DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DOCKETS TRANSMITTAL MEMO

Date: November 6, 2003

From: 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: Trifolium pretense L.

Firm: Hounghwa Global, Inc.

Date Received by FDA: 12/2/02; Amended 1/21/03

90-Day Date: 4/21/03

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.

Tanya L. Jackson, Ph.D

Tanya Jackson, Interdisciplinary Scientist, HFD 810

95S-0316

RPT167

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

APR - 2 2003

Mr. Zhijian Zhang
President
Hounghwa Global, Inc.
705 Canterbury Road
San Marino, California 91108

Dear Mr. Zhang:

This is in response to your letter to the Food and Drug Administration (FDA) dated November 20, 2002, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413 of the Federal Food, Drug, and Cosmetic Act (the Act)) and 21 CFR 190.6). On January 21, 2003, you submitted additional information to FDA. Your notification notified FDA of your intent to market Golden Phoenix, a product containing an extract from *Trifolium pratense* L., a substance that you assert is a new dietary ingredient.

The notification contains conflicting information concerning the conditions of use. On August 20, 2002, you indicated that *Trifolium pratense* L. extract in a capsule would "be suggested to be taken three times day, 2 capsules in the morning, 2 capsules in the afternoon, and 4 capsules at bedtime." On November 20, 2002, this information was not amended. On January 21, 2003, a statement was provided which indicated that the "new dietary ingredient *Trifolium pratense* L." contains 1 ug/capsule of ethyl-phenol, and recommended "one capsule each for morning and noontime and two capsules before sleep" or "two capsules each morning and noontime before meals and 4 capsules before sleep."

Under 21 U.S.C. 350b(a)(2), the manufacturer or distributor of 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 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 section 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 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 considered the information in your submission. In the human study and the other information submitted, it was unclear as to whether the test substances used in the studies are the same as that of the ingredient in your notification. Moreover, your submission provides no information that the test substances used in the referenced studies are qualitatively or quantitatively similar to your ingredient or how these studies are relevant to evaluating the safe use of your ingredient under the recommended conditions of use.

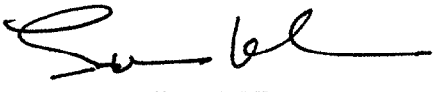
In addition, the one page of clinical information provided does not contain adequate information on the test article, any information describing elements of the clinical study design, or any specific clinical data. Therefore, no safety conclusions can be drawn from the information presented. You also provided a one paragraph statement describing a Golden Phoenix product sold overseas, and a marketing statement of satisfaction. This does not provide an adequate basis for the history of use or other evidence of safety. 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).

We have enclosed a copy of section 21 CFR 190.6 for your future reference. You also may wish to review FDA's Web site at http://www.cfsan.fda.gov/~dms/ds-ingrd.html for additional details on new dietary ingredient notification requirements.

Your submission will be kept confidential for 90 days from the date of receipt, and after April 21, 2003, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Please contact Victoria Lutwak at (301) 436-1775 if you have questions concerning this matter.

Sincerely yours,



Susan J. Walker, M.D.
Acting Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Enclosure

HFA-224 (yellow box copy)
HFS- 605 (Field Programs)
HFS-810 (Moore)
HFS-840 (Rader)
HFS-820 (Ferre-Hockensmith-4 copies)
R/D:HFS-820:CFerre-Hockensmith:2/27/03
Init. with comments:HFS-810:RMoore:3/3/03
Revised:HFS-820:CFerre-Hockensmith per SWalker comments:3/27/03
F/T: HFS-810: LBarr 3/31/2003

[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.

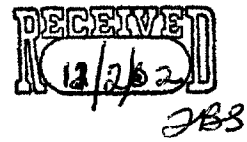
(d) If the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient, provides additional information in support of the new dietary ingredient notification, the agency will review all submissions pertaining to that notification, including 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]

Hounghwa Global, Inc.
705 Canterbury Road
San Marino, CA 91108



November 20, 2002

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

RE: Docket No. 95S-0316

Dear Ms Satchell,

This is in response to your letter dated Nov 6, 2002. We would like to clarify the following item:

1. Trifolium pretense L. has been used in the world for the last few hundred years. Please see the attached for the scientific reference. All of these references can prove that the product is safe.
2. Attached is a copy of "Traditional Chinese Medicine Dictionary" edited by Jiangsu Academy of New Medical Sciences and published by Shanghai Science and Technology Press in 1975. This shows that *Trifolium pretense L* is collected as poisonless.

My contact information is as follows:
Tel: 626 796 2988
Fax:626 395 9319
e-mail: hounghwa_global_us@yahoo.com

Thank you for your attention. If you have any questions or concerns, please feel free to contact me.

Sincerely,

Zhijian Zhang

Attachments

1. He Xiao-guo, Lin Lang-ze, Analysis of flavonoids from red clover by liquid chromatography-electrospray mass spectrometry, **Journal of Chromatogr A**, 1996, 755 127-132
2. David R. Biggs and Geoffrey A. Lane, Identification of Isoflavones Calycosin and Pseudobaptigenin in Trifolium Pratense, **Phytochemistry**, 1978. 17: 1683 - 1684
3. Ingram D. Sander K. Kolybaba, M. and Lopez, D. Case control study of phyto-oestogens and breast cancer. **Lancet**, 1997, 350: 990-994.
4. Trifolium Pratense L. **Traditional Chinese Medicine Dictionary** Volume 1: page 1012 – 1013