



Council for Responsible Nutrition

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Documents Management Branch
Food & Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

Re: PYRIDOXAMINE – Citizen’s Petition, Docket No. 2005P-0305 (70 Fed. Reg. 69976-7, dated November 19, 2005)

Dear Madam or Sir:

These comments further respond to the Food and Drug Administration’s Notice of Opportunity to Comment published in 70 FR 69976-7 (November 18, 2005) with respect to information that “bears on pyridoxamine’s prior marketing as a dietary ingredient or as a food, as well as other information that would inform the agency’s final decision on the status of pyridoxamine.”

I. Pyridoxamine is a Dietary Ingredient

As referenced in our December 16th comments, pyridoxamine is unequivocally a dietary ingredient because it is one of three primary natural forms of vitamin B6¹. The collective name of vitamin B6 is pyridoxine, but this term refers to three chemical forms: pyridoxal (an aldehyde structure), pyridoxamine (an amine structure) and pyridoxol (an alcohol structure). The vitamin functions of pyridoxine (vitamin B6) can be achieved by a dietary source of any of these three forms. The known biochemical functions of vitamin B6 are actually achieved by the activated forms of the vitamin in the amine and aldehyde structural forms and involve transfer of chemical groups between the activated pyridoxamine and activated pyridoxal. In this process, the vitamin B6 molecule is repeatedly transformed from pyridoxamine to pyridoxal and back. These actions of vitamin B6 are essential for functions and health related to protein metabolism, actions of certain other vitamins, glucose and lipid metabolism, red blood cell production and function, nerve actions, immune system, and hormone production and modulation.

Pyridoxamine commonly occurs in almost all foods containing vitamin B6 and is the predominant form of the vitamin in several common foods, including fish, chicken and beef liver, brewer's and baker's yeast, whole wheat, green pepper, and cooked sausages^{2, 3}.

¹ Mackey AD, David SR, Gregory III JF. Vitamin B6. *In: Modern Nutrition in Health and Disease*, 10th Edition. ME Shils, M Shike, CA Ross, B Caballero, RJ Cousins, eds., Lippincott Williams & Wilkins, Baltimore, 2006.

² Rabinowitz JC, Snell EE. The vitamin B group. XIV. Distribution of pyridoxal, pyridoxamine and pyridoxine in some natural products. *J Biol Chem* 1948; 176:1157-67.

II. Pyridoxamine Was Marketed as a Dietary Supplement Prior to the Passage of DSHEA and Prior to the 1999 BioStratum IND

The only remaining question is whether and when pyridoxamine has been marketed as a dietary supplement in the United States. Since CRN requested an extension of the comment period in December 2005, we have been surveying CRN's members in an attempt to provide documentation that pyridoxamine was marketed prior to the passage of the Dietary Supplement Health & Education Act (DSHEA) in October 1994. Unfortunately, because none of CRN's members currently market a product containing pyridoxamine, it has been difficult to muster the resources that would be required to launch a full-scale search of company records that have long been in storage, if they still exist at all. Because materials in this timeframe pre-date widespread usage of computer storage of data and electronic recordkeeping, such materials as catalogues, order forms, or other materials relating to the pre-DSHEA marketing of pyridoxamine as an ingredient in dietary supplements are no longer available, or if they are, have not been made accessible to CRN to date.

However, we have interviewed retired industry executives and academics and other people who were close to the industry prior to that time, and several recall that pyridoxamine was marketed in dietary supplements prior to October 15, 1994. This pre-DSHEA marketing is also documented in dietary supplement industry lists of so-called "grandfathered" ingredients. Shortly after the passage of DSHEA, the National Nutritional Foods Association (NNFA) generated a list of dietary supplement products and ingredients that were marketed prior to October 15, 1994, in order to preserve a record of those pre-DSHEA "grandfathered" products and ingredients. As described in the attached affidavit of Dr. Annette Dickinson, who was the Director, and subsequently Vice President, for Scientific and Regulatory Affairs at CRN during the relevant time period, the NNFA list was derived from information that had been compiled contemporaneously with the pre-DSHEA marketing of dietary supplements and ingredients, and for independent purposes. Because of its credibility in representing dietary ingredients that had been marketed prior to October 15, 1994, CRN used the NNFA list as the foundation of its own list of "grandfathered" dietary ingredients. Pyridoxamine hydrochloride was unquestionably included in the NNFA list, and was therefore included in, and remains on, CRN's "List of Dietary Ingredients 'Grandfathered' Under DSHEA." Attached, along with Dr. Dickinson's affidavit, is a copy of CRN's list and Dr. Dickinson's May 22, 1996 memorandum to CRN members circulating the NNFA list and describing the process for the development of CRN's list.

In addition, FDA should be particularly mindful of its position on this issue and its efforts to resolve this issue in favor of the petitioner because of the perpetual status conferred on products in the food supply as of 1994 and the inability of an FDA rulemaking to topple those rights. As previously noted, pyridoxamine, as a form of Vitamin B6, is naturally found in the food supply. Section 413 of the Federal Food, Drug, and Cosmetic Act (FD&CA) provides that a dietary ingredient which has been "present in the food supply as an article used for food in a form in which the food has not been chemically altered" need not comply with the 75-day notice requirements of the Act that would apply to new dietary ingredients first introduced after that time. 21 USC 350b(a)(2). Even if it was not

³ Vals F, Sancho MT, Fernandez-Muino M, Checa MA. Determination of vitamin B6 in cooked sausages. *J Agric Food Chem* 2001;49:38-41.

marketed as a dietary supplement prior to 1994, pyridoxamine, as an ingredient of green peppers, fish, liver and common food yeasts, all of which were in the food supply in 1994, is exempt from the new dietary ingredient (NDI) provisions of DSHEA. Therefore, it would not have been necessary for a marketer to provide a 75-day notice of a new dietary ingredient to FDA prior to marketing a pyridoxamine-containing dietary supplement, even if it first entered the market subsequent to October 15, 1994. Only the filing of an investigational new drug (IND) application by the drug manufacturer, as occurred in 1999, would have cut off this prospective opportunity to market the ingredient as a dietary supplement for the first time.

Even more critical to FDA's decision in this matter is the unequivocal fact that if evidence is discovered in the future that demonstrates that pyridoxamine was marketed at any time prior to BioStratum's filing of the IND application in 1999, then FDA will not be able to deny a dietary supplement company's right to reassert the dietary ingredient status of pyridoxamine at that time. The FD&CA, as amended by DSHEA, grants dietary ingredient status to products that were in the food supply at the time of DSHEA's passage. A subsequent grant of an IND by the agency cannot revoke a right conferred by the statute. Thus, although we recognize FDA's desire to provide certainty and predictability to the requestor in this case, the provision of DSHEA is clear: pyridoxamine, or any other ingredient found in the food supply in 1994, does not lose its dietary ingredient status simply because, as science advances, the pharmacologic properties or health benefiting attributes of the ingredient become more well-known. CRN and its members will continue to examine documentary evidence that may demonstrate the availability of pyridoxamine as a dietary supplement prior to 1999. FDA will be obliged to receive that data regardless of the immediate decision it makes in this rulemaking, and BioStratum will have no recourse to prevent the continued marketing of pyridoxamine as a dietary supplement.

In sum, sufficiently reliable evidence exists, and is attached, to demonstrate that pyridoxamine is a dietary ingredient that was marketed as a dietary supplement prior to the passage of DSHEA, and therefore prior to the BioStratum IND in 1999. CRN and its members will continue to search for additional records documenting this fact. Under the FD&CA, as amended by DSHEA, it is this evidence that determines the status of pyridoxamine as a dietary supplement ingredient, rather than any determination that FDA makes in response to the BioStratum citizen petition.

Very truly yours,



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