DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

JAN 16 P3:08

Date: JAN 09 2008

From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Symbiosis of *Streptococcus faecalis* T-110, *Bacillus mesentericus* TO-A and *Clostridium butyricum* TO-A

Firm: GloboAsia LLC

Date Received by FDA: August 23, 2007

90-Day Date: November 21, 2007

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Theresa Prigmore

(95S-0316)

(Rpt 425)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

NOV 6 2007

Albert Wai-Kit Chan
Law Offices of Albert Wai-Kit Chan, LLC
Word Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357

Dear Mr. Chan:

This is to inform you that the notification, dated August 15, 2007, 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 August 23, 2007. Your notification concerned the substance you called "a symbiosis of *Streptococcus faecalis* T-110, *Bacillus mesentericus* TO-A, and *Clostridium butyricum* TO-A" that you identify as a new dietary ingredient you intend to market in a dietary supplement product called "BIO-THREE™".

According to your notification, the recommended serving for adults is 2 tablets, three times a day and children between five and fifteen is half the adult dose. For adults, this would yield a daily intake of 30 mg *S. faecalis*, 150 mg *B. mesentericus*, and *150 mg C. butyricum* for adults. It further states that the product is "[r]ecommended as a dietary supplement for maintaining normal gastrointestinal function, to be consumed orally as a tablet, three times a day before meals, after meals, between meals or whenever convenient."

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) 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.

Your notification concerning "BIO-THREE™" does not comply with the requirements of 21 CFR 190.6 and is incomplete. According to 21 CFR 190.6(b)(5), any reference to published information offered in support of the notification shall be accompanied by reprints or

photostatic copies of such references accompanied by a complete and accurate English language translation. 21CFR 190.6(a) also states that notifications shall include an original and two copies. Your notification consisted of a single copy of information that you use to support the safety of your product.

In addition, because FDA could not determine the identity of your new dietary ingredient "symbiosis", 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)."

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "BIO-THREE™", 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 August 23, 2007. After the 90-day date, the notification will be placed on public display at FDA's Docket 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 me at (301) 436-1448.

Sincerely yours,

Linda S. Pellicore

Linda S. Pellicore, Ph.D.
Supervisor, Senior Toxicologist
New Dietary Ingredients Review Team
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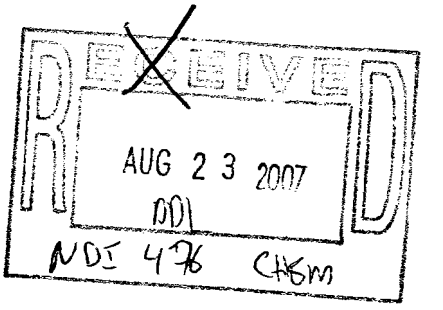

VIA EXPRESS MAIL (Label No. EV 453717828 US)
Susan J. Walker, M.D.
Division of Dietary Supplement Programs
Office of Nutritional Products,
Labeling and Dietary Supplements (HFS-810)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Re: 75-Day Premarket Notification for a New Dietary Ingredient

Dear Dr. Walker:

On behalf of our client, GloboAsia LLC, and pursuant to 21 CFR §190.6, GloboAsia LLC is filing this premarket notification of its intent to market a product consisting of a symbiosis of *Streptococcus faecalis* T-110, *Bacillus mesentericus* TO-A, and *Clostridium butyricum* TO-A (described herein as BIO-THREE™, which is not a federally registered mark) as a new dietary ingredient.

By way of background, this is the second premarket notification that we have submitted to the FDA. We submitted a premarket notification on January 24, 2006. On April 11, 2006, we were informed by your office that our notification was not prepared according to the requirement of 21 CFR §190.6. More specifically, our notification was rejected for failing to provide English translations of scientific publications containing evidence of the safety of using BIO-THREE™ as a dietary ingredient.

In this premarket notification for BIO-THREE™, we provide all of the information required under 21 CFR §190.6. As per the requirements, we are enclosing two copies of this premarket notification for your reference. We appreciate the helpful information provided by your office to assist us in preparing this notification.

1. Name and Complete Address

GloboAsia LLC
11427 Potomac Oaks Drive
Rockville, MD 20850

Contact Person: Albert Wai-Kit Chan, Esq.
Phone (718) 799-1000

2. New Dietary Ingredient

Symbiosis of:
Streptococcus faecalis T-110,
Bacillus mesentericus TO-A, and
Clostridium butyricum TO-A

3. Description of the Dietary Supplement that Contains the New Dietary Ingredient

A. Taxonomy

1. Introduction

BIO-THREE™ (Tablet) is a dietary supplement for balance of intestinal flora. The active ingredient is a symbiosis of three probiotic bacteria strains: *Streptococcus faecalis* T-110, a lactic acid bacterium; *Bacillus mesentericus* TO-A, an amylolytic bacillus; and *Clostridium butyricum* TO-A, a butyric acid bacterium. This product has been used in Japan for many years.

2. Formulation

The typical composition for one (1) tablet:

5 mg of *Streptococcus faecalis* T-110;
25 mg of *Bacillus mesentericus* TO-A;
25 mg of *Clostridium butyricum* TO-A;
4.6 mg of fully hydrolyzed polyvinyl alcohol JPE;
0.4 mg of povidone JP;
1.2 mg of magnesium stearate JP;
94.4 mg of lactose JP; and
a sufficient quantity of Potato starch JP.

One (1) tablet:
Diameter: 8.00-8.15 mm
Thickness: 4.45-4.75 mm
Weight: 200 mg

B. Level of the new dietary ingredient in the product

5 mg of *Streptococcus faecalis* T-110, 25 mg of *Bacillus mesentericus* TO-A, 25 mg of *Clostridium butyricum* TO-A per one (1) tablet.

Recommended daily dosage for adults: 2 tablets, three times a day.
Recommended daily dosage for children over 5 and under 15 years of age: half the adult dosage

C. Conditions of use if the product states in the labeling, or if no conditions of use are stated, the ordinary conditions of use

Recommended as a dietary supplement for maintaining normal gastrointestinal function, to be consumed orally as a tablet, three times a day before meals, after meals, between meals or whenever convenient. To obtain the highest efficacy, take between meals. If experiencing constipation, take the dietary supplement with a glass of water or luke-warm water. The dietary supplement should not be administered to infants less than 3 months old.

D. History of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe

Brief review of published clinical study on the benefit and safety of BIO-THREE:

1. Hiroyuki et al. (1989). **Clinical Reports of Treating Abnormal Bowel Movement with Bio-Three**. *Iyaku no Monn* 29:221-221.

Twenty patients with abnormal bowel movement were studied from December 1987 to March 1989. BIO-THREE was administered, alone or combined with other treatments, orally three times a day with a total dosage of 6 lozenges. The results showed 50% of the patients improved. For patients with chronic constipation, treatment with Bio-Three combined with BULKOSE or MgO showed better efficacy.

2. Yamaoka (1992). **Clinical Records Using Bio-Three Combined with Other Medications to Treat Various Symptoms of Irritable Bowel Syndrome**. *Diagnosis and Therapy* 80(Suppl.):702-704.

In this study, BIO-THREE was used as basic medication for Irritable Bowel Syndrome and was coupled with other secondary medications based on individual symptoms. Every gram of BIO-THREE contained 10 milligrams of lactobacillus particles, 50 milligrams of *Clostridium butyricum* particles and 50 milligrams of *Bacillus mesentericus* particles. According to the different degrees in symptoms, the investigator chose the dosage of 0.3 ~ 0.6g (taken in three times). BIO-THREE were effective in treating diarrhea, constipation etc.

3. Chimura (1998). **Ecological Treatment for Bacterial Vaginosis and Viginitis with Bio-Three**. *The Japanese Journal of Antibiotics* 51-12, 759.

Sixteen patients, aged 20-60 years old, with abnormal vaginal discharge were studied from March to June in 1997. BIO-THREE was applied to the vagina of patients suffering from bacterial vaginosis and viginitis. The dosage was 2 grams every time. Three days later, the state of their vaginas and the influence of the drugs on the bacterial strains in their vaginas were examined. Clinical observation on vaginal

discharge amount and vaginal redness showed that the vaginal character was improved and the pH in the vagina was significantly reduced.

4. Sakuma (1999). **Nutrition Management on Low Birth Weight Infants with Infection.** *JJPEN* 12:89-92.

Nutrition management for low birth weight infants with infection is a challenge. Sepsis relapse due to bacterial translocation has been found in these cases. BIO-THREE was shown to effectively prevent bacterial translocation by promoting normalization of gut microflora and fortifying the intestinal barrier. Each gram of BIO-THREE contained 10 mg *Clostridium butyricum*, 10 mg *Streptococcus faecalis* and 50 mg *Bacillus mesentericus*.

5. K. Joh et al. (1993). **Clinical result of the intestinal remedy (Bio-Three®) containing three live bacteria species for bacterial diarrhea.** *Prog. Med.* 13:621-626

This study demonstrates the therapeutic effects of using BIO-THREE alone on intestinal infections. BIO-THREE was administered at a daily dose of 1-3 g for 1-8 weeks (each gram of BIO-THREE contained 50 mg *Clostridium butyricum* TO-A, 10 mg *Streptococcus faecalis* T-110 and 50 mg *Bacillus mesentericus* TO-A). After treatment with BIO-THREE, bacterial infection was eliminated and clinical symptoms such as diarrhea and fecal state were improved in most of the 6 cases in this study. In all cases studied, the ratio of anaerobic bacteria to aerobic bacteria significantly increased after the administration which means improvement of intestinal flora.

6. Kato H. et al. (1994). **Effect of administration of Bio-Three® on abnormal bowel movement from endocrine and rheumatic diseases.** *Medicine and Pharmacy* 31:1483-1487

BIO-THREE was administered to 14 patients with various endocrine and rheumatic diseases who complained of abnormal bowel movement. Compared with healthy subjects, these patients showed reduction in anaerobic bacteria and increase in aerobic bacteria. After 1 to 7 weeks of administration, the symptoms were distinctly improved in 3 cases, improved in 6 cases, slightly improved in 4 cases and unchanged in 1 case. The ratio of total anaerobic bacterial count to total aerobic bacterial count, which is a measure of improvement of intestinal flora, significantly increased from 4.90 to 68.82 after administration of this drug.

7. Kosuke Joh et al. (1993). **A case having succeeded in eliminating drug resistant Salmonella by the administration of a live bacterial preparation,** *Medicine and Pharmacy* 29:1027-1030

In this case of an eight-year-old girl, discharge of *Salmonella enteritis* continued in spite of improvement of acute symptoms by the administration of antibiotic. The bacterial discharge, however, disappeared quickly after treatment with BIO-THREE. The increase of ratio of total anaerobic bacterial count to total aerobic bacterial count means inhibition of proliferation of multi-drug resistant Salmonella.

8. Yasuhiko Nagamine (2003). **Drug-induced hypersensitivity syndrome (DIHS) responds effectively to a mixed preparation of Streptococcus faecalis, Clostridium butyricum and Bacillus mesentericus.** *Research Bulletin of Hakujikai Foundation Geriatric Hospital* 12:63-72.

This study showed a mixed preparation of *Streptococcus faecalis*, *Clostridium butyricum* and *Bacillus mesentericus* was effective in controlling the symptoms of patients with drug induced hypersensitive syndrome (DIHS). The reasons for selecting these strains of bacteria includes (1) these strains of bacteria have stability against gastric and intestinal juices, thereby allowing them to reach the intestine as live-bacteria; (2) interaction of these bacteria can augment their effectiveness; and (3) these strains of bacteria can live together with other beneficial intestinal bacteria without inhibiting their proliferation and function. The cases examined in this study provide important insight for a novel strategy of using live bacteria in the management of DIHS.

Please send all correspondence to:

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