



APR 3 2006

Mr. Louis A. Montgomery
Louis Montgomery Enterprises
6542 Hypoluxo Road, Suite 114
Lake Worth, Florida 33467

Dear Mr. Montgomery:

This is to inform you that the notification, dated January 14, 2006, that you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on January 18, 2006. Your notification concerned the substance that you call "S-benzoylthiamine-O-monophosphate" or "benfotiamine" that you intend to market in a dietary supplement product.

According to your notification, you intend to distribute a product containing "benfotiamine" as the only dietary ingredient in capsule form. Regarding the conditions of use, your notification states that "[t]he bottle label will recommend users supplement their diets with 1-4 capsules per day (150-600mg.) of benfotiamine, or as advised by their nutritional or health care advisors, to effectively and safely increase durable levels of active thiamine in their tissues and viscera."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. 350b (a) (2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f) (1) (B) (section 402(f)(1)(B) of the Act) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

It is not readily apparent whether the substance that is the subject of your notification is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. The term "dietary supplement" is defined in 21 U.S.C. 321(ff). A

dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

Based on the information in your submission, it is unclear whether "benfotiamine" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1). Therefore, FDA can not determine, at this time, whether your product contains a dietary ingredient that may lawfully be marketed as a dietary supplement.

Nevertheless, FDA has carefully considered the information in your submission and the agency has concerns about the evidence on which you rely to support your conclusion that "benfotiamine" will reasonably be expected to be safe.

FDA was unable to establish the identity of "benfotiamine". For example, your notification includes a patent that describes multiple methods for syntheses, each with different starting materials and with different products all of which can be described using the name S-benzoylthiamine-O-monophosphate. However, the yields of products vary and the product(s) appear to have melting points with decomposition in the range of 150-170°C. This is not consistent with the information provided in your notification which states that you will obtain a compound with a melting point of about 200° C but provides no further information. No methods of analysis or statements of purity of the preparation(s) are provided. It is unclear which, if any, of these synthetic routes will be used by the manufacturer from which you intend to obtain "benfotiamine". You provide, as history of use or other evidence of safety of your ingredient, information about products produced by pharmaceutical companies in Germany and Japan. It is unclear how the product you intend to market is qualitatively and quantitatively similar to the substances described in the information that you rely on as evidence of safety of your product.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "benfotiamine" when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of January 18, 2006. After the 90-day date, the notification will be placed on public display at FDA's Docket

Page -3- Mr. Louis Montgomery

Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter please contact Dr. Linda Pellicore at (301) 436-2375.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'S. Walker', with a long horizontal flourish extending to the right.

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

**Pre-Market Notification Submission
for
S-BENZOYLTHIAMINE O-MONOPHOSPHATE
(BENFOTIAMINE)**

Number 1 of 3

January 14, 2006

Submitted by: Louis Montgomery Enterprises

January 14, 2006

Food and Drug Administration
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements
(HFS-820) Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD, 20740-3835

1043 6 MAY 11 3:47

1. Name/address of the distributor of the New Dietary Ingredient:

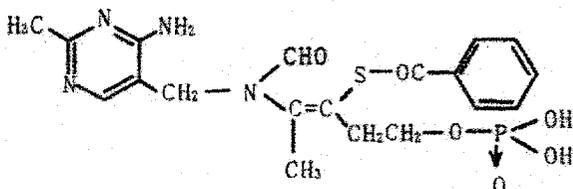
1.1. Louis Montgomery Enterprises, 6542 Hypoluxo Road, Suite 114, Lake Worth, FL 33467.

2. The name of the subject New Dietary Ingredient:

2.1. S-benzoylthiamine-O-monophosphate, common name **benfotiamine**, CAS Number 22457-89-2, chemical formula, molecular formula and structure depicted below:

White crystals or crystalline powder.

FORMULA: C₁₉H₂₃N₄O₆PS MOLECULAR FORMULA: 466.45



MELTING POINT: about 200°C (with decomposition)

2.2. Throughout this submission the term: "**benfotiamine**" means **S-benzoylthiamine-O-monophosphate, C₁₉H₂₃N₄O₆PS, CAS Number 22457-89-2**. Though materials I have submitted to support my conclusions regarding benfotiamine may make reference to other compounds, including calcium or sodium salts of benfotiamine, the material I am referring to and intend to import is: **S-benzoylthiamine-O-monophosphate, C₁₉H₂₃N₄O₆PS, CAS Number 22457-89-2**.

2.3. Benfotiamine (S-benzoylthiamine-O-monophosphate, CAS Number 22457-89-2) is a molecule that qualifies as a "dietary ingredient" under the meaning of 21 U.S.C. 321(ff)(1), specifically clauses (A), (E) and (F) of subparagraph (1).

2.3.1. (ff) The term "dietary supplement"—

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following **dietary ingredients**:

(A) a vitamin;

(B) a mineral;

(C) an herb or other botanical;

(D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, **metabolite**, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

2.3.2. Benfotiamine fits the *The American Heritage® Stedman's Medical Dictionary* definition of vitamin: Main Entry: **vi·ta·min**

Variant: *also vi·ta·mine /'vlt-&-m&n, Brit also 'vit-/*

Function: *noun*

: any of various organic substances that are essential in minute quantities to the nutrition of most animals and some plants, **act especially as coenzymes and precursors of coenzymes in the regulation of metabolic processes but do not provide energy or serve as building units**, and are present in natural foodstuffs or are sometimes produced within the body.

2.3.3. I note that although the definition above includes the phrase: "are present in natural foodstuffs," 21 U.S.C 350(a)(1)(A), (B) & (C) seems clearly to allow for synthetic vitamins: **350. Vitamins and minerals (a) Authority and limitations of Secretary; applicability**

(1) Except as provided in paragraph (2)—

(A) the Secretary may not establish, under section 321 (n), 341, or 343 of this title, maximum limits on the potency of any **synthetic** or natural vitamin or mineral within a food to which this section applies;

(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;

(C) the Secretary may not limit, under section 321 (n), 341, or 343 of this title, the combination or number of any **synthetic** or natural—

- (i) vitamin,
- (ii) mineral, or
- (iii) other ingredient of food,

within a food to which this section applies.

- 2.3.4. The Bioinformatics Center, Institute for Chemical Research, Kyoto University lists benfotiamine as a vitamin B-1 derivative in a list (see tab 1) of vitamins or "Agents affecting metabolism."
- 2.3.5. IPCS INCHEM lists benfotiamine as a member of the thiamine group (see tab 2). Thiamine has long been recognized as vitamin B-1. Benfotiamine is listed along with other common thiamine pre-cursors, such as thiamine hydrochloride and thiamine mononitrate. I note that active thiamine in the body (thiamine pyrophosphate) cannot be ingested with the expectation that it will survive the digestive process, but must rather be produced in the body either via the intake of thiamine containing foods, such as pork or unpolished rice, or via the intake of synthetic thiamine precursors, such as thiamine hydrochloride, thiamine mononitrate or benfotiamine. In all cases these pre-cursors are considered vitamins, as their sole function is to produce active thiamine in the body.
- 2.3.6. To quote from U.S. Patent Number 3,064,000, issued 14 Nov 1962, (see tab 3): "This invention relates to a novel thiamine derivative, S-benzoylthiamine-O-monophosphate..."; Also, "S-benzoylthiamine O-monophosphate of this invention is prominent in that it may be readily converted to (the) active form of thiamine in the body and it may be readily utilized in the body as the thiamine source."
- 2.3.7. The company that invented benfotiamine, The Sankyo Corp., launched a benfotiamine product under the trade name BIOTAMIN in 1961 identified as: "...a vitamin B1 preparation" (see tab 4).
- 2.3.8. On 26 Dec 2005, Tatsuya Ikeda, Export Manager for the Sankyo Corp., certified to me via email that BIOTAMIN is benfotiamine, CAS Number 22457-89-2 (see tab 5).
- 2.3.9. In his paper, *Pharmacokinetics of thiamine derivatives especially of benfotiamine*, (see tab 6) Dr. D. Loew states: "Benfotiamine, an allithiamine, contains an open thiazole ring...that is closed by reduction within the organism producing physiological thiamine." He further states: "It is quite clear that benfotiamine is absorbed much more better than water-soluble thiamine salts: maximum plasma levels of thiamine are about 5 times higher after benfotiamine, the bioavailability is at maximum 3.6 times as high as that of thiamine hydrochloride and better than other lipophilic thiamine derivatives." This paper makes it clear that the sole

function of benfotiamine is to efficiently metabolize into active thiamine in the body. It does this more effectively and more safely than the other thiamine pre-cursors, including those in common current use, such as thiamine hydrochloride.

- 2.4. Benfotiamine fits under the meaning of 21 U.S.C. 321(ff)(1)(E) because it may be **used by man to supplement the diet by increasing the total dietary intake** of thiamine. Benfotiamine has no other physiological effect except to produce durable levels of active thiamine in the body (**see especially tabs 3 and 6**).
- 2.5. Benfotiamine fits under the meaning of 21 U.S.C. 321(ff)(1)(F) because it is a metabolite of the vitamin thiamine or B-1. Encyclopedia.com defines "metabolite" thusly:

metabolite

Related: **Biographies Chemistry**

organic compound that is a **starting material in**, an intermediate in, or an end product of **metabolism**. Starting materials are substances, usually small and of simple structure, **absorbed by the organism as food**. **These include the vitamins** and essential amino acids. **They can be used to construct more complex molecules, or they can be broken down into simpler ones.**

- 2.5.1. Given that I have found no novel statutory definition of "metabolite," I find it appropriate to apply the commonly accepted definition above, in which case benfotiamine is clearly a metabolite of a vitamin, namely active thiamine or vitamin B-1, just as thiamine hydrochloride or thiamine mononitrate are metabolites of vitamin B-1.
- 2.6. As further evidence that benfotiamine is used abroad as a functional food ingredient, I note the sale of the energy/vitamin drink "Regain" by the Sankyo Corp. to the public in Japan (**see tab 7**). The first Regain energy/vitamin drink was introduced for sale to the public in Japan in 1988, with subsequent products following since that time. Regain is sold in shops open to the public and without a medical prescription. It is clearly identified as a vitamin/energy drink by its list of ingredients—most if not all of which are recognized as dietary ingredients in the US. Though the documents at tab 7 are not completely translated into English, they are sufficiently translated to establish that the Regain products contain a number of dietary ingredients, including Biotamin or benfotiamine, and that they are for sale to the public. I have previously established that Biotamin is the trade name used by the Sanko Corp. for benfotiamine. Mr. Tatsuya Ikeda of the Sankyo Corp. has certified to me that these Regain products are widely distributed in Japan and are for sale without a medical prescription. As for the identity of the vitamin B1 derivative referred to in the ingredients list at tab 7, I offer the Biotamin data sheet (**see tab 8**) to

identify the Japanese characters: “ビオタミン” as Biotamin, and the Japanese characters: “ベンフォチアミン” as benfotiamine. Those same Japanese characters are used to describe both Biotamin and benfotiamine as the vitamin B1 component of the Regain energy/vitamin drinks.

2.7. In addition to being referred to in the foreign literature as a vitamin or thiamine derivative, benfotiamine is also referred to in much of the foreign literature as a drug, pro-drug or medication. I note that all vitamins, including those we in the US commonly accept as dietary supplements, are also classified as drugs by those same foreign sources. I do not find this problematic as I believe US law should govern whether benfotiamine is to be treated in the US as a drug, new drug, or new dietary ingredient. The US statutory definition of drug is: “g)(1) The term “drug” means (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) or sections 403(r)(1)(B) and 403(r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement.” I would assert that benfotiamine has no direct therapeutic value. Its sole function is to produce durable levels of active thiamine in the body (**see especially tabs 3 and 6**). The potential therapeutic effect of durable levels of active thiamine in the body goes beyond the scope of this submission. I am solely interested in the manufacture and distribution of a benfotiamine dietary supplement as an excellent source of active thiamine. I am not interested in representing benfotiamine as a compound to diagnose, cure, mitigate, treat or prevent any disease in man. Also, benfotiamine is not listed as a drug in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them. Therefore, given its chemical structure, physiological function, and intended use, benfotiamine clearly fits the US statutory definition of a dietary supplement, providing an excellent source of active thiamine to the consumer. As I have found no documentation proving benfotiamine was marketed in the US prior to 15 Oct 1994, it clearly meets the statutory definition of “new dietary ingredient.” The remainder of this submission demonstrates there is a history of use or other evidence of safety

establishing that the dietary ingredient benfotiamine, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.

3. Upon meeting my regulatory burden under 21 U.S.C. 350b(a)(2), I intend to:
 - 3.1. **Import** bulk, pharma-grade benfotiamine, CAS Number 22457-89-2, from a reliable, GMP-certified supplier, then **manufacture** in an FDA-certified facility under GMP conditions in the US benfotiamine capsules for oral ingestion. These capsules will contain **150mg. of benfotiamine** and no other active ingredients.
 - 3.2. **Distribute** these benfotiamine capsules as a dietary supplement to consumers in the US. The bottle label will recommend users supplement their diets with 1-4 capsules per day (150mg. – 600mg.) of benfotiamine, or as advised by their nutritional or health care advisors, to effectively and safely increase durable levels of active thiamine in their tissues and viscera.
4. History of use or other evidence that benfotiamine, when used as recommended or suggested on the label, will reasonably be expected to be safe:
 - 4.1. On November 13, 1962 the United States Patent Office issued US Patent Number 3,064,000 (**see tab 3**) for S-BENZOYLTHIAMINE O-MONOPHOSPHATE AND A PROCESS FOR PREPARING THE SAME. To quote from two locations in the patent:
 - 4.1.1. "S-benzoylthiamine O-monophosphate of this invention **has lower toxicity than thiamine hydrochloride** as shown in Table III." (See page 2, column 3 of the patent, just above Table III.)
 - 4.1.2. "S-benzoylthiamine O-monophosphate of this invention is prominent in that it may be readily converted to active form of thiamine in the body and it may be readily utilized in the body as the thiamine source. Moreover, this thiamine derivative may be readily absorbed in the body maintaining thiamine levels of viscera high for a long period of time." (See page 2, column 3 of the patent, just below Table III.)
 - 4.1.3. Though the patent also mentions the calcium and sodium salts of benfotiamine, the relevant information above pertains to benfotiamine itself and not its calcium nor sodium salts.
 - 4.2. Based on laboratory mouse LD50 tests, **benfotiamine has a more favorable toxicological profile than many of the other B-complex vitamins by a wide margin, including especially the more common vitamin B-1 precursor/provitamin: thiamine hydrochloride.** (See the table on the following page and the toxicology sheets at **tab 9.**)

Compound	Vitamin	LD50 Results (Oral, Lab Mice)
S-benzoylthiamine O-monophosphate (benfotiamine)	B-1	15,000 mg/kg
Thiamine hydrochloride	B-1	8,224 mg/kg
Niacin	B-3	3,720 mg/kg
Ademine	B-4	783 mg/kg
Calcium Pantothenate	B-5	10,000 mg/kg
Pyridoxine Hydrochloride	B-6	5,500 mg/kg
Folic Acid	B-11 (Folate)	10,000 mg/kg
Cyanocobalamine	B-12	5,000 mg/kg

(Riboflavin (B-2) was not included in the table because all available data for riboflavin was based on lab rats vs. mice (10,000 mg/kg))

4.3. According to the scientific paper *Pharmacokinetics of Thiamine Derivatives Especially of Benfotiamine*, authored by Dr. D. Loew of Wuppertal, Germany, and published in the International Journal of Clinical Pharmacology and Therapeutics, Vol. 34, No. 2 – 1996 (pgs. 47-50) (see tab 6):

4.3.1. "Due to their greater bioavailability and better tissue passage **lipid-soluble thiamine analogues like benfotiamine are preferable to water-soluble thiamine derivatives...**" (pg. 49, column 2)

4.3.2. "Due to its excellent pharmacokinetic profile and to its **excellent tolerability** benfotiamine should be preferred..." (pg. 49, last para.)

4.3.3. I note that even though extra vigilance is often called for when dealing with lipid-soluble vitamins such as vitamins A, D, E & K, (lest they accumulate to toxic levels in the fatty tissues) benfotiamine's lipid-solubility functions merely to facilitate it's absorption through the gut, upon which it metabolizes into active thiamine (thiamine pyrophosphate) and does not build up in the fatty tissues nor create a cumulative toxicity issue.

4.4. For me, the most convincing history of use data I found regarding benfotiamine (see tab 10) was obtained from the Bundesinstitut für Arzneimittel und Medizinprodukte (The German Federal Institute for Drugs and Medical Devices) from whom I learned:

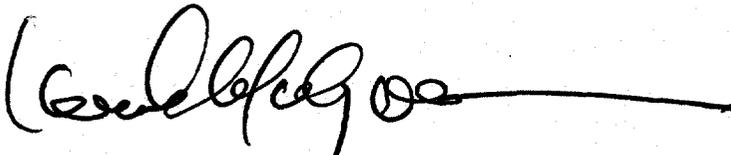
4.4.1. Benfotiamine, CAS Number 22457-89-2, has been available for sale at pharmacies in Germany without prescription since 1978.

- 4.4.2. Typical daily oral dosages of benfotiamine range from 50mg. to an authorized maximum of 900mg.
- 4.4.3. Based only on prescription data for one benfotiamine preparation sold in Germany (Milgamma Mono), there were 2.4 million defined daily dosages prescribed during the calendar year 2002. (One may infer that the actual annual number of defined daily dosages of benfotiamine consumed is much higher than 2.4 million, as it is widely available without a prescription from pharmacies throughout Germany.)
- 4.4.4. Within their database, **in the 27 years since 1978**, there have been only **18 adverse reactions reported** involving benfotiamine single component preparations, and in **only 10** of those reports **was benfotiamine suspected** as the possible cause. In the other 8 reports, benfotiamine was reported as a concomitant compound in the list of other compounds involved. Of the 10 reports where benfotiamine was suspected as the causal agent, 7 reports indicated transient headache as the adverse reaction. **(Please see tab 10 for my inquiry to BfArM and their complete response.)**
- 4.4.5. To quote from their response: "With regard to benfotiamine, routine pharmacovigilance has been performed using data from different sources (spontaneous ADR reports, periodic safety update reports, scientific literature). In doing so, **no safety signals pertaining to benfotiamine ...have been identified.**"
- 4.4.6. Again, though the BfArM refers to benfotiamine as a drug, it is also clear from their data that benfotiamine is a thiamine pre-cursor used clinically to correct thiamine deficiencies. It is available to the public without a medical prescription, and many Germans buy benfotiamine off the shelf as a thiamine supplement. I have previously elaborated on why I believe benfotiamine correctly falls under the meaning of the relevant US statutes dealing with dietary ingredients and supplements.
- 4.5. I offer the reference at **tab 11** as further evidence that daily dosages of benfotiamine in the 600mg. range are well-tolerated without reports of adverse reactions.
- 4.6. I contacted the Japanese Ministry for Health, Labor & Welfare, only to learn from Ms. Rei Nakagawa (nakagawa-rei@mhlw.go.jp) that the ministry does not maintain safety data for pharmaceuticals.
- 4.7. I contacted the Sankyo Corporation, original developer of benfotiamine, and confirmed that Sankyo has been marketing benfotiamine in Japan and elsewhere in Asia under the trade name Biotamin since 1961. Confirmation of this is available on the Sankyo Corp. website at: (<http://www.sankyo.co.jp/english/history/history1960.html>) **(see also tab 4)**. Sankyo continues to market benfotiamine in various forms both in Japan and for the export market. A Sankyo Corp. representative has told me in

conversation that Biotamin (benfotiamine, CAS Number 22457-89-2) has been marketed in Japan for so long and has been so well accepted and tolerated that safety data on it has long been archived and would be somewhat difficult to retrieve and translate.

- 4.8. I have learned that benfotiamine is marketed by a number of firms worldwide in markets from Japan and throughout Asia as well as most of Western and especially Eastern Europe and Russia. Though it would be impractical to cite and provide photocopies of all the literature I have reviewed to prepare this submission, I will certify that I have not uncovered any reports in any of the literature pertaining to benfotiamine that would lead one to assume that benfotiamine cannot reasonably be expected to be safe. To the contrary, benfotiamine is consistently cited in the literature as being highly tolerable and very non-toxic. Most if not all of the literature I have reviewed cite benfotiamine as the preferable source of active thiamine in the body.
5. It is therefore my position that this PMN contains adequate information to establish that benfotiamine is a new dietary ingredient with sufficient clinical data and history of use data to conclude that it may reasonably be expected to be safe when used as recommended. I therefore respectfully request your office grant me a letter of acknowledgement which will allow me to import pharma-grade, bulk benfotiamine (CAS Number 22457-89-2), manufacture a finished product as described in paragraph 3. herein, and distribute that dietary supplement to consumers in the US.

Very respectfully,



Louis A. Montgomery