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VIA FEDERAL EXPRESS

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

Re: Response to CRN Comments to Pyridoxamine Citizen Petition, Docket No. 2005P-0305/CP1

On behalf of BioStratum, Inc. ("BioStratum" or "the Company"), these further comments are being filed to Docket No. 2005P-0305/CP1 (Pyridoxamine Citizen Petition) to respond to comments filed by the Council for Responsible Nutrition ("CRN") on September 14, 2005. For the reasons explained in the Pyridoxamine Citizen Petition and these further comments, CRN is incorrect in its assertion that pyridoxamine is a grandfathered dietary ingredient.

I. CRN Comments

CRN's comments assert that pyridoxamine was marketed as a food or dietary supplement prior to October 15, 1994, the enactment date of the Dietary Supplement Health and Education Act ("DSHEA") and, thus, is a grandfathered dietary ingredient. Dietary ingredients marketed in the United States prior to October 15, 1994 are considered "grandfathered" under DSHEA, which means that they can be included in dietary supplements without any ingredient approval or notification process.[1]

As explained below and in the Pyridoxamine Citizen Petition, BioStratum has determined that pyridoxamine was not marketed as a food or dietary supplement in the United States until after July 1999, when the Company submitted its Investigational New Drug ("IND") application to the Food and Drug Administration ("FDA" or "the Agency") to investigate this substance as a drug for the treatment of diabetic nephropathy. Because pyridoxamine was not marketed as a food or dietary supplement prior to October 15, 1994, it is considered a "new dietary ingredient."[2]

[1] 21 U.S.C. § 350b.

[2] 21 U.S.C. § 350b(c).

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Under the Federal Food, Drug and Cosmetic Act's ("FFDCA's") "prior-market clause," 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.[3] Consistent with Biostratum's fulfillment of these requirements as set forth in the Pyridoxamine Citizen Petition, pyrodixamine is considered a drug under the FFDCA and can not be legally sold as a dietary supplement.

Analysis of key assertions in CRN's comments are provided below.

A. CRN Assertion #1: "Pyridoxamine is unequivocally a dietary ingredient because it is one of the three primary natural forms of vitamin B6, and it is one of the two predominant forms in animal products used as human foods"

CRN asserts that pyridoxamine is a dietary ingredient, rather than a drug, because (1) it is one of the three primary natural forms of vitamin B6, and (2) it is one of the two predominant forms in animal products used as human foods. BioStratum acknowledges that vitamin B6 (pyridoxine) is a recognized grandfathered dietary ingredient. Despite being a member of the vitamin B6 family, however, pyridoxamine is a chemically distinct molecule that is not a grandfathered dietary ingredient by virtue of its metabolic relationship to vitamin B6.

From a metabolic perspective, "vitamin B6" classically refers to a family of related 3-hydroxy-2-methyl-pyridine derivatives, including pyridoxine ("PN"), pyridoxal ("PL") and pyridoxamine ("PM"), that can be metabolized *in vivo* to the metabolically active coenzyme pyridoxal 5'-phosphate ("PLP"). PLP-dependent enzymes are involved in many critical metabolic pathways, including the decarboxylation of amino acids to yield amines, the phosphorolytic cleavage of glycogen, and the formation of alpha aminolevulinic acid (a precursor to hemoglobin).[4]

Notwithstanding their participation in similar metabolic pathways, PN, PL and PM are chemically distinct molecules that differ in the functional group branched from the fourth position on the pyridine ring. PN contains a hydroxymethyl (-CH2-OH) group at position 4, PL contains an aldehyde (-CH-O) group, and PM contains an aminomethyl (-CH2-NH2) group, as shown in the following structures. These structural differences are covalent in nature; therefore, from a chemical perspective, PN, PL and PM are distinct molecules.

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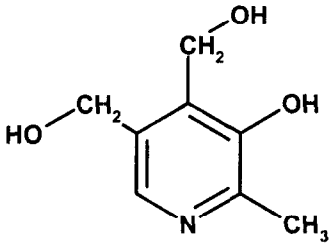
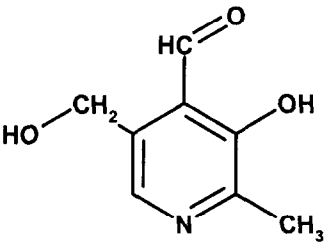
[3] 21 U.S.C. § 321(ff)(3)(B)(ii).

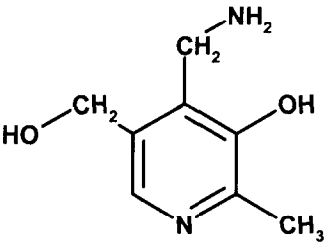
[4] Ink LI, Henderson LM. Vitamin B_6 metabolism. Ann. Rev. Nutr. 4:455-79 (1984); Merril AH, et al. Metabolism of vitamin B_6 by human liver. J. Nutr. 114:1664-74 (1984); Merril AH, Henderson LM. Vitamin B_6 metabolism by human liver. Annals N.Y. Acad. Sci.110-17 (1990).



PYRIDOXINE (PN)



PYRIDOXAL (PL)



PYRIDOXAMINE (PM)

Although the above is an accurate classical description of the vitamin B6 family, confusion over the nomenclature has arisen through the common usage of the term "vitamin B6" in nutritional and dietary supplement contexts. PN, and not PM, is the principal dietary ingredient present in the marketed dietary supplement versions of "vitamin B6." Accordingly, the statement of identity on these products as "vitamin B6," in fact, refers to PN.

As an authoritative example of this discrepancy in nomenclature, the United States Pharmacopoeia cross-references the entry for "Vitamin B6 Tablets" with PN in the dietary supplement monographs section.[5] Furthermore, PN is the only classical vitamin B6 family member that is listed under the various dietary supplement monographs for water-soluble vitamins.[6] As further evidence of this distinction, an extensive safety database has been compiled for PN, in which the authors refer to pyridoxine in the opening paragraph as "vitamin B6."[7]

Consistent with the foregoing, while PM is considered a member of the vitamin B6 family from a classic metabolic perspective, it is *not* synonymous with the vitamin B6 included in dietary supplement products. Moreover, PM is distinct, from both a chemical and regulatory perspective, from the other members of the vitamin B6 family, including PN, which *is* synonymous with the vitamin B6 included in dietary supplement products.

Finally, pyridoxamine's asserted status as one of the "three primary natural forms of vitamin B6" and "one of the two predominant forms in animal products used as human foods" is not determinative of whether this substance is grandfathered. FDA has explained that "[t]he mere existence of ... a component of a product present in the food supply, does not by itself bring that substance within the scope of the prior market clause. Rather . . . circumstances must establish that in marketing a product containing such a component, a person was, in actuality, marketing the component."[8] As explained below and more fully in the Pyridoxamine Citizen Petition,

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5 UNITED STATES PHARMACOPOEIA 28 & NATIONAL FORMULARY 23, at 2136 (2005).

6 Id. at 2142.

7 Cohen M, Bendich A. Safety of pyridoxine—a review of human and animal studies. Toxicol. Lett. 34(2-3):129-39 (1986).

8 Id. at 25.

there is no evidence that pyridoxamine was affirmatively and specifically marketed as a food or dietary ingredient.

B. CRN Assertion #2: "There is very strong evidence that pyridoxamine was marketed as a dietary supplement prior to October 15, 1994, and is therefore an 'old' dietary ingredient under the Dietary Supplement Health and Education Act ('DSHEA')"

CRN alleges the existence of "very strong evidence" that pyridoxamine was marketed as a dietary supplement prior to October 15, 1994, and is therefore grandfathered or an "old" dietary ingredient under DSHEA. Prior to the publication of the results of BioStratum's Phase II clinical trials investigating the use of pyridoxamine to treat diabetic nephropathy, there is no evidence that pyridoxamine was marketed as a food or dietary supplement in the United States.

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 Pyridorin™ (pyridoxamine).[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 FFDCA 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.

CRN asserts that the inclusion of pyridoxamine in a CRN list compiled in early 1995 of dietary ingredients marketed prior to the passage of DSHEA, conclusively demonstrates that pyridoxamine was marketed prior to October 15, 1994 and is thus grandfathered. The mere presence of pyridoxamine on CRN's list is far from determinative of this fact. FDA has never suggested that the CRN or other industry-developed grandfathered ingredient lists have any legal status or are even accurate. Under the FFDCA, the decision of whether a dietary ingredient is grandfathered exclusively resides with FDA, not industry trade groups such as CRN whose members have a keen pecuniary interest in having as many dietary ingredients as possible designated as grandfathered.

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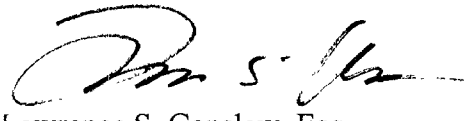
[9] Also of note, the European Union's Food Supplements Directive (2002/46/EC), which establishes a positive list of vitamins and minerals as well as the chemical forms in which they may be used as food supplements, does not list pyridoxamine. Directive 2002/46/EC of the European Parliament and of the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

[10] 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 23.

For the reasons explained herein and in the Pyridoxamine Citizen Petition, CRN is incorrect that pyridoxamine is a grandfathered or otherwise legal dietary ingredient. Accordingly, FDA should disregard CRN's comments and provide the relief requested in the Pyridoxamine Citizen Petition.

Sincerely,



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