DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: = FEB 06 2004

From: Interdisciplinary Scientist/Pharmacist , 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: Pueraria mirifica

Firm: American Phyto Lab

Date Received by FDA: 7/18/03

90-Day Date: 10/18/03

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.

Gloria Chang

95-0316

RPT204

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, Maryland 20740

OCT - 3 2003

Mr. J. Miers, Scientific Affairs
American Phyto Lab
757 Siesta Key Tr., Suite 1115,
Deerfield Beach, Florida 33441

Dear Mr. Miers:

This is to inform you that the notification you submitted, dated July 18, 2003, 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 July 18, 2003. Your notification concerns the substance, called *Pueraria mirifica* that you intend to market as a new dietary ingredient.

According to the notification, you recommend that post-menopausal women take one to two 100 mg capsules/day and pre-menopausal women take one to two 100 mg capsules/day for 15 days/month. Men under 50 years of age can take up to two 100 mg capsules/day. Men over 50 years of age can take one to two 50 mg capsules/day. You recommend that women under 18 years of age, women using birth control or prescription estrogen and pregnant or nursing mothers not use this type of product.

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, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing *Pueraria mirifica* will reasonably be expected to be safe.

The notification does not adequately describe the composition of the dietary supplement containing *Pueraria mirifica*. For example, a chromatogram in the notification shows a *Pueraria mirifica* preparation that contains approximately 159 mg/100g phytoestrogens.

According to the notification, *Pueraria mirifica* preparations contain 15 mg/100g to 42 mg/100g miroestrol. However, the notification states on page two, that *Pueraria mirifica* contains "trace amounts of miroestrol". The amount of miroestrol in the dietary supplement containing *Pueraria mirifica* is unclear based on the information submitted in the notification.

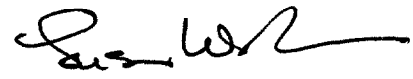
The notification discusses the results of a 90-day study in rats and two clinical trials. The rat study used a suspension of *Pueraria mirifica* root powder in water. One clinical study used 200 mg crude drug capsule containing *Pueraria mirifica* dried root powder. However the source plant for the preparations tested in the two studies was not identified. The second clinical study used a purified miroestrol preparation. The relationship between the dietary supplement containing *Pueraria mirifica* and the materials tested in the three studies mentioned in the notification is not clear. The composition of these materials would be expected to vary considerably both with respect to the amount of miroestrol present, as well as the amounts of other phytosterols. The notification does not provide adequate information to determine whether the test substances used in the referenced studies are qualitatively or quantitatively similar to the dietary supplement containing *Pueraria mirifica*. In addition, the notification does not explain how the three studies submitted are relevant to the safety evaluation of the dietary supplement containing *Pueraria mirifica* under the recommended conditions of use.

For the reasons discussed above, the information in your notification does not provide an adequate basis to conclude *Pueraria mirifica* 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 July 18, 2003. 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 Victoria Lutwak at (301) 436-2375.

Sincerely yours,



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RECEIVED
JUL 18 2003
BY: L.B./FDA

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BY L.B. FDA

Dear Sir

We would like to file a pre-market review for a food called Pueraria Mirifica. This plant was properly classified by Suvatabandhu, Airy Shaw et al. in 1952. Its local name is white kwoa kreu. It is indigenous to northern Thailand and has been eaten over the last 100 years safely with no know side effects. It is in the family Leguminosae and is high in isoflavones. Of particular interest is a phytoestrogen in the chromene group found in trace amounts in this plant that is similar to estradiol called miroestrol.

Table 1.Chromene,isoflavonoid,and coumestran derivatives in Pueraria Mirifica

Chromene	Isoflavones	Isoflavone	Coumestans Glycosides
miroestrol	daidzein	diazin	coumestans glycosides
deoxymiroestrol	genistein	genistin	coumestrol
	kwakhurin	mirificin	mirificoumestan
	kwakhurin hydrate	puerarin	mirificoumestan hydrate
		puerarin-6" monacetate	

APL

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The plant has been well studied over the last 50 years, initially by the Germans, then the Thais, the English and more recently by the Thais and Japanese. There has been great deal of interest in the plant because of its "youthful effects." The Thai government has sanctioned the use of this plant through their FDA and has sanctioned it as a dietary supplement. There is currently a government effort to educate its citizens throughout all of Thailand to include Pueraria Mirifica in the diet. Formerly Pueraria Mirifica was primarily consumed in Northern Thailand where it grows.

Currently Pueraria Mirifica supplements are sold throughout Asia---especially Japan and also in Europe. They are being sold primarily in 100mg capsules with a recommendation of 1 to 3 per day. **They are being used in the same fashion as soy or clover supplements are: for phytoestrogen support.**

We have supplied assays of our farmed version of Pueraria Mirifica. It is relatively high in isoflavones and contains trace amounts of miroestrol. It is accepted that Pueraria Mirifica contains 15mg/100g (wild) of miroestrol (wild) 15mg/100mg to 42 mg /100g (farmed) or .042/100mg (farmed).

Our recommendation to manufacturers is as follows: for post-menopausal women one to two 100 mg capsules/day, for pre-menopausal one to two 100 mg capsules/day 15 days/month. Dosage recommendations for men over 50 years of age: one to two 50 mg capsule per day. Men under 50 can use up to two 100 mg capsules. Our recommendation to manufacturers is that women using birth control or prescription estrogen, pregnant or nursing mothers not use this type of product. Young women under 18 years of age should be discouraged from using this product. The only side effect is headaches for women that are sensitive to estradiol. **Since the amount of miroestrol is low this is not overly common.**

We have included a short paper by the pre-eminent **Dr. Wichai Cherdshewasart of Chulalongkorn University in Bangkok, an acute toxicity done by the Thai government and a small booklet printed by the Medicinal Plant Research Institute, Department of Medicinal Sciences, Ministry of Health.** Dr Wichai is considered the leading expert regarding this plant in Thailand and the world. In November I had the pleasure of meeting Dr. Wichai at the Chulalongkorn University in Bangkok, Thailand. We discussed several issues regarding the plant. Recently a new phytoestrogen called deoxymiroestrol was extracted from Pueraria Mirifica. A Japanese-Thai group did the research. Although this phytoestrogen is very unique I was told by Dr Wichai that the researchers went through close to two tons of wild Pueraria Mirifica to do this extraction. Dr. Wichai has worked with closely Dr. Chaiyo Chaichantipyuth who is also on the faculty at Chulalongkorn University and knows Dr. Sunee Chansakaow (both are Thai). Both of these researchers were part of the research team that did the extraction for the new phytoestrogen. Currently the levels of this phytoestrogen are so low it would be very difficult to measure. Miroestrol is the dominant phytoestrogen in Pueraria Mirifica. Dr Wichai's paper was included, because chemistry's and cbc's were run on the subjects with no abnormal results. The Cain paper has also been included because it gives a nice background of the plant, its chronology up to the date of publication and discusses consumption. Also very important it discusses miroestrol a phytoestrogen which most American academics are unfamiliar with. Very important in the Cain paper it discusses a small study where miroestrol was synthesized in England. They gave adult women 5 mg and 1 mg of miroestrol respectively. **This dosage was approximately 12 to 333 times the trace amounts of miroestrol in the recommended dosage of Pueraria Mirifica. The main side effect was headaches and nausea. We have included an acute toxicity study (animal) done by the Thai government. The results are self-explanatory. A photo-copied booklet published by the Thai government documenting a hundred years of consumption, ethnobotanic use, chemical composition, a repetition of the Thai government acute toxicity study (animal).**

Submitted by: J. Miers, Scientific Affairs

Chemical Composition of Pueraria mirifica Herb

Source: Medicinal Plant Institute department of Medical Sciences, Thailand, July 2000

The components that make Pueraria mirifica different from any other phytoestrogen plants in the Family Leguminosae are Miroestrol and Deoxymiroestrol, which possess highest activity among the known phytoestrogens due to structural similarity to estradiol. Miroestrol was the first compound isolated from this plant by a group of German chemists in 1940,but the plant had actually been mistaken reported then for Butea superba. It was later reclassified as a new plant called Pueraria mirifica (Airy Shaw et Suvatabhandu).

The isolation and identification of deoxymiroestrol from the root of Pueraria mirifica has just been reported in the February issue of the Journal of Natural Products. The authors proposed that since deoymiroestrol is easily oxidized to miroestrol it could be the dominant phytoestrogen factor in Pueraria Mirifica contrary to earlier reports. It is still accepted that the two phytoestrogens co-exist in the root of the plant, miroestrol being dominant.

Dr. Wichai Cherdshewasart, an Associate Professor in the Department of Biology, Faculty of Science, Chulalongkorn University, the first and most famous Thai University, received his Bachelor of Science in Zoology in 1975,and his Masters in Zoology in 1977.

He became a Master of Science in Molecular Biology in 1986 and obtained his Doctorate, with great distinction in 1991,at the Vrije University Brussel, Belgium. In 1989 he was awarded the Certificate in Plant Biotechnology by the ICRO-Universitad Complutense de Madrid, Spain.

In 1993, Dr. Cherdshewasart was honored by the Professorship Fund of the Faculty of Science, Chulalongkorn University. His outstanding research achievements resulted in more than 20 articles in international publications, text and method books, proceedings and symposia.

In 1996, Dr. Chershewasart was awarded the Taguchi Prize for his outstanding research in the field of biotechnology. Dr. Wichai Chershewasart began his research on Pueraria mirifica in 1991 and soon thereafter on Butea Superba. He started his research first by traveling all over rural parts of Thailand to search for and select the best, most effective cultivars of these herbs. He achieved this through examining botanical characteristics, chemical analysis, consumption history, toxicology testing, as well as laboratory and clinical trails.