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

Re: Response to Jarrow Formulas Comments to FDA's Notice of Opportunity to Comment on the Status of Pyridoxamine, 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 the comments filed on behalf of Jarrow Formulas, Inc. ("JFI") on December 19, 2005 in response to the Food and Drug Administration's ("FDA's" or "the Agency's") issuance of a Notice of Opportunity to Comment on the status of pyridoxamine.[1/]

As JFI filed its comments on the last day of the 30-day comment period for the Notice, BioStratum is filing these further comments after the stated comment period out of necessity. Given the timing of JFI's comments, BioStratum appreciates FDA's consideration of this response even though it is being filed after December 19, 2005.

JFI asserts that: (1) pyridoxamine is a naturally-occurring form of vitamin B6 available in foods such as brewer's yeast, and is therefore an established dietary ingredient; (2) pyridoxamine cannot be classified as a drug based on its high potency in a supplement product; (3) pyridoxamine was on the market as a dietary supplement in 1991; and (4) the inclusion of pyridoxamine in JFI's PyridoxAll product is distinguishable from the situation addressed in *Pharmanex v. Shalala*.[2/] For the reasons set forth below, JFI is incorrect in its overall assertion that pyridoxamine is a grandfathered dietary ingredient, and the foregoing specific assertions are also without merit.

1/ 70 Fed. Reg. 69976 (Nov. 18, 2005).

2/ Pharmanex v. Shalala, Memorandum Decision and Order, 2001 U.S. Dist. LEXIS 4598 (D. Utah 2001).

I. JFI Assertion #1: Pyridoxamine is a naturally occurring form of vitamin B6, and is thus an established dietary ingredient

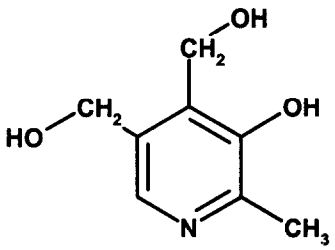
JFI asserts that pyridoxamine is a dietary ingredient, rather than a drug, because (1) it is one of the three primary natural forms of vitamin B6, and (2) pyridoxamine is naturally-occurring in brewer's yeast, frozen fish, fresh and dried yeast, milk, eggs, beef, chicken, and pork. Pyridoxamine's relationship to vitamin B6 was previously addressed in BioStratum's September 29, 2005 response to the September 14, 2005 comments filed by the Center for Responsible Nutrition ("CRN"). Accordingly, the biochemical and nutritional facts concerning pyridoxamine's status as part of the vitamin B6 family were presented to FDA prior to its tentative conclusion that pyridoxamine is excluded from the dietary supplement definition under the exclusion clause at 21 U.S.C. § 321(ff)(3)(B)(ii).[3/] As explained, while BioStratum acknowledges that vitamin B6 (pyridoxine) is a recognized grandfathered dietary ingredient, pyridoxamine is a chemically distinct molecule and is not a grandfathered dietary ingredient by virtue of its metabolic relationship to vitamin B6 (pyridoxine). JFI's comments and referenced materials do not raise any novel issues in this regard.

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/]

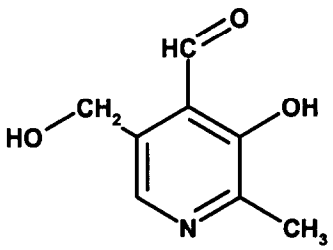
Notwithstanding their participation in similar metabolic pathways, PN, PL and PM are chemically distinct molecules that differ in the functional group branched from the fourth position on the pyridine ring. PN contains a hydroxymethyl (-CH2-OH) group at position 4, PL contains an aldehyde (-CH-O) group, 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.

3/ 70 Fed. Reg. 69976 (Nov. 18, 2005).

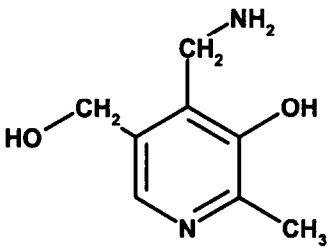
4/ Ink LI, Henderson LM. Vitamin B_6 metabolism. Ann. Rev. Nutr. 4:455-79 (1984); Merril AH, et al. Metabolism of vitamin B_6 by human liver. J. Nutr. 114:1664-74 (1984); Merril AH, Henderson LM. Vitamin B_6 metabolism by human liver. Annals N.Y. Acad. Sci.110-17 (1990).



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/] The interchangeability of PN with vitamin B6 is also evident in two of the scientific references on vitamin B6 cited in JFI's own comments, which are titled "Pyridoxine."[8/]

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. JFI's references to website materials and textbooks acknowledging that PM is metabolically a member of the vitamin B6 family do not change this conclusion.

Moreover, pyridoxamine's asserted presence in brewer's yeast, frozen fish, fresh and dried yeast, milk, eggs, and other animal foods, is not determinative of whether this substance is grandfathered. FDA has explained that "[t]he mere existence of ... a component of a product

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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/ V. Sardesai, Introduction to Clinical Nutrition (N.Y.: Marcel Dekker, 1998), at 213; Goodman and Gillman's, The Pharmacological Basis of Therapeutics (Pergamon Press 1990, 8th ed.), at 1538.

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."[9/] JFI has not provided any evidence that pyridoxamine was affirmatively and specifically marketed as a food or dietary ingredient before BioStratum filed its Investigational New Drug application ("IND") to investigate pyridoxamine as drug for the treatment of diabetic nephropathy in July 1999. Of note, while JFI intimates that consumers have purchased brewer's yeast for benefits derived from pyridoxamine, it conveniently does not support the underlying assertion that marketers of brewer's yeast have affirmatively marketed these products as containing pyridoxamine. If this was the case, JFI obviously would have stated the same.

II. JFI Assertion #2: Pyridoxamine cannot be classified as a drug based on its high potency in a supplement product

JFI contends that, under the Proxmire Vitamin Act (21 U.S.C. § 350), a vitamin may not be classified as a drug based solely on its high potency in a particular supplement product. The issue for consideration in FDA's Notice for Opportunity to Comment, however, was not the potency at which pyridoxamine may be legally marketed in a dietary supplement, but rather whether pyridoxamine may be legally marketed as a dietary supplement at all. As explained above, while pyridoxamine is considered a member of the vitamin B6 family from a classic metabolic perspective, it is a chemically distinct molecule and *not* synonymous with the vitamin B6 included in dietary supplement products. Because pyridoxamine is not a grandfathered or otherwise legal dietary ingredient, it may not be legally marketed as a dietary supplement, regardless of potency level.

III. JFI Assertion #3: Pyridoxamine was marketed as a dietary supplement in 1991

JFI asserts that pyridoxamine was marketed as a dietary supplement in 1991, prior to the October 15, 1994 enactment date of the Dietary Supplement Health and Education Act ("DSHEA"). This assertion is wholly based on the December 19, 2005 affidavit of David Litell (the "Litell Affidavit"), in which Mr. Litell states that he "recall[s] the inclusion of the dietary supplement ingredient Pyridoxamine in a B-Complex vitamin capsule" marketed by EXCEL around 1991. At most, this affidavit suggests that pyridoxamine may have been included in a prior marketed vitamin capsule, although the language used ("recall the inclusion") suggests that Mr. Litell is far from certain about this fact. Moreover, it is telling that Mr. Litell does not identify a manufacturer of the pyridoxamine purportedly included in EXCEL's B-Complex vitamin capsule, which must be separately and specifically manufactured.

Regardless, the Litell Affidavit does not suggest that pyridoxamine itself was affirmatively marketed as a supplement prior to October 15, 1994. Nowhere in the Litell Affidavit is it stated

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9/ 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 25 (hereinafter "Pharmanex Final Administrative Decision").

that pyridoxamine was referenced in the labeling of the B-Complex vitamin capsule or otherwise promoted by EXCEL. Neither does JFI provide any other evidence (e.g., copies of labeling) of the prior marketing of pyridoxamine through its asserted inclusion in the EXCEL B-Complex vitamin capsule. As previously noted, the mere presence of a component in a prior-marketed supplement product is not sufficient to bring the component within the scope of the prior market clause, but rather, "circumstances must establish that in marketing a product containing such a component, a person was, in actuality, marketing the component."[10/] This is not established in the Litell Affidavit.

IV. JFI Assertion #4: The JFI product and its inclusion of pyridoxamine is distinguishable from the *Pharmanex* precedent

JFI contends that its product's inclusion of pyridoxamine is distinguishable from the precedent established in *Pharmanex v. Shalala,*[11/] and lists eight specific reasons that assertedly support this conclusion. Several of these reasons—that pyridoxamine is contained in traditional brewer's yeast, the relationship of pyridoxamine to the vitamin B6 family, and the alleged prior marketing of pyridoxamine as evidenced by the Litell Affidavit—are addressed above.

The remaining reasons appear to concern whether JFI's manufacturing and marketing of pyridoxamine in its product PyridoxAll can be differentiated from the fact pattern set forth in the *Pharmanex* opinion. In that case, the court concluded that lovastatin was the relevant "article" for purposes of the exclusion clause under 21 U.S.C. § 321(ff)(3)(B)(ii) as a result of its finding that Pharmanex, in manufacturing and marketing Cholestin, a red yeast rice product, was actually manufacturing and marketing the drug lovastatin.[12/] This determination was based on several factors, including findings that Cholestin was a "non-traditional" red yeast rice, that Pharmanex deliberately selected and used a "specific strain" of red yeast fungus in its manufacturing to ensure significant levels of lovastatin, that Pharmanex used a patented process for an "improved" red yeast rice product, that traditional red yeast rice does not contain lovastatin, and that Pharmanex promoted the lovastatin content of Cholestin.[13/]

JFI attempts to distinguish its manufacturing and marketing of pyridoxamine from the scenario in the *Pharmanex* case by suggesting that: (1) JFI does not use an "improved" or "high potency" form of vitamin B6; (2) pyridoxamine is not derived from a specific "strain" of vitamin B6; (3) PyridoxAll is not manufactured or processed in any special or artificial way to "heighten" the amount of pyridoxamine; (4) JFI has no patent for an "improved" vitamin B6; and (5) JFI makes

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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 25 (hereinafter "Pharmanex Final Administrative Decision").

11/ Pharmanex v. Shalala, Memorandum Decision and Order, 2001 U.S. Dist. LEXIS 4598 (D. Utah 2001).

12/ Id. at 12.

13/ Id. at 9-11.

no label or advertising claims for pyridoxamine *per se*. JFI, however, misunderstands FDA's further interest in this matter and the *Pharmanex* precedent.

Whether JFI is currently manufacturing and marketing pyridoxamine consistent with the *Pharmanex* standard is irrelevant to the Agency's limited further inquiry identified in its Notice for Opportunity to Comment. The Notice was concerned only with FDA's tentative determination that pyridoxamine is excluded from the dietary supplement definition under the exclusion clause in 21 U.S.C. § 321(ff)(3)(B)(ii). Thus, unlike the situation in *Pharmanex* case, there is no question as to what substance is the relevant "article" for purposes of 21 U.S.C. § 321(ff)(3)(B)(ii)—the "article" under consideration in the Notice is pyridoxamine, and the Agency specifically requested information that relates to whether this substance may legally be marketed in or as a dietary supplement. Information concerning the current marketing of specific products that contain pyridoxamine is irrelevant to this inquiry, except, of course, to the extent that such products were also marketed prior to the enactment date of DSHEA. Accordingly, JFI's attempt to distinguish its manufacturing/marketing of pyridoxamine in PyridoxAll from the red yeast rice in the *Pharmanex* case is completely irrelevant.

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

Sincerely,

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