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December 19, 2005

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VIA FedEx (phone is 301-436-1441)

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Comment from Jarrow Formulas, Inc. objecting to BioStratum Citizen’s Petition  
And In Support of Allowing Dietary Supplements Containing Pyridoxamine  
**Docket No. 2005P-0305**

Dr. Robert Moore, and To Whom It May Concern:

Patton Boggs LLP represents Jarrow Formulas, Inc. (“JFI”), which is a large Los Angeles-based company, founded in 1977, that develops, manufactures, markets, and sells dietary supplements. In particular, we represent JFI with respect to FDA and FTC regulatory compliance matters. This Comment, sent on behalf of JFI, is our detailed response to the Food and Drug Administration’s (“FDA”) call for industry comments on the Citizen Petition filed by BioStratum on July 29, 2005, requesting that the FDA declare that pyridoxamine is a drug and thus disallow it in dietary supplement products. 70 Fed. Reg. 69976 (November 18, 2005). Our position, based on the scientific literature on nutrients is that pyridoxamine is a naturally-occurring form of Vitamin B6 (a “vitamer”) that was on the market in a dietary supplement before October 15, 1994, and thus is a valid and proper dietary ingredient--not a drug.

JFI formulates and markets a dietary supplement, a Vitamin B Complex product containing pyridoxamine and called PyridoxAll™. This dietary supplement contains no drug

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claims or disease claims, on either the label (enclosed<sup>1</sup>) or in advertising. For example, JFI makes no PyridoxAll™ label or promotional claims relating pyridoxamine in any way to diabetes. By letter of August 22, 2005 BioStratum's legal counsel demanded that JFI cease and desist marketing and selling PyridoxAll™ or any product concerning pyridoxamine. Distributors and retailers of JFI's PyridoxAll™ also received letters from BioStratum similar to the August 22<sup>nd</sup> letter. JFI certainly "respects federal laws," but as in many legal issues, the laws or regulations must be applied to specific facts. Here, the facts are biochemical and nutritional, and it is those facts—as to the precise nature of pyridoxamine--that are in dispute, and not the law.

Contrary to BioStratum's cease and desist letters and Citizen's Petition, our position is that pyridoxamine is a valid dietary supplement and dietary ingredient, not a "purported" one, and not a drug. It is not the case that pyridoxamine is only "recently available" as a dietary supplement, and represented in the August 22 letter and the Petition. Instead, pyridoxamine is by definition a vitamer, that is, a form of vitamin B6, as documented in scientific articles and books on nutritional chemistry from 1949 through the present. (Please see documentation from the scientific literature attached). Indeed, pyridoxamine is listed as one of the names or forms of vitamin B6 in the website of the Office of Dietary Supplements, NIH Clinical Center, of the National Institute of Health (NIH). In an article therein entitled "dietary Supplement Fact Sheet: Vitamin B6," we read: "Vitamin B6 is water-soluble vitamin that exists in three major chemical forms: pyridoxine, pyridoxal, and pyridoxamine [citing a nutrition textbook (1999, 9<sup>th</sup> ed.) and a

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<sup>1</sup> Enclosures attached in order of first reference in this Comment.

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scientific article from 1989].<sup>2</sup> Later in this article, the Office of Dietary Supplements states: “The table of selected food sources of vitamin B6 suggests many dietary sources of B6.”<sup>3</sup> It also is not a new dietary ingredient (“NDI”), given that was on the market in a dietary supplement in 1991. (Please see Affidavit of David Litell, attached.)

Pyridoxamine occurs naturally as one of the three individual forms of vitamin B6.<sup>4</sup> Pyridoxamine is the amine form of vitamin B6, and all of the B6 forms or vitamers are found in food.<sup>5</sup> Pyridoxamine di-hydrochloride is found in dried brewer’s yeast; indeed pyridoxal and pyridoxamine are the **predominant forms of vitamin B6** found in frozen fish, fresh and dried years, milk and eggs.<sup>6</sup> The pyridoxamine form is especially plentiful in animal foods such as beef, chicken, and pork.<sup>7</sup>

As stated clearly on the label of PyridoxAll™ (attached), pyridoxamine is one of the three naturally-occurring forms of Vitamin B6, which in turn is naturally occurring in Brewer’s Yeast. Both Vitamin B6 and Brewer’s Yeast have been on the market as well-established dietary

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<sup>2</sup> See copy of NIH website article attached, 7 pages, at p. 1.

<sup>3</sup> Id., at p. 2. Also see, Ekhard Ziegler and L.J. Filer, Jr., eds., Present Knowledge in Nutrition (7<sup>th</sup> ed. 1996) at p. 174.

<sup>4</sup> J. Rabinowitz and E. Snell, Distribution of Pyridoxal, Pyridoxamine, and Pyridoxine in some Natural Products, J. Biol. Chem. Aug. 1948; 176: 1157-1167. (Attached). V. Sardesai, Introduction to Clinical Nutrition (N.Y.: Marcel Dekker, 1998), p. 213.

<sup>5</sup> J. Groff and S. Gropper, Advanced Nutrition and Human Metabolism (1996 3<sup>rd</sup> ed.), at p. 304.

<sup>6</sup> Rabinowitz and Snell at p. 1163, p. 1164.

<sup>7</sup> Sardesai at p. 214. Also see, Ekhard Ziegler and L.J. filer, Jr., eds., Present Knowledge in Nutrition (7<sup>th</sup> ed. 1996) at p. 174-175.

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supplements well before July 1999, the time of BioStratum's filing a IND application for Pyridorin (pyridoxamine dihydrochloride) as a drug for diabetic patients. See Citizen's Petition. Furthermore, for decades U.S. consumers have regularly bought and consumed Brewer's Yeast for its Vitamin B6 content and benefits. Part of this benefit derived from the *naturally-occurring* pyridoxamine therein.

In the classic text on the biochemistry of nutrients, Goodman and Gillman's The Pharmacological Basis of Therapeutics, includes the chemical structures of "the three forms of vitamin B6," with pyridoxamine as one of the three.<sup>8</sup> The authors state categorically that: "Several related *natural* compounds (pyridoxine, pyridoxal, pyridoxamine) have been shown to possess the same biological properties, and therefor all should be called vitamin B6."<sup>9</sup> (Emphases added.)

The definition of "dietary supplement" in Section 3 of the Dietary Supplement Health and Education Act (DSHEA), begins with "a vitamin, a mineral, an amino acid . . . ." See 21 U.S.C. § 321 (ff) (emphasis added). Thus, pyridoxamine, as a natural form of Vitamin B6, is one of the most basic and established of dietary ingredients. Moreover, any constituent of a dietary ingredient (say, Vitamin B6) may be declared on the supplement label, under 21 C.F.R. § 101.36(b)(3)(iii), at the option of the labeler. Consequently, pyridoxamine may be legally declared as a constituent of Vitamin B6 in a Supplement Facts box. Finally, as also stated on the

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<sup>8</sup> Goodman and Gillman's The Pharmacological Basis of Therapeutics (Pergamon Press 1990 (8<sup>th</sup> ed.), at 1538; also see pp. 1538-1540.

<sup>9</sup> Goodman and Gillman at p. 1538.

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PyridoxAll™ product label, B6 is found in the human body mostly in the liver—*primarily as pyridoxamine.*

While we agree that vitamins are occasionally used as drugs (e.g., injected vitamin B 12), vitamins ingested as dietary supplements—and intended, labeled, and marketed as supplements—are never drugs. The Proxmire Vitamin Act, passed by Congress in 1976, essentially provides that a high amount or potency does not confer drug status, for a vitamin or mineral. Title 21 U.S.C. § 350. Vitamins and minerals, states as follows:

**(a) Authority and limitations of Secretary; applicability**

... **(B)** the Secretary may not classify any natural or synthetic vitamin or mineral (or combination thereof) as a drug solely because it exceeds the level of potency which the Secretary determines is nutritionally rational or useful; [Emphasis added.]

Thus a vitamin—even in high doses and even if synthetic—is not a drug unless intended and marketed for treatment of disease. Specifically, the pyridoxamine as used in JFI's PyridoxAll™ (even if used in amounts greater than that found in Brewer's Yeast) is a dietary ingredient and not a drug, given that it is a form of vitamin B6, and its intended use is to supplement the diet and not to cure, treat, or mitigate diabetes, high blood sugar, or any other disease or abnormal condition. It is within the scope of the Proxmire Vitamin Act, which was not superceded by DSHEA, and must be read in conjunction with it.

Nor is pyridoxamine a drug-like extract of Vitamin B6. As you know, pyridoxamine has been analogized to lovastatin—in the Tan Sheet and elsewhere<sup>10</sup>--and this issue compared to the central issue in the Pharmanex opinion; however, the JFI product and its inclusion of a form of

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<sup>10</sup> The Tan Sheet, at p. 14 (August 22, 2005).

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Vitamin B6 is quite distinguishable on the facts. See 2001 WL 741419 (D. Utah). Using the court's language from the Pharmanex opinion, this present situation is distinguishable from the FDA's interpretation of lovastatin in Cholestin for the following reasons:

1. Pyridoxamine is contained in "traditional" Brewer's Yeast; it is not necessary to create an "improved" form, nor was this done by JFI.
2. Pyridoxamine is a naturally-occurring form of traditional Vitamin B6; it is not necessary to create an "improved" or "high potency" form, nor was this done by JFI.
3. Pyridoxamine is not indirectly derived from any specific "strain" of Vitamin B6; it is one of the innate forms of that vitamin, hence scientifically called a "vitamer."
4. The Vitamin B6 in PyridoxAll<sup>TM</sup> is not manufactured or processed by JFI or its manufacturer in any special or artificial way to "heighten" the amount or presence pyridoxamine.
5. JFI has no patent issued or patent application pending regarding an "improved" Vitamin B6.
6. JFI does not use pyridoxamine as a "marker" for any special effect of PyridoxAll<sup>TM</sup>.
7. JFI makes no label or advertising claims for the effects of pyridoxamine *per se*.
8. Before July 1999, indeed before October 15, 1994, pyridoxamine and other forms of Vitamin B6 were included in and referenced on labels of Vitamin B6 and or B Complex supplements. For instance, an EXCEL Vitamin-B Complex supplement containing pyridoxamine was on the market in the early 1990's, approximately 1991. (See Affidavit of David Litell, attached.) A supplement containing pyridoxamine thus was indeed

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marketed prior to pyridoxamine being researched as a drug (even using the FDA's interpretation of "marketed").

For all of the reasons above, we believe that pyridoxamine is a valid and legal dietary supplement ingredient or dietary ingredient under the statutory definition in Section 3 of DSHEA, which does not violate the "prior-market clause." For similar reasons, JFI does not believe that PyridoxAll™ or other supplements containing pyridoxamine are "adulterated." Rather, since pyridoxamine is simply a form of Vitamin B--which certainly and undeniably is "grandfathered" under Section 8 of DSHEA, then pyridoxamine is not a new dietary ingredient (NDI), and does not require an NDI Notification. Conversely, it is not the case that pyridoxamine is derivable from Vitamin B6 only through "chemical alteration"; it is an innate form of B6 that occurs in nature. Thus, pyridoxamine is not an NDI which could render a finished dietary supplement product adulterated.

As shown through excerpts of major, classic texts on the biochemistry of nutrients, and from the website of NIH, Pyridoxamine is simply one form (a natural form) of a very common vitamin, namely Vitamin B6, and thus a valid and proper dietary supplement ingredient. Pyridoxamine was on the market in the U.S. in a Vitamin B complex in the early 1990's, prior to being studied for drug use. In light of all the above considerations, Pyridoxamine is not "a drug," should not be determined as such by the FDA, and thus should not be disallowed in dietary supplements.



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Thank you for your serious consideration to this analysis.

Sincerely,

A handwritten signature in cursive script that reads 'Susan D. Brienza'.

Susan D. Brienza

SDB:mb

Enclosures: Copy of PyridoxAll™ label  
Copies of 5 article & book excerpts re: Vitamin B6  
Copy of NIH website describing Vitamin B6  
Litell Affidavit & Biography

cc: Jarrow L. Rogovin  
Sid Shastri, M.Sc.  
David Litell