DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 12/17/02

0407 '03 JAN 27 P1:59

From: Gloria Chang, IDS/Pharmacist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient: NKCP (Extract of Natto)

Firm: Lane Labs-USA

Date Received by FDA: 3/28/02

90-Day Date: 6/26/02

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 **after 6/26/02. Please make sure that it is placed in sequence with the other notification Docket Code numbers. Hence, this notification should be placed after Rpt 124 is submitted to you and before Rpt 126.** Thank you for your assistance.

Gloria Chang

Gloria Chang, IDS/Pharmacist

Attachments

95S-0316

RPT 125

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, Maryland 20740

June 11, 2002

Jennifer Nissen, ND
LaneLabs - USA
25 Commerce Drive
Allendale, New Jersey 07401-1600

Dear Dr. Nissen:

This is to inform you that your original notification dated January 31, 2002 that you submitted pursuant to 21 U.S.C. 350b(a)(2) was received on February 1, 2002 by this office of the Food and Drug Administration (FDA). Following receipt of your notification, Ms. Gloria Chang and Dr. Steve Gitterman of my staff contacted you to request additional information and clarification to review the safety information provided in your notification. We also informed you that the day this office received the requested information would be the effective filing date of your notification. We received the amendment to your notification on March 28, 2002, the revised filing date. Your notification concerns NKCP, a nattokinase-containing substance that you assert is a new dietary ingredient.

In a follow-up telephone conversation with you on February 12, 2002, we requested clarification on the conditions of use of NKCP. We specifically asked if there were any duration of use limitations or if any subgroups should be excluded from the population of consumers. In your letter dated February 12, 2002 received by FDA on February 15, 2002, you stated that NKCP can be safely taken by any adult over 18 years old and that your label would indicate that pregnant or lactating women and anyone on pharmaceutical medications should consult a healthcare provider before taking this or any other dietary supplement. In your March 28, 2002 letter, you indicate that there was an error in the stated amount of nattokinase of 6% in your original submission and that the actual amount of nattokinase enzyme in NKCP is 0.01% and you requested that we replace the originally submitted page 2 with your corrected page 2. You noted that all other information in the original submission remains the same and is accurate. You also stated that the recommended usage is two (250 mg) caplets daily for a total daily serving dose of 500 mg of NKCP containing 0.01% nattokinase and the condition of use is to maintain healthy circulatory function. The notification also described the dosage form as an enteric-coated caplet.

The Federal Food, Drug and Cosmetic Act (21 U.S.C. 350b(a)(2)) requires that a manufacturer or distributor submit certain information to FDA at least 75 days before a new dietary ingredient or a dietary supplement containing it is introduced or delivered for introduction into interstate commerce. This information must include the basis on which the manufacturer or distributor has concluded that the new dietary ingredient or a dietary supplement containing it 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 dietary ingredient, when used under the conditions recommended or suggested in the product's labeling, will reasonably be expected to be safe. If this requirement is not met, the new dietary ingredient or dietary supplement containing it 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 or injury.

FDA has carefully evaluated the information in your submission. FDA has concerns as discussed below about the evidence on which you rely to support your conclusion that NKCP containing nattokinase will reasonably be expected to be safe under recommended conditions of use.

You state that NKCP is an extract from Natto, a fermented soybean food that is regularly eaten in Japan. Even though your notification provided some information on typical exposure to Natto in the human diet, it does not provide a basis to conclude that the amount of Natto regularly consumed in the typical diet is a valid basis for determining that the amount provided by the recommended daily serving of the concentrated nattokinase enzyme in a dietary supplement is reasonably expected to be safe.

In both your February 12, 2002 and March 28, 2002 letters, you did not indicate any subpopulations with certain medical conditions that should be excluded from use, although you state that the product is for use by adults over 18 years of age. Therefore, FDA interprets this to mean that you are suggesting that your product may be consumed on a long-term or chronic basis by the general adult population. Based on this information and the evidence that you rely on to support your conclusion that your ingredient will reasonably be expected to be safe for the suggested or intended use, FDA has the following concerns.

Your notification contains the results of an acute single dose (5000 mg/kg) oral toxicity (gavage) study in rats where 5000 mg of NKCP (containing 0.1% nattokinase) per kilogram (kg) of body weight was administered to ten healthy rats. You concluded that the LD_{50} was greater than 5000 mg/kg. You also submitted a 90-day subacute dietary toxicity study conducted in rats which concluded that the prothrombin time in the rats was not affected even by orally administered doses of up to 1,325 -1,541 mg/kg/day of NKCP. The other two animal studies that were referenced in your notification included an incomplete description of study measuring blood coagulation activity after injection of NKCP at doses of 100 mg/kg and 250 mg/kg into the duodenum of an unknown number of rats. The activated partial thromboplastin time (APTT) was significantly increased at the low dose and approximately doubled at the high dose. Another study referenced was a study in dogs with induced thrombosis. In comparison with the control group, the group of dogs receiving doses of nattokinase showed complete recanalization of blood circulation with 5 hours of administration. Although the details of these studies were incomplete or lacking, these studies do demonstrate the potentially potent fibrinolytic activity of nattokinase. Inherent in this degree of anticoagulant activity is the risk of unintended bleeding. This may be a significant safety concern, particularly in consumers that may have a preexisting or existing medical condition where such an effect could result in clinically significant bleeding complications.

The notification also referenced two human clinical studies. We note that you did not provide full-text copies or reprints of the published references cited in support of your notification in accordance with 21 CFR 190.6. Based on the excerpts that you provided, the human and animal studies focus primarily on the fibrinolytic activity of nattokinase (NKCP). The human study titled "Oral Administration to Humans and Determination of Fibrinolytic Activities" noted that the fibrinolytic activity in the blood was significantly enhanced over an 8-day period. This enhancement is thought to involve absorption of nattokinase across the intestinal tract. The excerpt you submitted of the other human study titled "The test of oral administration of NKCP in human" included only a short statement and graph chart regarding test results in 8 healthy subjects who orally took 500 mg of NKCP (the amount (mg) of nattokinase was not specified) in an enteric capsule daily for 7 days. We are also not sure of the origin of the excerpt. Your notification does not provide a complete description of this human study in terms of: whether the study was published or unpublished; a reference citation if the study was published; the investigator(s)' names, credentials and affiliations, location and date when the study was conducted; and other particulars about the study's design, methodology used, etc. Thus, no conclusions of safety can be drawn from the brief summary statement you provided us about this study.

The notification specifically notes that nattokinase has fibrinolytic activity and that "NKCP is a product developed to allow easy intake of therapeutically significant amounts of nattokinase." The notification also includes a statement that oral administration of nattokinase leads to increased fibrinolysis in blood over a long period of time. However, all of the supporting studies reported in your notification were of a short duration, without any evidence demonstrating safety with chronic exposure. The human clinical study referenced was a small study that primarily focused on the fibrinolytic activity rather than safety. Further, much of the animal and human data presented concern the ability of nattokinase, Natto, or NKCP to lyse clots or to otherwise enhance certain measures of fibrinolytic activity. This is of particular concern considering that your notification notes that the product has a "chimney sweeping" effect on blood vessels with constant intake. While the doses of nattokinase used in both the animal and human studies exceed the level provided in NKCP, your notification does not provide evidence demonstrating that your recommended daily serving dose would not pose a safety risk if used for long-term or chronic use. The notification does not provide adequate assurance that NKCP will reasonably be expected to be safe for its suggested or intended use for a general population.

Therefore, the information in your notification does not provide an adequate basis to conclude that NKCP containing 0.01% of nattokinase enzyme is reasonably expected to be safe when used under the recommended or suggested conditions of use. Hence, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains the new dietary ingredient NKCP 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 products into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days from the date of receipt, and after June 26, 2002, your submission will be placed on public display at FDA's Dockets Management Branch (Dockets) (docket No. 95S-0316). However, any trade secret or otherwise confidential commercial information in the notification will not be made available to the public.

Prior to June 26, 2002, you may wish to identify in writing specifically what information in your notification you believe is proprietary for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final determination about what information in the notification should be redacted before it is posted to Dockets.

Should you have any questions concerning this matter, please contact us at (301) 436-2371.

Sincerely yours,

Gloria Chang for Felicia Satchell

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

LANELABS
The Innovative Company

March 28, 2002

Dear Ms. Chang;

RE: NKCP New Ingredient Submission

The following information is being provided at your request regarding to the conflicting nattokinases percentages presented in our submission for NKCP.

After re-confirming with Daiwa, the Japanese manufacturer of NKCP, we discovered that there was an error in our original submission, due translation confusion among the terms natto, nattokinase and NKCP. The original submission stated that NKCP contains 6% (+-1) nattokinase. This is in error. The actual amount of Natto protein in NKCP is .5%, as correctly reported to you in our February 27 letter to you by Joe Marino. The actual amount of the natokinase enzyme in NKCP is .01%.

Attached is a corrected Page 2 on the submission. Please replace the originally submitted Page 2 with this corrected page.

All other information in the original submission remains the same and is accurate. We assume that this one slight numerical error will not require a delay in the application process, especially considering that the percentage of nattokinase is now lower than originally presented (.01% versus 6%).

We apologize for any confusion.

Sincerely,

Dr. Jennifer Nissen
Naturopathic Doctor
Lanelabs USA, Inc.

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2. NAME OF NEW DIETARY INGREDIENT

a. NKCP is an extract from Natto, a fermented soybean food regularly eaten in Japan.

3. DESCRIPTION

a. NKCP is a white or light brown odorless powder. It is composed of 8 Lys residues with negative sugar.

b. NKCP contains .01% Nattokinase or 8-12 units/gram of nattokinase (see spec sheet). Nattokinase is a simple protein with a single polypeptide consisting of 275 residues with Ala at the N-terminal (calc. mol. Wt. 27,700). See Reference A and Tab 3.

c. Each caplet will contain 250 mg of NKCP, enterically coated.

d. Recommended usage: Two caplets daily (500 mg daily).

4. CONDITIONS OF USE

To maintain healthy circulatory function.

5. HISTORY OF USE

NKCP is an extract from Natto, a fermented soybean food regularly eaten in Japan. While some have theorized that Natto may have prehistoric origins, it first became a part of the Japanese culture during the later part of the Edo Period (1600-1868) when soy beans could be easily packed in straw containing a natural bacillus, then buried for a week or more under ground. Today, Natto is sold everywhere in Japan, even in the local grocery stores in portable Styrofoam containers. It is also available in specialty stores in the U.S. Natto is used it in many ways, including blended in salads as a condiment and blended with wheat, miso, cabbage and egg as a vegetarian hamburger. The people in Nepal make a similar fermented soybean product that they refer to a Natto Triangle. Natto has historically been known for its gastrointestinal and cardiovascular health benefits inherent in nattokinase.

Natto has been safely eaten for centuries, typically 50-100 grams per day. Its pungent flavor and odor is not likely to be accepted by American palettes. NKCP offers the benefits of Natto as an odorless dietary supplement.

LANELABS
The Innovative Company

Rec 2/15/02 G. Chang

Gloria Chang
Division of Standards and Labeling Regulations
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
February 12, 2002

Dear Ms. Chang;

The following letter contains the additional information as you requested in our phone conversation on February 12, 2002.

1. NKCP can be taken safely by any adult, over 18 years old, wishing to enhance their cardiovascular health.

2. Pregnant or lactating women, and anyone on pharmaceutical medications should consult a health care provider before taking this or any other dietary supplement. This statement will be included on our label.

3. Information about the following paper was requested. This paper is unpublished. The research was conducted at the university by Dr. Sumi in 1994. (Sumi, H., Structure and Fibrinolytic Properties of Nattokinase, Department of Nutrition, Faculty of Health and Welfare Science, Okayama Prefectural University, Okayama, Japan.)

4. NKCP contains 6% nattokinase. The remainder of the caplet is 95% carbohydrate, .5% protein and .1% lipid. Please see attached Analysis Certificate for details.

5. The specified dosage is one caplet twice daily. Because NKCP is safe for human use, as demonstrated by many years of use in Japan, at the recommended dosage there are no limits to the duration in which this product can be used to maintain cardiovascular health.

6. NKCP is sold in caplet form. A caplet is a solid tablet that is in the shape of a small, oval capsule. This product will be enteric coated to delay the digestion of the caplet.

Please feel free to call me if you have any questions.

Sincerely,

J. Nissen, ND

Dr. Jennifer Nissen
Naturopathic Doctor
Lanelabs USA, Inc.

JAPAN INSTITUTE OF OILS & FATS, OTHER FOODS INSPECTION (FOUNDATION)

TOKYO LABORATORY
3-27-8, Nihonbashi-Hamacho, Chuo-ku,
Tokyo 103-0007
Tel:(03)3669-6723

AUTHORIZED BY THE MINISTRY OF AGRICULTURE, FORESTRY & FISHERIES.
JAPANESE GOVERNMENT REGISTERED No.48
SPECIALISTS OF OIL.FAT.PROCESSED FOOD PRODUCT. ETC

OSAKA LABORATORY
3-8-9, Tenjinbashi, Kita-ku,
OSAKA 530-0041
Tel:(06)6358-6414

Report No.21-0233 Tokyo, Jan. 31, 2002

ANALYSIS CERTIFICATE

Requested by: Daiwa Pharmaceutical Co., Ltd.

Sample: NKCP Lot No.B2HJ0101

Date received: Jan. 22, 2002

This is to certify that the following results have been obtained according to our analysis on the above-mentioned sample submitted by the applicant.

RESULTS

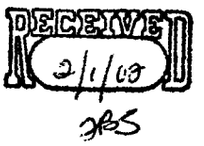
Energy:	383 kcal/100g
Protein:	0.5 g/100g
Lipid:	0.1 g/100g
Carbohydrate:	95.1 g/100g
Sodium:	29 mg/100g
Vitamin K_2:	91 μg/100g
Moisture:	4.1 g/100g
Ash:	0.2 g/100g
Arsenic(as As_2O_3):	not detected
	(detectable content 0.2ppm)
Heavy metals(as Pb):	4 ppm
Aerobic plate count:	below 3×10^2/g
Coliform group:	Negative

Japan Institute of Oils & Fats,
Other Foods Inspection,Foundation

CHIEF INSPECTOR Y. Kinoshita

JAPAN INSTITUTE OF OILS & FATS, OTHER FOODS INSPECTION (FOUNDATION) TOKYO LABORATORY

LANELABS
The Innovative Company



January 31, 2002

Felicia Satchell
Division of Standards and Labeling Regulations
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

Dear Ms. Satchell;

The following parts of our submission should be designated as confidential as they contain proprietary information that could benefit competitors: Section 3, including Spec sheet, C of A, and Structure; Section 5, 6, and 7, including toxicological tests.

Thank you for your assistance. Please contact me if you have any questions.

Sincerely,

Jennifer Nissen, ND
LaneLabs USA, Inc.
Manager of Nutritional Research

LaneLabs - USA • LaneLabs International • Lane Medical • Lane Malignancy Testing • Anti-Aging
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January 31, 2002

Felicia Satchell
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
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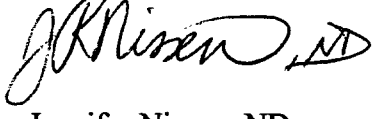
Food and Drug Administration
5100 Paint Branch Parkway
College Park , MD 20740

Dear Ms. Satchell;

The following parts of our submission should be designated as confidential as they contain proprietary information that could benefit competitors: Section 3, including Spec sheet, C of A, and Structure; Section 5, 6, and 7, including toxicological tests.

Thank you for your assistance. Please contact me if you have any questions.

Sincerely,



Jennifer Nissen, ND
LaneLabs USA, Inc.
Manager of Nutritional Research

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NKCP 75 Day Notification Letter

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