DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: JAN 23 2003 0425 '03 JAN 27 P2:20

From: Consumer Safety Officer, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification:	Liquid Gold Root Extract (LGRE)
Firm:	PHYTOS, Inc.
Date Received by FDA:	July 16, 2002
90-Day Date:	October 14, 2002

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.

Rhonda R. Kane

Rhonda R. Kane, M.S., R.D.

Attachments

95S-0316

RPT 1 #3

PHYTOS

Rhonda Kane
Consumer Safety Officer
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
HFS 821
5100 Paint Branch Parkway
Room 4D0008
College Park, MD 20740

Date:**December 13, 2002**

From: Philip E. Wolfson MD

To: Office of Nutritional Products, Labeling, and Dietary Supplements

Subject: **Your redaction of** Pre-market Notification for a New Dietary Ingredient-Gold Root--*Heliopsis longipes Both of our submisssions*

Dear Ms. Kane:

As per our telephone conversations, and regarding both of our submissions, there is no material that cannot be disclosed.

Sincerely your,

Philip E. Wolfson, MD
President & CEO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD 20740

September 26, 2002

Philip E. Wolfson, M.D.
President & CEO
PHYTOS, Inc.
6 Crest Road
San Anselmo, California 95960

Dear Dr. Wolfson:

This responds to a new dietary ingredient premarket notification, dated June 11, 2002, you submitted to the Food and Drug Administration pursuant to 21 U.S.C. 350b(a)(2). You amended your notification by documents dated July 9 and July 16, 2002. FDA received the last amendment on July 16, 2002, which is the filing date for the amended notification. Your notification concerns the substance "Liquid Gold Root Extract (LGRE)" which you describe as the liquid extract of the root of the Mexican plant *Heliopsis longipes* S.F. Blake (Asteraceae) and that you assert is a new dietary ingredient. You confirmed in your July 9, 2002 amendment that PHYTOS, Inc. would serve as both the manufacturer and distributor of LGRE.

This notification represents a resubmission of the earlier notification you sent FDA in February 2002 about a dried extract of *Heliopsis longipes* S.F. Blake (Asteraceae) or Gold Root Extract (GRE) that you wanted to market as a lozenge or chewing gum containing 5 mg to 50 mg GRE per piece. On April 30, 2002, FDA responded in a letter to your first notification stating that a dietary supplement in the form of a lozenge or chewing gum did not meet the statutory definition of a dietary supplement contained in 21 U.S.C. 321(ff) because it is not "intended for ingestion" as such. The current notification states that you want to market for use by adults 18 years of age and older, excluding pregnant and lactating women, a liquid dietary supplement called LGRE that provides per teaspoon 30 mg of the spray-dried extract of Gold Root or *Heliopsis longipes* S.F. Blake (Asteraceae). Your recommended level of intake is 1-2 teaspoons of LGRE every 3-4 hours as needed.

Under 21 U.S.C. 350b(a), 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 notification and has significant concerns about the evidence on which you rely to support your conclusion that LGRE is reasonably expected to be safe. You state in your notification that *Heliopsis longipes* S.F. Blake (Asteraceae) is an herbaceous plant found in Mexico and that the roots of *Heliopsis longipes* "have been used primarily as a spice or flavoring and for stimulation of salivation." You also state in your submission that the plant "has been used for many centuries and ample evidence exists establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling, reasonably will be expected to be safe." However, your notification neither contains sufficient information or scientific evidence to support this statement nor provides data on how historical use of the root of *Heliopsis longipes* as a spice or traditional medicine is relevant to your reaching a conclusion that your recommended level of intake of up to 16 teaspoons of LGRE (containing 480 mg of spray-dried extract) as a daily dietary supplement will reasonably be expected to be safe.

Further, your notification refers to pilot clinical studies PHYROS, Inc. has conducted and you report that no adverse effects were reported or observed, but your notification contains no study data or other evidence (published or unpublished) that corroborates these statements. In addition, the notification includes short-term toxicity studies of "Gold Root Extract" conducted with rats where the conclusions on safety were drawn without a discussion of the results.

For the reasons discussed above, the information in your notification does not provide an adequate basis to conclude that LGRE, a liquid extract of *Heliopsis longipes* S.F. Blake, when used under the conditions recommended in the product's labeling, 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 a reasonable assurance that it will 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. Therefore, after October 14, 2002, the notification and this response will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information that is in the notification will not be disclosed to the public.

Prior to October 14, 2002, you may wish to identify for FDA in writing the specific information in your notification that you believe is proprietary. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Dockets.

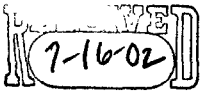
Please contact me at (301) 436-2371 if you have any questions concerning this matter.

Sincerely yours,

Felicia B. 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

PHYTOS



Rhonda Kane
Consumer Safety Officer
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
HFS 821
5100 Paint Branch Parkway
Room 4D0008
College Park, MD 20740

Date: **July 16, 2002**

From: Philip E. Wolfson MD

To: Office of Nutritional Products, Labeling, and Dietary Supplements

Subject: **Clarification to** Pre-market Notification for a New Dietary Ingredient-Gold Root--*Heliopsis longipes*

Dear Ms. Kane:

Please accept the following clarification to our submission:

Each teaspoon of our LGRE Liquid product contains one dosage unit of LGRE equivalent to 30mg of the spray dried extract of Gold Root. Therefore two teaspoons will contain 60mg of the spray dried extract.

Please add this to the paragraph below which now appears as:

Conditions of use

To help support and promote a healthy throat and stomach and to promote salivation, ingest 5-10cc (1 or 2 tsps) of an LGRE liquid product every 3 to 4 hours as needed. Each teaspoon of our LGRE Liquid product contains one dosage unit of LGRE equivalent to 30mg of the spray dried extract of Gold Root. Therefore two teaspoons will contain 60mg of the spray dried extract. Phytos LGRE is intended for use by adults, ages 18 and over. As there is no information available about safety in pregnant or lactating women, Phytos recommends against consumption of LGRE in pregnant and lactating women.

Sincerely yours,

Philip E. Wolfson, MD
President & CEO

6 Crest Road • San Anselmo, CA 94960 • 415.339.9026 ph • 415.339.9031 fax • phytos@phytos.com

PHYTOS

Rhonda Kane
Consumer Safety Officer
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
HFS 821
5100 Paint Branch Parkway
Room 4D0008
College Park, MD 20740

RECEIVED 7-11-02

Date: **July 9, 2002**

From: Philip E. Wolfson MD

To: Office of Nutritional Products, Labeling, and Dietary Supplements

Subject: **Amendment to** Pre-market Notification for a New Dietary Ingredient- Gold Root--*Heliopsis longipes*

Dear Ms. Kane:

Thanks so much for your assistance with our submission.
Below, I have made the changes you suggested or were required for clarification of our submission.

We previously submitted on June 11, 2002:

Pursuant to Section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350b (a)(2)), Phytos wishes to inform the Food and Drug Administration of our intention to market a new dietary ingredient: a liquid extract of the root of the Mexican plant Gold Root *Heliopsis longipes*. **Phytos is acting as both manufacturer and distributor of the New Dietary Ingredient.** Accordingly, three copies of this notification are submitted for your reference.

Also attached please find the supporting materials for safety and pertinent product information. They included the:

- NLEA Proximate analysis of the extract.
- Summary of toxicity studies—Full reports are available should you wish to review these. **We have re-sent the two earlier studies, which you should have previously received as complete reports, and now in this package you have the full 28-day study report.**
- Photocopies of the references cited and translations where appropriate. **These have been completed where pages were missing and modified with several deletions and the reference list revised as below**

Based on the information submitted, we anticipate that FDA will agree with PHYTOS that this new dietary ingredient made from the root of Heliopsis longipes can reasonably be expected to be safe under the recommended conditions of use.

Please do not hesitate to contact me if you have any further questions concerning this matter. Your attention and efforts are appreciated.

Sincerely yours,

Philip E. Wolfson, MD
President & CEO

PHYTOS, Inc. · 6 Crest Road · San Anselmo, California 94960 · 415.~~721.0895 (ph+fax)~~ 339-9026 phone · phytos@phytos.com
(415) 339-9031 fax

Name/Address
Philip E. Wolfson MD
President & CEO
PHYTOS
6 Crest Road,
San Anselmo, CA 94960
415-339-9026
Fax: 415-339-9031
phytos@phytos.com

Notifying party: Philip E. Wolfson MD, President & CEO - Phytos

Name of New Ingredient
Liquid Extract of Gold Root - *Heliopsis longipes* S.F.Blake (Asteraceae)

Description of dietary supplement that contains the new dietary ingredient:
When a Liquid Gold Root Extract (LGRE) product is swallowed and ingested, it helps lubricate and soothe the throat, and helps support and promotes a healthy throat and stomach. Having a lemon like taste, its pleasant, tingling sensation in the oropharynx is also accompanied by promotion of copious salivation due to local and systemic actions, the latter aided by swallowing. LGRE is prepared as a flavored liquid suitable for regular daily ingestion, and may be integrated with other ingredients that promote the health of the throat and stomach.

Salivation is an important element in oral hygiene (refs. are provided in the addendum), as saliva tends to wash the mouth of food and promotes a balanced ecology of the oral cavity including the gums and teeth. LGRE's stimulation of salivation makes our products useful and beneficial to promote oral and dental hygiene.

Level of the new dietary ingredient
Each dosage unit of Phytos' LGRE contains 30mg of our spray dried extract dissolved in 1cc of purified water.
This liquid dosage unit of LGRE will be dispersed in a carrier consisting of USP syrup and purified water also containing one or more of a variety of natural flavors such as berry, licorice, honey, etc, and natural colorings.
Phytos will be marketing its product as bottled liquid extracts.

Conditions of use
To help support and promote a healthy throat and stomach and to promote salivation, ingest 5-10cc (1 or 2 tsps) of an LGRE liquid product every 3 to 4 hours as needed. Phytos LGRE is intended for use by adults, ages 18 and over. As there is no information available about safety in pregnant or lactating women, Phytos recommends against consumption of LGRE in pregnant and lactating women.

History of use
Heliopsis longipes S.F.Blake (Asteraceae) is an herbaceous plant found in a remote region of Guanajuato State, Mexico. The roots of *H. longipes have* been used primarily as a spice or flavoring and for stimulation of salivation. It has been used for many centuries and ample evidence exists establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling, reasonably will be expected to be safe.

Constituents of the Plant
Heliopsis longipes roots are known to contain a bioactive alkamide (an isobutylamide), affinin, identified as *N-isobutyl-2E, 6Z,* 8E-decatrienamide or N-isobutyldeca-trans-2, cis-6,-trans-8-trine-amide. Isobutylamides are found in other plants such as *Echinacea* and are generally considered to be safe for human use.

An NLEA proximate analysis of LGRE is provided in the appended materials.

QC

To ensure safety PHYTOS has ensured that extraction and standardization meet both GMP and GLP standards.

Standardization

Phytos has prepared a GC/MS standard for the affinin constituent of the plant. This is being used to standardize the quantity of LGRE from batch to batch of raw material, thus providing for quality control in the production of our products. Phytos has prepared a chromatographic fingerprint of the plant, thus protecting against adulteration in the QC of our products.

Extraction

Clean dry roots are macerated in a circulating alcohol/water solution. After 2 days time the residual solid is filtered off and the liquid phase is spray dried using maltodextrin as the carrier. Quality control and GMP procedures are applied at all stages of the extraction process. The dry extract is assayed for affinin standardization and dissolved in liquid for use as above, with appropriate flavorings and carriers for ingestion and uses as above.

Safety

a) Toxicology

In the literature appended, there is some toxicological information about H. *longipes* and affinin. In addition, Phytos has conducted its own safety and efficacy studies.

b) Animal Studies

Phytos has provided its own independent laboratory assessment of GRE including mutagenicity, lethality and 28 day, 2 dosage rodent feeding trial. Reports are provided in the documentation enclosed. No morbidity or mortality occurred, i.e. there were no negative findings.

c) Human Studies

Phytos has conducted its own open label, and double-blind pilot clinical studies, the latter with IRB approval from the University of the Pacific School of Dentistry, and in collaboration with Bastyr University's IRB. No adverse effects were reported or observed.

Reference List

Molina-Torres J, et.al.
Antimicrobial properties of alkamides present in flavoring plants traditionally used in Mesoamerica: affinin and capsaicin. J Ethnopharmacol. 1999 Mar; 64(3): 241-8.

Martinez M, 1959 Plant Utiles De La Flora Mexicana. Edicionas Bolas
English translation of same.

Martinez M, 1990 Las Plantas Medicinales. De Mexico Edicionas Bolas
English translation of same.

Ogura M, et.al.
Ethnopharmacologic studies. I. Rapid solution to a problem-oral use of *Heliopsis longipes--by* means of a multidisciplinary approach. J Ethnopharmacol. 1982 Mar;5(2):215-9.

Gutierrez-Lugo M.T. et.al.
Antimicrobial and cytotoxic activities of some crude drug extracts from Mexican Medicinal Plants. Phytomedicine 1996 2 (4): 341-347

(Romero et.al—deleted)
(Fisher—deleted)

Extract analysis report: Nutritional Labeling Education Act Abbreviated Nutrient Package (Proximate)

Toxicology reports: a) Bacterial Reverse Mutation Screen
b) Acute Oral Toxicity Study in Rats
c) GRE 28-day study

Acknowledgment of receipt of Heliopsis longipes voucher specimen by the California Academy of Sciences

Thus, this new dietary ingredient made from the root of Heliopsis longipes can reasonably be expected to be safe under the recommended conditions of use.

Thanks for your consideration,

Philip E. Wolfson, MD
President & CEO

PHYTOS

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
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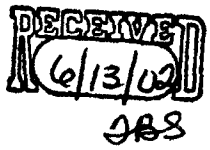

Date: June 11, 2002

From: Philip E. Wolfson MD

To: Office of Nutritional Products, Labeling, and Dietary Supplements

Subject: Pre-market Notification for a New Dietary Ingredient- Gold Root--*Heliopsis longipes*

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