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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)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

RE: Notification of New Dietary Ingredient

Dear Ms. Satchell;

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 USC 350b(a)(2), and consistent with the final regulations published by the FDA in the Federal Register of September 23, 1997 (62 Fed. Reg. 49886-49892), 21 CFR 190.6, "Requirements for Premarket Notification", LaneLabs USA, Inc. ("LaneLabs") hereby submits the following information concerning a new dietary ingredient that LaneLabs intends to begin marketing for use in dietary supplements. Pursuant to the applicable provisions of DSHEA, LaneLabs will not introduce the ingredient or deliver it for introduction into interstate commerce until at least 75 days after the date FDA receives this notification.

1. NAME AND ADDRESS OF MANUFACTURER

DISTRIBUTER OF SUPPLEMENT:

LaneLabs USA, Inc.
25 Commerce Drive
Allendale, NJ 07401
(201) 236 9090

MANUFACTURER OF ACTIVE AGENT

Daiwa Pharmaceutical Co., Ltd.
1-16-19 Sangenjaya, Setagaya-ku, Tokyo #154-0024
phone: 011813-5430-4050

MANUFACTURER OF CAPLET

Contract Pharmacal Corporation
160 Commerce Drive
Hauppauge, NY 11788
(631) 231 4610

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 6% (+/-1%) 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 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 as 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 palates. NKCP offers the benefits of Natto as an odorless dietary supplement.

The recommended daily usage of NKCP (500mg) contains the same amount of nattokinase as 25 grams of Natto. Based on the long, safe history of Natto consumption and the low level of nattokinase in NKCP, we believe NKCP is safe for human consumption. (see Manufacturers Brochure, Tab 2)

Daiwa Pharmaceutical has been selling NKCP in Japan for five years. Dr. Hiroyuki Sumi, professor and the leading researcher of natto extracts, is currently an advisor for Daiwa and oversees quality and safety issues. Japan Bioscience Institute also sells a competitive natto extract in Asia under the brand name Biozyme. Natto extracts are sold in Korea and Taiwan. There have been no reports of toxicity or safety issues with NKCP or other natto extracts according to Daiwa records.

6. SAFETY DATA

Please see following documentation that establishes this dietary ingredient, NKCP, when used under conditions suggested on the label, will be reasonably expected to be safe.

Acute Oral Toxicity Study in Rats (Product Safety Labs, East Brunswick, NJ) Reference B

An acute oral toxicity study was conducted with rats to determine the potential for NKCP to produce toxicity from a single dose via the oral route. Based on the results of this study, the single acute oral dose of the test substance is greater than 5000 mg/kg of body weight.

Five thousand milligrams of the test substance per kilogram of bodyweight was administered to ten healthy rats by oral gavage. The animals were observed for mortality, signs of gross toxicity, and behavioral changes at least once daily for 14 days.

Bodyweights were recorded prior to administration and again on Days 7 & 14 (termination). Necropsies were performed on all animals at the time of sacrifice. All animals gained weight and appeared active and healthy. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behavior. Gross necropsy findings at terminal sacrifice were unremarkable. The LD 50 was >5000 mg/kg.

Sub-acute Dietary Toxicity: 90 Day Rodent study Reference C

A 90 day dietary toxicity study was conducted in Aia:N (SD) BR rats to determine the potential of NKCP to produce toxicity. Four groups of 10 rats/sex each were presented with a diet containing 0, 200, 2000, and 20,000 ppm of the test substance. These dose levels represent the range of doses that may be encountered by humans through both normal and exaggerated dietary exposure.

Animals were observed daily for clinical signs and mortality. Individual food consumption and body weights were recorded weekly. Blood was sampled from a small

subset of animals on Day 91 of the study for hematology and clinical chemistry assessments. Gross necropsies were performed on all rats and a limited selection of organs and tissues were evaluated histologically. Organs (liver and kidneys) were weighed from animals sacrificed by design at the end of the study.

There were no mortalities, clinical signs, body weight or nutritional effects or clinical pathology, gross or histopathological alterations in any test group that were considered attributable to dietary administration of NKCP.

Under conditions of this study, and based on the toxicological endpoints evaluated (which were limited in scope) the no-observed-adverse-effect level (NOAEL) was 20,000 ppm for male and female rats. This level was equivalent to 1,325 and 1,541 mg/kg/day for male and female rats, respectively.

**Ames Test
Reference D**

NKCP was tested in the *Salmonella typhimurium*/*E. coli* Plate Incorporation Mutation Assay in the presence and absence of induced rat liver S-9.

The definitive Mutation Assay (B-1), using the plate incorporation method, was performed with four *Salmonella typhimurium* tester strains and one *E. coli* strain. Under the conditions of this study, NKCP was negative (non-mutagenic) in the *Salmonella typhimurium*/*E. coli* Plate Incorporation Mutation Assay.

Thank you for your time and attention to this matter. Please contact me with any questions or additional requests.

Sincerely,



Dr. Jennifer R. Nissen
Naturopathic Doctor
Manager of Nutritional Research
LaneLabs USA, Inc.
(201) 236-9090 x 7161