



Memorandum

NOV 13 2003

1592 '04 JAN -3 21:58

Date: _____
From: Gloria Chang, IDS/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: **Extract of *Chrysanthellum americanum* (L.) Vatke**

Firm: PhytoMedica, LLC

Date Received by FDA: 2/05/03

90-Day Date: 5/06/03

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

95S-0316

RPT 172



APR 21 2003

Holly J. Bayne, Attorney at Law
Counsel to PhytoMedica, LLC
601 Pennsylvania Avenue, N.W.
Suite 900 South Building
Washington, D.C. 20004

Dear Ms. Bayne:

This is in response to your notification dated February 4, 2003, which you submitted on behalf of PhytoMedica, LLC pursuant to 21 U.S.C. 350b(a)(2) and Title 21 of the Code of Federal Regulations (21 CFR) Part 190.6 and received by the Food and Drug Administration (FDA) on February 5, 2003, which is the effective filing date.

Your notification concerns the substance you describe as a dried botanical extract of *Chrysanthellum americanum* (L.) Vatke subspecies *afroamericanum* B.L. Turner (*Chrysanthellum americanum*) obtained using a traditional extraction process using a hydro-alcoholic solution that is removed during processing. You indicate that PhytoMedica will market and distribute the substance in bulk form to manufacturers of finished dietary supplement products for tableting and/or encapsulation. Under conditions of use, you state that *Chrysanthellum americanum* extract is intended for use as a dietary supplement consisting of 100 milligrams (mg) of the dried extract, to be taken one to two times per day. You state that the labeling statements will generally describe hepato-protective and antioxidant effects of the dietary ingredient and its usefulness in promoting healthy digestive function.

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 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the product's labeling, will reasonably be expected to be safe. If this requirement is not met, the new dietary ingredient or dietary supplement containing it may be 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 concerns about the evidence on which you rely to support your conclusion that the ingredient the dried extract of *Chrysanthellum americanum* will reasonably be expected to be safe for the suggested or intended uses. We note that the evidence of safety that you submitted was indexed under Tabs 1 to 7.

- The cover letter of February 4, 2003 of your notification states that the ingredient is “a botanical extract of *Chrysanthellum americanum* (L.) Vatke subspecies, *afroamericanum* B.L. Turner (*Chrysanthellum americanum*).” It is unclear whether this ingredient is extracted from the plant *Chrysanthellum indicum* DC Subsp. *Afroamericanum* B.L. Turner or *Chrysanthellum americanum* (L.) Vatke. According to a 1985 English translation of paper summary by D. Honore-Thorez (Tab 7), the plant *Chrysanthellum indicum* DC Subsp. *Afroamericanum* B.L. Turner is the real *Chrysanthellum* “*americanum*” and that it has been confused with *Chrysanthellum americanum* (L.)Vatke or *Chrysanthellum procumbens* Rich. Ex. Pers for some time.
- Tab 1 shows the results of an acute oral toxicity study on a test substance called “Chrysanthellum – lot/batch 2890” which was a dark brown powder. No other specification was given.
- In Tab 2, Berkem, supplier of *Chrysanthellum americanum* extract, provides a statement that the test substance used in the acute oral toxicity test in rats by EVIC is the same extract which PhytoMedica, LLC intends to distribute in the United States (US) as a dietary supplement (Tab 2). However, it is not clear in the certificate of analysis sheet (Tab 4) what the substance was tested against? Was it a certified standard of the claimed plant *Chrysanthellum indicum* DC. Subsp. *Afroamericanum* B.L.Turner, or the plant *Chrysanthellum americanum* (L.)(Vatke)?
- The French Patent application (Tab 5) describes the therapeutic uses and summary of the pharmacological and toxicity studies on extract of the plant known as *Chrysanthellum americanum* Vatke. Again, according to the paper by D. Honore-Thorez (Tab 7) it is different from *Chrysanthellum indicum* DC. Subsp. *Afroamericanum* B.L. Turner, the ingredient intended to be marketed in US.
- The information in this notification provides little data on the safety of the ingredient that is the subject of this notification except that from an acute toxicity test (Tab 1). Information in Tab 5 is a patent application of a medication based on *Chrysanthellum americanum* extract from the plant known as *Chrysanthellum americanum* Vatke. Toxicity studies in animals were presented by a brief description, no data were provided. Pharmacological activities of the extract were noted in humans by mentioning various single-case reports which are irrelevant to the safety of the ingredient.
- The paper by Honore-Thorez (Tab 7) summarized the pharmacological and toxicity studies on *Chrysanthellum indicum* D.C. Subsp. *Afroamericanum* B.L.Turner; however, no data was shown. Since most of the studies were published in French including those as Tab 5 and 7 (with English translation), copies of the English translation of other cited papers are needed for evaluation.

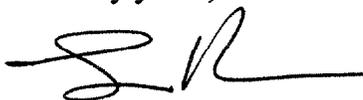
In summary, the submission provides insufficient information about the identity of the plant source of the dietary ingredient that is the subject of the notification, or evidence or data describing its toxicity or lack thereof, that would provide a basis to reach a conclusion that it is reasonably expected to be safe.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude "*Chrysanthellum americanum*" extract when used under the conditions recommended or suggested in the labeling or 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 notifications will be kept confidential for 90 days after the filing date of February 5, 2003. After May 5, 2003, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to May 5, 2003, you may wish to identify in writing specifically what information in your notification 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,

A handwritten signature in black ink, appearing to read "S. Walker", with a long horizontal flourish extending to the right.

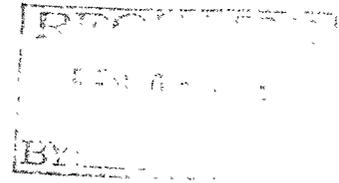
Susan J. Walker, M.D.
Acting Director,
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

The Law Office of
Holly Bayne, P.C.

Holly Joy Bayne, Attorney at Law

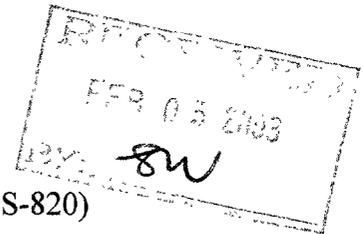
Licensed to Practice in the
District of Columbia and California

February 4, 2003



BY U.S. CERTIFIED MAIL

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 20740-3835



**Re: PhytoMedica, LLC - New Dietary Ingredient Notification for
Chrysanthellum americanum extract**

To Whom It May Concern:

This notification is filed on behalf of PhytoMedica, LLC (PhytoMedica), located at 207 Ardmore Street, Fairfield, Connecticut 06430, by The Law Office of Holly Bayne, P.C., pursuant to Section 413 (a)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 350b (a)(2). Accordingly, PhytoMedica wishes to notify the Food and Drug Administration (FDA) that it intends to market a new dietary ingredient which is a botanical extract of *Chrysanthellum americanum* (L.) Vatke subspecies *afroamericanum* B. L. Turner (*Chrysanthellum americanum*). Information establishing that the dietary ingredient will reasonably be expected to be safe when used in a dietary supplement under the conditions of use recommended in labeling for the product, as set forth below, is attached to this notification.

PhytoMedica will market and distribute the *Chrysanthellum americanum* extract in bulk form to manufacturers of finished dietary supplement products for tableting and/or encapsulation. The *Chrysanthellum americanum* extract is manufactured by Berkem, a manufacturer and supplier of food, dietary supplement, cosmetic and pharmaceutical ingredients, located at Le Mirais-Ouest 24680 Gardonne, France. Berkem's manufacturing facility and quality systems are ISO 9002-certified by COFRAC, French Committee of Accreditation. The *Chrysanthellum americanum* extract is a dried botanical extract, manufactured according to a traditional extraction process using a hydro-alcoholic solution that is removed during processing.

The *Chrysanthellum americanum* extract is intended for use as a dietary supplement consisting of 100 milligrams (mg) of the extract, taken one to two times per day. PhytoMedica intends to market *Chrysanthellum americanum* with labeling statements that generally describe hepato-protective and antioxidant effects of the dietary ingredient and its usefulness in promoting healthy digestive function.

The documents forming the basis upon which PhytoMedica has determined that the *Chrysanthellum americanum* extract will reasonably be expected to be safe when used under the conditions recommended in labeling of the dietary supplement are itemized below. In accordance with FDA regulation, 21 C.F.R. § 190.6 (a), an original and two copies of this notification, including all attachments, are provided herewith. Some of the enclosed documents are entitled to confidential treatment and non-disclosure and are identified as "confidential."

PhytoMedica submits the following information demonstrating the safety of *Chrysanthellum americanum* extract:

- 1) Acute Oral Toxicity Study of *Chrysanthellum americanum* and demonstration of LD50 according to the criteria defined in the European Directive 67/548/EEC, its successive amendments and the OECD Guideline for Testing of Chemicals (Acute Oral Toxicity – Fixed Dose Method). See Tab 1.
- 2) Acute Oral Toxicity Study: raw test data, original documents in French. English translation and affidavit of accuracy prepared by TransPerfect Translations, 1101 Pennsylvania Ave., NW, Washington, D.C. 20004 (TransPerfect Translations). See Tab 2.
- 3) Statement from Berkem, supplier of *Chrysanthellum americanum* extract and sponsor of the enclosed Acute Oral Toxicity Study, confirming that the substance tested is the same extract of *Chrysanthellum americanum* that PhytoMedica intends to market in the United States as a dietary supplement ingredient. See Tab 3.
- 4) Certificate of Analysis for *Chrysanthellum americanum* extract. See Tab 4.
- 5) French Patent describing therapeutic use of extract of *Chrysanthellum Americanum* Vatke, and acute and chronic toxicity studies demonstrating safety. English translation and affidavit of accuracy prepared by TransPerfect Translations. See Tab 5.
- 6) Unpublished summary of acute and chronic toxicology data demonstrating safety of *Chrysanthellum americanum*. See Tab 6.

- 7) Published scientific review article concerning description, identification and therapeutic uses of *Chrysanthellum "Americanum."* (Original article in French, published in J. Pharm. Belg., (1985) 40:5, 323-331. English translation and affidavit of accuracy prepared by TransPerfect Translations.) See Tab 7.

*

*

*

Please contact the undersigned directly at (202) 220-3154 if you have any questions regarding this notification.

Sincerely yours,



Holly J. Bayne
Counsel to PhytoMedica

HJB/
Enclosures