DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

0039 6 FEB -2 P2:27

Date: JAN 11 2006

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: Gynostemma Pentaphyllum extract

Firm: Kedeyoung Industry (Shanghai) Co. Ltd

Date Received by FDA: 10/18/05

90-Day Date: 1/16/06

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.

Victoria Lutwak

19955-0316

RPT311

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

DEC 29 2005

Yuan Lin, Ph.D.
Marco Polo Technologies, Inc.
5900 Conway Road
Bethesda, MD 20817

Dear Dr. Lin:

This is to inform you that the notification, dated October 12, 2005, that you submitted on behalf of your client, KEDEYOUNG INDUSTRY (SHANGHAI) CO., LTD. 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 October 18, 2005. Additional information was received on December 20, 2005. Your notification concerned the substance that you identified as "Gynostemma" which you extract from *Gynostemma pentaphyllum* (Thunb.) Makino. You intend to market "Gynostemma" as a new dietary ingredient in a dietary supplement product that you call "Manjusaka".

Your notification states that "Manjusaka" will be marketed "in tablet form (500 mg+/-10% each).... Recommended dosage: For adults, take 2 tablets 2-3 times daily, one hour before meal (*sic*)."

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 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 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.

FDA has carefully considered the information in your submission and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "Gynostemma" will reasonably be expected to be safe.

The relationship of the test materials used in the animal safety studies to the new dietary ingredient that you intend to market is unclear. For example, the publication by Xianmin *et al.* describes the formulation of the test material used in a 90 day rat toxicity study without stating the part of the plant that was extracted, the solvent used for the extraction, or degree to which the extract was concentrated. Therefore, it is unclear how the test substances are qualitatively or quantitatively similar to the test substances described in the information that you rely on for the safety for "Gynostemma".

In addition, FDA was unable to interpret the photomicrograph reproductions and the descriptions of the results contained in the supplied English translations in the publication authored by Xianmin *et al.*

According to your notification, "Manjusaka" also will contain dried mycelium from the fungus that produces the mushroom *Cordyceps sinensis*. FDA was unable to determine the identity of this ingredient. A brief outline of a fermentation procedure and the statement that "(f)or a similar product in the US market, Cordymax Cs-4 (produced by a fermentation process similar to ours)" were inadequate to establish the identity of the ingredient you plan to use in your product.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Gynostemma" 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 October 18, 2005. 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 Linda S. Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,

Linda S. Pellicore

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

MARCO POLO TECHNOLOGIES, INC.
A Green Pharmaceutical Company

TO: Dr. Susan Walker (HFS-810)
The Division of Dietary Supplement Program
Office of Nutritional Products, Labeling, and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

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DATE: December 14, 2005

Dear Dr. Walker:

This is in response to telephone communication, regarding the dietary supplement "Manjusaka", dated December 14, 2005. In our conversation, Dr. Linda Pellicore raised two questions about the manufacturing of Cordyceps and the safety dosage of the dietary ingredient in Manjusaka.

1. Manufacturing process of Cordyceps:
   Cordyceps mycelia were manufactured by a fermentation process. Briefly, a stock culture of *Cordyceps sinensis* was sequentially expanded from 100 ml to 5 liters. The 5 liter culture was used to inoculate a fermenter of 20,000liter in size. The fermentation was carried out in a well defined medium and at 15 to 25℃, pH 5-7. After the culture reached a specified concentration, the mycelia were harvested and oven dried.
2. To support the safe use of the new ingredient, Gynostemma and the dietary supplement, Manjusaka, a number of papers and an acute toxicity report using Manjusaka were submitted as attachments to the original submission. These studies are relevant to our product due to the fact that these studies demonstrated the recommended dose in our product is at 100 to 200 folds less than the toxicity levels of the acute and subacute levels used in animals.

a. Acute oral toxicity test of Manjusaka (Attachment 6, original submission):
   A single dose acute toxicity study in 40 mice (20 with test article, 20 as control) demonstrated that no toxicity was observed at 20 g/kg (or 1200 g/60 kg). The recommended daily dose for adult is 6 g/60 kg/day (assume 60 kg as adult weight). Thus the recommended dose is 200 times below the acute toxicity level in mice.

b. Toxicity study of *Gynostemma pentaphyllum* (Attachment 3, Yang et al 1990):
   Acute toxicity: LD_{50} 12g/kg (720 g/60kg) in mice and 15g/kg (900 g/60kg) in rat.

5900 Conway Road, Bethesda, Maryland 20817 Phone: (301) 897-5211; Fax: (301) 530-5526

Subacute toxicity: Repeat dosing of up to 2.28 g/kg (136.8g/60kg) showed no sign of toxicity in rats.

The daily recommended dose of Gynostemma is 1.2 g/60 kg adult/day. This dosage is 100 times below the subacute toxicity level in Rats and 750 times below the LD_{50} in acute toxicity in rats.

b. Genotoxicity (Ames test and Micronucleus test) and organ toxicity: Under the experimental conditions, no abnormal findings were reported.

The original and 2 copies of this letter are submitted for your review.

Sincerely yours,

Yuan Lin, Ph.D
Marco Polo Technologies, Inc.
5900 Conway Road, Bethesda, MD 20817
301-897-5211 (phone)
e-mail: ylin01@sprynet.com or
ylin60@yahoo.com

MARCO POLO TECHNOLOGIES, INC.
A Green Pharmaceutical Company

TO: Dr. Susan Walker (HFS-810)
The Division of Dietary Supplement Program
Office of Nutritional Products, Labeling, and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

DATE: October 12, 2005

OCT 18 2
CFSAN/FDA

Dear Dr. Walker:

Pursuant to Section 413(a)(2) of the Federal Food and Drug, and Cosmetic Act (21 U.S.C. 350(a)(2), KEDEYONG INDUSTRY (SHANGHAI) CO., LTD., Shanghai, China, wishes to inform the Food and Drug Administration of its intent to market a dietary supplement, "**Manjusaka**" which contains a new dietary ingredient, Gynostemma, in the US market. Accordingly, an original and two copies of this notification are submitted for your reference.

Should you have any questions concerning this product, please contact me at Marco Polo Technologies (contact information listed below). I will be out of the country from October 29 to November 9. During this period I can be reached by e-mail.

Sincerely yours,

Yuan Lin

Yuan Lin, Ph.D
Marco Polo Technologies, Inc.
5900 Conway Road, Bethesda, MD 20817
301-897-5211 (phone)
e-mail: ylin01@sprynet.com or
ylin60@yahoo.com

2005-7060
Aims

PREMARKETING NOTIFICATION

A. Name and complete address of Manufacturer/Distributor

KEDEYONG INDUSTRY (SHANGHAI) CO., LTD.
No.141, Xin-Song Road
Shi-Hu-Dang Town, Song-Jiang District, Shanghai City
People's Republic of China

Authorized representative in the US
Dr. Yuan Lin
Marco Polo Technologies, Inc.
500 Conway Road
Bethesda, MD 20817
301-897-5211(phone)
E-mail: ylin01@sprynet.com or ylin60@yahoo.com

B. Name of product and dietary ingredients

Name of product: **Manjusaka**

1. Description of **Manjusaka**

Manjusaka is in tablet form (500 mg+/-10% each). Each package contains 240 tablets. There is no structure/function claim on the label. Table 1 summarizes the ingredients in **Manjusaka**.

Table 1. Botanical ingredients in **Manjusaka**

Latin Name	Common Name	Part used	mg/tablet
Gynostemma pentaphyllum (Thunb.)Mak.	Gynostemma	Leaf and stem	200*
Cordyceps sinensis (Berg.) Sacc.	Cordyceps	Mycelium	150
Triticum aestivum L.	Wheat	Seed	125*
Glycyrrhiza grabra L.	Licorice	Root	25**

*Amount includes excipient (starch) used during drying.
**Amount includes excipient (dry powder of raw licorice) used during drying.

2. Manufacturing process and concentration ratio of each ingredient

Each ingredient was manufactured separately and combined in the ratio indicated in Table 1. Cordyceps was produced by fermentation in a biotechnologically aseptic environment. The other 3 ingredients were prepared by water extraction of raw materials (dried herbs) purchased from designated suppliers. The extract was filtered to remove particulate material and the supernatant was dried. Table 2 lists the concentration ratio from raw herbs to the final product.

Table 2. Concentration ratio of raw herbs to final product

Ingredient	Concentration ratio*	Amount excipient used
Gynostemma	4.6*	32.5% of final weight
Cordyceps	4.5	No excipient added
Wheat	4.1*	28.5% of final weight
Licorice	3.7*	18.9% of final weight

*Concentration ration was calculated as follows:

100 kg of Gynostemma was extracted and concentrated down to 14.5 kg. 7 kg of starch was added as an excipient to a final weight of 21.5kg. Thus the concentration ration is 100/21.5=4.6. Similar calculations were performed for Wheat and Licorice. For Cordyceps, mycelium was harvested and dried. The ratio is the wet weight/dry weight.

3. Recommended dosage: For adults, take 2 tablets 2-3 times daily, one hour before meal.

C. Description of New Ingredient: Gynostemma

Gynostemma, *Gynostemma pentaphyllum* (Thunb.) Mak, is a traditional Chinese medicinal herb, often used as an antioxidant or liver-protective agent. It is commonly found in Southern China, Japan, India and Korea. The fact that it contains a large number of gypenosides, closely related to the saponins found in ginseng, suggests that it might share other biological activities with ginseng such as antitumor, cholesterol lowering, immunopotentiating effects.

Pharmacological studies

Phytochemical studies have identified over 90 dammarane-type glycosides (glypenosides), some of which are identical to ginsenosides isolated from *Panax ginseng*. Using GC-MS, Cui et al (1999) identified and characterized a large number of these compounds.

Using liver homogenate of rats, Lin et al (2000) were able to demonstrate that water extract of Gynostemma enhances
the recovery of chemically induced liver injury.

The LD50 in mice was more than 12.6 g/kg and that in rats was 15g/kg (Yang et al, 1990). These results indicated that Gynostemma belongs to the "non-poisonous class" of herbs. No rats or mice died in this test and the cumulative coefficient K>5.3.

Figure 1. Gynostemma plant

Recommended dosage

Each 500 mg tablet contains 200 mg of gynostemma. The serving size is 2 tablets each time to be taken 2-3 times daily.

Traditional use recommended a decoction of 3 gram of gynostemma each time and 3 times daily. In a similar product in the US market, Sustain Super Adaptogen Formula, which uses extracts of gynostemma and Siberian ginseng, the dosage of each capsule is 500mg and the suggested dosage is 2 capsules each time and twice daily.

Based on the traditional use and the LD50 of animal studies, the ingestion of the amount of gynostemma recommended in the label can be reasonably expected to be safe.

Warnings

Gynostemma is not recommended for children or pregnant or lactating women

Drug interactions

There is no drug interactions reported in the literature.

D. Evidence of safety

Three sets of safety data are included. One is the **contamination** levels of microorganisms and heavy metals in the final product, **Manjusaka**; the second is the **dosage** of each ingredient recommended. In addition, the **acute toxicity** of the final product in mice is also included.

1. Contaminations: The manufacturing site at No.141, Xin-Song Road,

Shi-Hu-Dang Town, Song-Jiang District, Shanghai, is a licensed GMP site. Outmost care was taken at each step of the manufacturing process to avoid contamination.

1.1 Microbial and heavy metal contamination: At the end of each production batch, the following tests were performed to ensure that the final product meets the contamination limits. Table 3 lists the test results of a representative batch of **Manjusaka** and the contamination limits for microorganisms, and heavy metals.

Table 3. Contamination limits for microorganisms, heavy metal and pesticides

	Results of a representative batch	**Upper allowable limits****
Microorganism*		
Total plate count	18000 cfu/g	1×10^5 cfu/g
Coliform	<3/g	3/g
Yeast and mold count	18 col/g	100 col/g
Heavy metal*		
Arsenic	<0.2 ppm	-
Lead	0.4 ppm	0.5-1 ppm
Mercury	0.1 ppm	1 ppm
Cadmium	<0.2 ppm	0.1 ppm

*See Attachment 2 for test methods and results;
**The upper limits for microorganisms are those recommended by USDA for foods; the upper limits for heavy metals are those recommended by FDA as "Action Level for Poisonous or Deleterious substances" for foods, 1998.

Lots must pass above tests before releasing into the market.

2. Dosage of each ingredient recommended

Gynostemma: See section C, New ingredient

Cordyceps

Each 500mg tablet contains 150mg of cordyceps. The serving size is 2 tablets each time to be taken 2-3 times daily.

For a similar product in the US market, Cordymax Cs-4 (produced by a fermentation process similar to ours), the recommended dosage by the Physician's Desk Reference is two 525 mg capsules three times daily (Attachment 4). According to "Chinese Herbal Medicine: Materia Medica" by Bensky and Gamble, the toxicity level in animals is: "IP injection of 5g/kg into mice caused no fatalities, but doses of 30-50 g/kg were universally fatal"(Attachment 4).

Thus the ingestion of the amount of cordyceps in **Manjusaka** recommended in the label can be reasonably expected to be safe.

Wheat

This ingredient meets the criteria that "it has been present in the food supply as an article used for food in a form in which the food has not been chemically altered"(21

CFR Part 190). Even though this ingredient has been extracted by water and concentrated, there is no chemical alteration during the process. Thus this ingredient can be expected to safe.

Licorice

Each 500mg tablet contains 25mg of Licorice. The serving size is 2 tablets each time to be taken 2-3 times daily.

Both licorice and licorice root extract are listed as OTC ingredients for miscellaneous internal use in FDA's "OTC DRUG REVIEW INGREDIENT STATUS REPORT", September 1, 1994. It is commonly used as an ingredient for candy. Thus it can be considered as an ingredient used in food. The extraction process (water extract) does not chemically alter the ingredient. The amount of 5-15 gram of root was recommended in German commission E monographs (Attachment 5). Based on the publication on the LD50 in animal for oral use (14-18 g/kg in rat and mice, Attachment 7), and the fact that licorice is an ingredient used in food, we believe the ingestion of the amount of Licorice in **Manjusaka** recommended in the label can be reasonably expected to be safe.

3. Acute toxicity test of final product, **Manjusaka**

The acute oral toxicity of **Manjusaka** was tested in mice at a single dose of 20g/kg (Attachment 6). No mortality was observed on 40 animals and was considered to have an acute oral LD_{50}>20g/kg.

To date, over 200,000 packages of **Manjusaka** have been sold in China and other Asian countries since 2001. This product is sold directly from our distributor with a customer service direct line for proper usage and adverse reaction reporting. So far, we have not received any complaints for severe adverse reactions. Based on the ingredients used in this product and the stringent limits for contamination, we believe **Manjusaka** when used at the amount recommended in the label can be reasonably expected to be safe.

Attachments:

1. Letter of authorization to Dr. Yuan Lin
2. Test report of microorganisms and heavy metals
3. Key references for Gynostemma on the safety, efficacy and pharmacology of Gynostemma and its extract (Those published in Chinese were translated into English)
4. Recommended dosage for Cordyceps by PDR and animal toxicity test
5. Recommended dosage by THE CHINESE MATERIA MEDICA and LD50 (Chinese Drug of Plant Origin) of Licorice
6 Acute oral toxicity test of **Manjusaka**