidence of adequate and well-controlled clinical studies to support these claims for pyridoxamine dietary supplement products, or authoritative statements being made by any scientific bodies regarding the mitigation of disease by pyridoxamine dietary supplements. The promotional materials provided by pyridoxamine supplement manufacturers do not reference specific evidentiary support for the claims being made.

In addition to causing the pyridoxamine supplements to be misbranded under the FFDCa and violative of FTC's truth-in-advertising law, the claims made for these products present a health risk to consumers who may purchase the products for medical intervention or treatment use. In FDA's 2001 Warning Letter to Ocean Spray, FDA expressed concern that statements made on the company's website posed "a serious safety threat, as they not only overstate any possible benefit associated with grapefruit juice consumption but also understate the very real risks associated with concomitant use of certain drugs and grapefruit juice. . . . The consumer would need to find a subsequent unnumbered footnote to receive a partial list of medications that may be affected by grapefruit juice and to receive a mild admonition to consult with a physician or pharmacist before taking the listed drugs."^{37/} Pyridoxamine is the subject of an IND and, as

In response to the Ocean Spray enforcement action, the Washington Legal Foundation submitted a Citizen Petition requesting that the Agency formally adopt a policy stating that information presented on a company's website, including hyperlinks to other third party sites does not constitute "labeling" for purposes of the FFDCa. See Citizen Petition to Exempt Internet Information From FDA Labeling Requirements, submitted by Washington Legal Foundation (Apr. 13, 2001). FDA declined the Citizen Petition and explained the Agency's position that, in certain circumstances, web information about FDA-regulated products can fall within the Act's definition of labeling. See Letter from Margaret M. Dotzel, Associate Commissioner for Policy, U.S. Food and Drug Administration, to Daniel J. Popeo and Paul D. Kamenar, Washington Legal Foundation (Nov. 1, 2001). In particular, the Agency cited an example of companies that promote FDA-regulated products on their websites and allow consumers to purchase the product directly from the website. FDA explained that in such instances, the website is likely to be labeling for purposes of the FFDCa. Id. at 2.

^{36/} FDA, Draft Guidance for Industry; Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act (2004).

^{37/} Ocean Spray Warning Letter, supra note 35.

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such, should only be taken under the supervision of a physician, currently in the context of a clinical trial with all appropriate human protections. Consumers who purchase pyridoxamine supplements for medical intervention or treatment use could suffer adverse events due to drug interaction or dosage issues. Moreover, exacerbating the potential risks is the fact that these products may contain more pyridoxamine than labeled, a common problem for dietary supplements overall,^{38/} including those containing B vitamins.^{39/} A BioStratum analysis of 100 mg pyridoxamine capsules marketed by Smart Nutrition—using a validated High Pressure Liquid Chromatography (“HPLC”) method previously employed to assess the impurity profile of pyridoxamine HCl according to the methods BioStratum submitted in its Pyridorin™ IND—revealed that the Smart Nutrition capsules actually contained approximately 140 mg of pyridoxamine.

An example of the impermissible and unsupportable claims being made for illegal dietary supplement products containing pyridoxamine is set forth below. This is a representative example only, and enforcement action should not be limited to this supplement product.

a. Smart Nutrition

Smart Nutrition sells 100 mg capsules of pyridoxamine dietary supplements from its website, and also potentially by phone, mail, etc.^{40/} Until recently, the listing for pyridoxamine on Smart

^{38/} ConsumerLab.com’s extensive laboratory analyses of dietary supplements have determined that many of these products do not contain the dietary ingredients claimed on the label. For example, ConsumerLab.com studies have found that 25 percent of ginkgo biloba, 20 percent of saw palmetto, 33 percent of glucosamine, chondroitin and combined glucosamine/chondroitin, and 50 percent of SAME products do not contain the dietary ingredients claimed in their product labels. ConsumerLab.com, Consumer Labs Product Reviews on Ginkgo Biloba, Saw Palmetto, Glucosamine and Chondroitin, and SAME (2004), at <http://www.consumerlabs.com>.

^{39/} ConsumerLab.com found that the recommended doses of 9 of 21 tested B vitamin supplement products exceeded established Tolerable Upper Intake Levels (“ULs”) for adults—in fact more than 10 times higher in some cases—above which there is increased risk of side effects with regular use including skin flushing, tingling and pain. ConsumerLab.com, Product Review: B Vitamins (including Thiamin, Niacin, B6, B12, and Folate) (2004), at <http://www.consumerlabs.com/results/vitaminb.asp>.

^{40/} Smart Nutrition (2005), at http://www.smartnutrition.info/Merchant2/merchant.mvc?Screen=PROD&Product_Code=Pyridox_BS&Category_Code=BS (Attachment 1). Smart Nutrition is located at 1765 Garnet Ave #66, San Diego, CA, 92109.

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Nutrition's website included an active link labeled "www.pyridoxamine.org,"^{41/} which directed the consumer to a separate page that included the following claims for pyridoxamine:^{42/}

- "Pyridoxamine inhibits Advanced Glycation End products (AGE) and Advanced Lipoxidation End products (ALE) which are *implicated in the progression of diabetic health problems;*"
- "Pyridoxamine *inhibits retinopathy and neuropathy* in diabetic rats;"
- "Pyridoxamine *may prove useful in chronic diseases like diabetes & arteriosclerosis;*"
- "Pyridoxamine *inhibits hyperlipidemia* and protects against vascular damage;"
- "Pyridoxamine may be useful for *treating diabetic retinopathy;*" and
- "Pyridoxamine inhibits renal disease and decreases hyperlipidemia in diabetic rats."

The www.pyridoxamine.org website included a link labeled "order" directing the consumer back to Smart Nutrition's website. Accordingly, Smart Nutrition has been selling pyridoxamine dietary supplements directly to consumers through its website with impermissible claims and, consistent with the foregoing, this intertwined promotional material is product labeling.

In its June 14, 2005 untitled letter to Smart Nutrition, FDA confirmed that Smart Nutrition violated the FDCA by promoting pyridoxamine for conditions that caused the product to be a drug under section 201(g)(1) of the Act. Consistent with this determination, the Agency should take enforcement action against other marketers of illegal pyridoxamine dietary supplement products.^{43/}

^{41/} Smart Nutrition, Brain Products (2004), at <http://smart-nutrition.net/olympia-brain.html> (Attachment 2). Pyridoxamine (2004), at <http://www.pyridoxamine.org/> (Attachment 2).

^{42/} In addition to the link located on Smart Nutrition which directed the consumer to www.pyridoxamine.org, a reciprocal link labeled "order" was found on the opening page of the www.pyridoxamine.org website. This link directed the consumer to the Smart Nutrition website, and the listing for pyridoxamine capsules (Attachment 2). These links apparently were removed within approximately the last month, but it remains unclear whether Smart Nutrition is continuing to make these types of impermissible claims for its pyridoxamine dietary supplement product through other mechanisms (e.g., pamphlets, point-of-purchase displays, advertisements, etc.).

^{43/} Letter from Susan J. Walker, M.D., Director, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition, FDA, to Jeff Charles, President, Smart Nutrition (June 14, 2005).

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6. *Impurities Found in Dietary Supplements Containing Pyridoxamine Raise Safety Concerns*

In addition to the safety issues raised by the illegal claims for dietary supplements containing pyridoxamine, samples of at least one of these dietary supplements revealed substantial impurities that pose a tangible public health risk.

BioStratum purchased pyridoxamine capsules from Smart Nutrition and conducted a purity analysis on the capsules using a validated HPLC method previously employed to assess the impurity profile of pyridoxamine HCl according to the methods BioStratum submitted in its Pyridorin™ IND.^{44/} The Pyridoxamine HCl BioStratum manufactures according to current Good Manufacturing Practices (“cGMP”) contains only 0.07% impurities. By contrast, the pyridoxamine capsules obtained from Smart Nutrition contain an impurity contributing 8.3% of the capsule. For the purpose of identifying this impurity, the corresponding HPLC fraction was analyzed by liquid chromatography/mass spectrometry (“LC/MS”). Subsequent ultraviolet spectra and LC/MS spiking studies confirmed the impurity to be 5-deoxypyridoxamine. Other pyridoxamine dietary supplements may contain these or other impurities, potentially at higher levels. Contamination is a common problem for dietary supplement products, as documented in FDA’s March 2003 proposed rule for Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements,^{45/} as well as in a multitude of independent laboratory studies.^{46/}

^{44/} See IND 58,684.

^{45/} In its proposed rule, FDA offered several examples to illustrate the wide range of dietary ingredient and dietary supplement adulteration caused by manufacturing, packaging, or holding practices, including the following: (1) a 1998 survey of American Herbal Products Association (“AHPA”) members identified 43 botanicals that are commonly adulterated with contaminants, including aflatoxin and mycotoxin (toxic compounds produced by certain molds) that are known to contaminate certain herbal and botanical dietary supplements; and (2) FDA has been involved in the recall of dietary supplements contaminated with lead, salmonella, Klebsiella pneumonia, botulism, and glass, all of which could cause serious illness or injury and, in the case of lead, may result in chronic irreversible cognitive defects in children and progressive renal failure in adults. 68 Fed. Reg. 12157, 12162 (March 13, 2003).

^{46/} ConsumerLab.com has conducted over 80 laboratory studies of dietary supplement products, including vitamins, minerals, and herbals, and has routinely identified harmful impurities in these products. For example, ConsumerLab.com found that over 20% of 46 tested multivitamins/multiminerals failed to dissolve properly due to lead contamination, and up to 10% of 56 tested supplements containing iron, magnesium, or potassium are contaminated with lead. ConsumerLab.com, Know Your Multivitamins/Multiminerals; Many Failed Our Product Tests! (2004), at <http://www.consumerlabs.com/results/multivit.asp>; ConsumerLab.com, ConsumerLab.com Finds Lead Contamination Remains a Problem for Certain Mineral Supplements (2004), at http://www.consumerlabs.com/news/news_071602.asp.

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The medical literature provides evidence of the potential toxicity of 5-deoxypyridoxamine, which is an effective antimetabolite that interferes with Vitamin B6 activity in animals.^{47/} One example of antimetabolite activity exhibited by 5-deoxypyridoxamine is the inhibition of the enzyme pyridoxine pyruvate transaminase, a ubiquitous coenzyme contributing to many biochemical pathways related to Vitamin B6.^{48/} In addition, a closely related derivative, 4-deoxypyridoxamine, interferes with the transport of pyridoxine into cells.^{49/} As a consequence of this antimetabolite activity, Cohen and Bendich assert that ingestion of Vitamin B6 complex while taking a product containing such antimetabolites can lead to abnormally high levels of pyridoxine, which has recognized neurotoxicity.^{50/}

Consistent with the foregoing, pyridoxamine dietary supplement products pose a health risk to the public because: (1) the products are not being manufactured and marketed consistent with cGMPs; (2) data establishing the conditions for safe human use do not exist in the medical literature; and (3) the products may contain relatively high levels of impurities with toxic potential.

C. Conclusion

Dietary supplements that contain the drug pyridoxamine are adulterated under the FFDCFA because pyridoxamine (1) is not a grandfathered dietary ingredient, (2) has never been the subject of a 75-day notification, and (3) prior to the marketing of pyridoxamine dietary supplements, was previously 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. Moreover, marketed pyridoxamine dietary supplements have been sold using impermissible drug or disease claims that lack adequate substantiation, and samples of one of these illegal products revealed a substantial impurity that raises serious concerns regarding the safety of these products.

BioStratum's drug Pyridorin™ is being investigated for a critical, largely unmet medical need—to slow or prevent the progression of diabetic nephropathy in patients with Type 2 diabetes. Removing dietary supplements that contain the active ingredient in this investigational drug from the market is, understandably, of the utmost importance to and seriousness for BioStratum. The

^{47/} Heyl, Harris, Folkers, The vitamin B6 group. The structure and synthesis of pyridoxamine and pyridoxal J. Am. Soc. Chem. 75:653-655 (1953); see generally, Rabinowitz JC, Snell E. Vitamin B6 antagonists and growth of microorganisms. II. 5-Desoxy pyridoxal and related compounds. Arch Biochem Biophys. 43(2):408-15 (1953).

^{48/} Ayling JE, Snell EE. Relation of structure to activity of pyridoxal analogs as substrates for pyridoxamine pyruvate transaminase. Biochemistry. 7(5):1626-36 (1968).

^{49/} Said HM, Ortiz A, Vaziri ND. Mechanism and regulation of vitamin B(6) uptake by renal tubular epithelia: studies with cultured OK cells. Am J Physiol Renal Physiol. 282(3):F465-71 (2002).

^{50/} Cohen M, Bendich A. Safety of pyridoxine--a review of human and animal studies. Toxicol Lett. 34(2-3):129-39 (1986).

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existence of these illegal dietary supplements seriously jeopardizes BioStratum's continued ability to sponsor and support these clinical investigations, the potential approval of this important product, and BioStratum's reasonable investment-backed expectations that its strict adherence with the significant regulatory requirements for new drugs will not be made worthless by the overt availability of illegal dietary supplements containing its investigational drug.

Accordingly, FDA should: (1) confirm in writing that dietary supplements that contain the drug pyridoxamine are adulterated under the FFDCa, and (2) exercise its enforcement authority under the FFDCa to remove dietary supplements containing pyridoxamine from United States interstate commerce.

III. 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).

IV. Economic Impact

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

V. 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.

Respectfully submitted,



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