



JUN 28 2002

Mr. John A. Sichel, R.Ph.
President
Pure Research Products Naturally LLC
6107 Chelsea Manor Court
Boulder, Colorado 80301-3148

Dear Dr. Sichel:

This is to inform you that the notification, dated April 10, 2002, you submitted pursuant to 21 U.S.C. 350b(a)(2) was received and filed by this office of the Food and Drug Administration (FDA) on April 16, 2002. Your notification concerns the substance stated as "*Lactobacillus delbrueckii ssp bulgaricus* lysate" that you assert is a new dietary ingredient for use in "immediate immune system support." Our letter will refer to this ingredient as "*Lactobacillus delbrueckii* subsp. *bulgaricus* lysate" to conform to the internationally accepted rules on bacteria nomenclature, including the abbreviation for subspecies (subsp.).

On May 29, 2002, we received your follow-up letter, dated May 24, 2002, stating that "Del-Immune" is the new name of the dietary supplement containing this ingredient. Your notification refers to the former names for this product as "Preparate," for marketing in the U.S., and as "Extrabiolat," for marketing in Russia. Because your May 24, 2002 letter concerning the name change of your product does not represent a substantive amendment, we did not revise the filing date of the notification. Our letter will use the name Del-Immune to apply to information in your notification about your product.

The law at 21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into commerce. This information must include 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 section 350b(a)(2), there must be a 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. If this requirement is not met, the new dietary ingredient is deemed 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 and injury.

Our main concern in reviewing your notification is that it contains disease claims for Del-Immune. If not corrected, making these claims would remove your product from consideration as a new dietary ingredient. The law at 21 U.S.C. 321(g)(1)(B) defines a drug as an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of a disease. Your notification contains three pages behind tab 8 that pertain to an English translation of a package insert for instructing consumers on how to use Del-Immune. FDA considers such a package insert to be part of a product's labeling. The insert contains numerous statements that Del-Immune can treat or prevent a wide variety of diseases (e.g., cancer, tropic ulcers, chronic bronchopulmonary localization diseases, liver diseases, dermatitis, the flu and many others). As a result, your product is represented to be a drug under 21 U.S.C. 321(g)(1)(B) and is subject to regulation as a drug under the provisions of the Federal Food, Drug and Cosmetic Act. If you want Del-Immune to be evaluated for its use in the treatment or prevention of any disease, you should contact FDA's Center for Drug Evaluation and Research, Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855. Otherwise, no disease claims can be made in either your labeling materials or the new dietary ingredient notification on Del-Immune.

In addition, we found your notification to be incomplete because it does not meet all requirements of 21 CFR 190.6. A copy of the cited section of the Code of Federal Regulations is enclosed for your reference. In any new notification you send us, please address the following technical issues:

1. You sent us only two copies of the notification, whereas a minimum of three (i.e., 1 original and 2 copies) must be submitted.
2. It appears that there are missing pages behind tab 7 that you identified as being a trade secret and confidential and are entitled "Preparation of a food supplement with curative and prophylactic properties." This narrative ends mid sentence on page 4 and does not appear to provide a complete description of what your notification implies is the process for preparing the *Lactobacillus delbrueckii* subsp. *bulgaricus* lysate powder contained in Del-Immune.
3. Although you provided us contact information for your company, you did not identify if is the distributor or manufacturer of Del-Immune.
4. Your signature, as the submitter, and the date are missing on page 4 of the notification on the two copies we received.
5. Federal regulations at 21 CFR 190.6 state that a notification must include copies or reprints of references cited in support of the notifier's conclusion that the new dietary ingredient is reasonably expected to be safe when used as recommended in a dietary supplement. Under the subheading "Reference and Published Materials" on page 4 of your notification, you mention that you conducted an Internet search of *Lactobacillus delbrueckii* subsp. *bulgaricus*, identifying 256 supporting references, most of which relate to the use of live bacteria in the production of cheese and fermented milk

products. No copies or reprints of any of the identified references were provided. Your notification should include copies of key references, preferably from the peer-reviewed scientific literature, that support your determination of safety for your product.

Further, we identified conflicting or unclear information in your notification as discussed below:

1. Identity of the New Dietary Ingredient: Your notification should contain an unambiguous identification of the bacteria used to produce Del-Immune and confirm whether the product contains any live bacteria or only lysed bacteria.
2. Conditions of Use for the New Dietary Ingredient: Your notification should clearly describe, as a part of your safety narrative, the target population of consumers in terms of gender, age, and any subgroups that should be excluded (e.g., infants, children, pregnant or lactating women, persons with certain medical conditions or those taking particular medications) along with and duration of use (e.g., for a certain number of months versus every day). The label you submitted for Del-Immune includes a warning statement “keep out of the reach of children.” In comparison, the instructions for use information found behind tab 8 describe the use of the product with infants and children as young as 6 months up to 5 years. If you intend for Del-Immune to be taken by infants and children, your notification should include data and other scientific evidence that documents the product’s safety when used as you recommend by this vulnerable subgroup.
3. Study Data on the New Dietary Ingredient: The “Confirmation of Safety in Human Use” data in your notification found behind tab 1 contains a summary report on human studies conducted in Russia using a substance called “Matrix E.” This summary report does not appear to provide sufficient details to support a determination of safety.

In conclusion, your notification represents *Lactobacillus delbrueckii* subsp. *bulgaricus* as a drug and is an incomplete submission containing conflicting and unclear information. Consequently, it does not provide an adequate basis to conclude that the use of *Lactobacillus delbrueckii* subsp. *bulgaricus* lysate in the dietary supplement Del-Immune will reasonably be expected to be safe when used as recommended. 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 it does not present a significant or unreasonable risk of illness or injury. Introduction of such products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Page 4 – Mr. John A. Sichel, R.Ph.

*correction
2002*

Your notification will be kept confidential for 90 days from the date of its receipt. After July 15, 2000, your notification and this response will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public. We acknowledge that you identified in your notification behind tabs 7 and 8 information that you believe to be proprietary for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

Please contact me at (301) 436-2371 if you have any questions concerning this matter.

Sincerely yours,



Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Enclosure

[Code of Federal Regulations]
[Title 21, Volume 3]
[Revised as of April 1, 2001]
From the U.S. Government Printing Office via GPO Access
[CITE: 21CFR190.6]

[Page 569-570]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 190--DIETARY SUPPLEMENTS--Table of Contents

Subpart B--New Dietary Ingredient Notification

Sec. 190.6 Requirement for premarket notification.

(a) At least 75 days before introducing or delivering for introduction into interstate commerce a dietary supplement that contains 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, the manufacturer or distributor of that supplement, or of the new dietary ingredient, shall submit to the Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Parkway, College Park, MD 20740, information including any citation to published articles that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe. An original and two copies of this notification shall be submitted.

(b) The notification required by paragraph (a) of this section shall include:

(1) The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient;

(2) The name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or other botanical;

(3) A description of the dietary supplement or dietary supplements that contain the new dietary ingredient including:

(i) The level of the new dietary ingredient in the dietary supplement; and

(ii) The conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement;

(4) The 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, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the new dietary ingredient has concluded that the new dietary supplement will reasonably be expected to be safe. Any reference to published information offered

in support of the notification shall be

[[Page 570]]

accompanied by reprints or photostatic copies of such references. If any part of the material submitted is in a foreign language, it shall be accompanied by an accurate and complete English translation; and

(5) The signature of the person designated by the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient.

(c) FDA will acknowledge its receipt of a notification made under section 413 of the Federal Food, Drug, and Cosmetic Act (the act) and will notify the submitter of the date of receipt of such a notification. The date that the agency receives the notification submitted under paragraph (a) of this section is the filing date for the notification. For 75 days after the filing date, the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient shall not introduce, or deliver for introduction, into interstate commerce the dietary supplement that contains the new dietary ingredient.

(d) If the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient, provides additional information in support of the new dietary ingredient notification, the agency will review all submissions pertaining to that notification, including responses made to inquiries from the agency, to determine whether they are substantive and whether they require that the 75-day period be reset. If the agency determines that the new submission is a substantive amendment, FDA will assign a new filing date. FDA will acknowledge receipt of the additional information and, when applicable, notify the manufacturer of the new filing date, which is the date of receipt by FDA of the information that constitutes the substantive amendment.

(e) FDA will not disclose the existence of, or the information contained in, the new dietary ingredient notification for 90 days after the filing date of the notification. After the 90th day, all information in the notification will be placed on public display, except for any information that is trade secret or otherwise confidential commercial information.

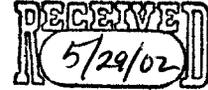
(f) Failure of the agency to respond to a notification does not constitute a finding by the agency that the new dietary ingredient or the dietary supplement that contains the new dietary ingredient is safe or is not adulterated under section 402 of the act.

[62 FR 49891, Sept. 23, 1997, as amended at 66 FR 17359, Mar. 30, 2001]

Pure Research Products Naturally LLC
6107 Chelsea Manor Court
Boulder, Colorado 80301

303 530-7761
Fax 303 530-0222

Division of Standards and Labeling Regulations
Food and Drug Administration
200 C Street, SW
Washington, DC 20204



24 May 2002

To the FDA Reviewer of the submission for Preparate

Contacting your office via telephone and internet to determine what is necessary under these circumstances has been extraordinarily difficult. Therefore I hope this letter is adequate.

Please note the copy of the Pre-market Notification cover letter dated 11 April 2002 for a product named Preparate.

The name of the product has been changed to Del-Immune. Only the name has been changed and the information submitted in the Pre-Market Notification is correct as it stands. Please note this change.

New labels are also attached for your review.

According to the information provided to me by Shelly Maifarth at the FDA office in Denver and by Melinda K. Plaiser, Associate Commissioner for Legislation, Department of Health and Human Services I should have received a notification for the date the original documents were received. This notification has never been received...is there a problem ?

Thank you in advance for your assistance.

Respectfully,

John A. Sichel, RPh
President
Pure Research Products *Naturally*

PROOF

<p>suggested use: 1 to 2 capsules as needed</p> <p>warning: keep out of the reach of children. store in a cool place</p> <p>These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, cure, treat or prevent any disease.</p> <p>Manufactured by ELAN, Ltd., St. Petersburg, Russia Distributed by Pure Research Products Naturally, LLC Boulder, Colorado 80302</p>	<p>Pure Research Products Naturally LLC</p> <p>Del-Immune</p> <p>a lysate powder of Lactobacillus delbrueckii ssp. bulgaricus</p> <p>immediate immune system support</p> <p>Net Contents: 30 capsules</p> <p>a dietary supplement from St. Petersburg, Russia</p>	<p>supplement facts:</p> <table border="1"> <tr><td>servings per container</td><td>30</td></tr> <tr><td>amount per serving</td><td>125 mg</td></tr> <tr><td>calories per serving</td><td>2</td></tr> </table> <p>Active Ingredient: a lysate powder of Lactobacillus delbrueckii ssp. bulgaricus</p> <p>other ingredients: brown rice powder natural product • chemical free</p> <p>©Pure Research Products Naturally LLC Boulder, Colorado 80301</p>	servings per container	30	amount per serving	125 mg	calories per serving	2
servings per container	30							
amount per serving	125 mg							
calories per serving	2							

<p>suggested use: 1 to 2 capsules as needed.</p> <p>warning: keep out of the reach of children.</p> <p>store in a cool place</p> <p>These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, cure, treat or prevent any disease.</p> <p>Manufactured by ELAN, Ltd., St. Petersburg, Russia. Distributed by Pure Research Products Naturally, LLC. Boulder, Colorado 80302</p>	<p>Pure Research Products Naturally LLC</p> <p>Del-Immune</p> <p>a lysate powder of Lactobacillus delbrueckii ssp. bulgaricus</p> <p>immediate immune system support</p> <p>Net Contents: 100 capsules</p> <p>a dietary supplement from St. Petersburg, Russia</p>	<p>supplement facts:</p> <table border="1"> <tr><td>servings per container</td><td>100</td></tr> <tr><td>amount per serving</td><td>125 mg</td></tr> <tr><td>calories per serving</td><td>2</td></tr> </table> <p>Active Ingredient: a lysate powder of Lactobacillus delbrueckii ssp. bulgaricus</p> <p>other ingredients: brown rice powder natural product • chemical free</p> <p>©Pure Research Products Naturally LLC Boulder, Colorado 80301</p>	servings per container	100	amount per serving	125 mg	calories per serving	2
servings per container	100							
amount per serving	125 mg							
calories per serving	2							

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Unwind: 3-4

Colours: Black, PMS 2726, PMS 571, PMS 1225

Note: Colours are approximate and based on inkjet printer capabilities.

Proof should be used for colour breaks, layout and spelling.

Approved as is: _____

Make following changes and re-proof: _____

The Columbine Label Company
4131 S. Natches Ct., Unit K
Englewood, CO 80110
(303) 788-1504 FAX (303) 788-1539

IMPORTANT:

Please proofread carefully. Columbine Label Company cannot be held responsible for incorrect printing based on your approved proof.

Pure Research Products Naturally LLC
6107 Chelsea Manor Court
Boulder, Colorado 80301

303 530-7761
Fax 303 530-0222

Division of Standards and Labeling Regulations
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

11 April 2002

To the FDA Reviewer of this submission:

The attached Pre-market notification, re: Preparete, has been prepared by following the suggestions presented in the FDA publication "New Dietary Ingredients in Dietary Supplements" dated February 2001 (Updated September 10, 2001). This document plus several other helpful aids were provided by Ms Shelley Maifarth, FDA Compliance Officer, in the Denver offices. Her assistance and patience is greatly appreciated.

Ms Maifarth suggested the Pre-market Notification be prepared as if *Lactobacillus delbrueckii bulgaricus* is a new dietary ingredient. That is the course I have followed. After extensive research I later learned this specific bacteria has been utilized for many years by the food and dairy industries in the production of cheese, yogurt, and cultured milk. I have also learned the product is often one of the mixed Lactobacilli that may occur in the natural production of yogurt.

The *Lactobacillus delbrueckii bulgaricus* variant that is used in the production of Preparete exhibits profound and unique immune system activity thus the proposed condition of use is "immediate immune system support". This condition is also used in the marketing of yin chiao immune health drops and Echinacea goldenseal drops distributed by Wild Oats, Inc in Boulder, Colorado.

Thank you in advance for reviewing this Pre-market Notification. Like everyone else who submits these documents, we hope all of the bases have been covered and the review will not require the full 75 days before we will be able to start marketing activities.

I am available to answer questions or to obtain answers from the inventors and manufacturer.

Respectfully,



John A. Sichel, RPh.
President

