DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: JAN 23 [illegible] 0430 '03 JAN 27 P2:22

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:	*Echium plantagineum* Seed Oil
Firm:	Pharmax LLC
Date Received by FDA:	July 29, 2002
90-Day Date:	November 27, 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

RPT147

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

OCT - 9 2002

Ms. Cathryn E. Wood
Technical Scientist
Cultech Limited
Unit 3 Christchurch Road
Baglan Industrial Park
Port Talbot
SA12 7BZ United Kingdom

Dear Ms. Wood:

This letter responds to a new dietary ingredient premarket notification you submitted on behalf of the distributor Pharmax LLC, located in Bellevue, Washington, to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2). You replaced your initial notification, dated May 7, 2002, with a revised notification dated June 17, 2002. Subsequently, you amended the notification with documents dated July 24, 2002 that FDA received on July 29, 2002, which is the filing date of your notification. Your notification concerns *Echium plantagineum* Seed Oil that you assert is a new dietary ingredient. You state that this complex triglyceride oil high in omega-6 and omega-3 fatty acids is obtained by extracting the seeds of the plant *Echium plantagineum* L. You further identified Crossential SA14, a super-refined *Echium plantagineum* Seed Oil supplied by Croda Leek Limited in the United Kingdom, as the oil you want to market as a dietary supplement.

The notification informs FDA that Pharmax LLC intends to market *Echium plantagineum* Seed Oil as a dietary supplement in soft gel capsules containing 1000 mg of the oil per capsule and as a liquid in 300 ml bottles. You identified the target population of consumers as individuals above 12 years of age, and recommended a daily intake level of 5 ml of oil in liquid form or 1-2 capsules, preferably at mealtimes or as directed by a health care provider. However, the notification states that pregnant and lactating women will be advised to use this dietary supplement under the supervision of their health care provider. In addition, individuals on blood thinning or anti-coagulant therapy will be advised to monitor clotting time and prothrombin time regularly when using this dietary supplement due to the potential that bleeding time might be prolonged by omega-3 fatty acids.

The law at 21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into commerce. This information must include 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 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 new dietary ingredient 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 and injury.

FDA has carefully reviewed the Pharmax LLC notification. Discussion under Section 6.4.6 of the June 17, 2002 notification acknowledges that pyrrolizidine alkaloids (PAs) are toxic substances that naturally occur in particular plants, including *Echium plantagineum*. The product specification states that the level of PAs should not exceed 15 ng/g of oil. Appendix 6 of the notification represents the analysis results for a single batch of Echium oil (No. L1/00033/1124A), showing that the sample contained 11 ± 2 ng PAs/g of oil. Your notification concludes that the reported level of PAs in *Echium plantagineum* Seed Oil will not cause harm, but you submitted no data to support this assertion. None of the information in your notification demonstrates that the level of PAs found in *Echium plantagineum* Seed Oil is safe for long-term chronic use of up to 2 grams of oil per day by individuals 12 or more years of age.

The risk evaluation section of the World Health Organization (WHO) publication entitled *Health and Safety Guide No. 26, Pyrrolizidine Alkaolids Health and Safety Guide*[1] states: "No-observed-adverse-effect levels have not been established in experimental animal studies with PAs. Estimates of intakes causing toxic effects in human beings indicates that they are more sensitive than rats and domestic animals....In view of the established ability of some PAs to produce cancer in rats, plant product containing them should not be eaten or drunk." As noted above, *Echium plantagineum* Seed Oil is a source of PAs intended for daily human consumption without confirmation of its safety.

For the reasons discussed above, the Pharmax LLC notification does not provide an adequate basis to conclude that the use of *Echium plantagineum* Seed Oil in a dietary supplement will reasonably be expected to be safe when used as recommended. Therefore, the 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 it 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. Therefore, after November 27, 2002, the notification and this response will be placed on public display at

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1 International Programme on Clinical Safety: *Health and Safety Guide No. 26, Pyrrolizidine Alkaloids Health and Safety Guide*, World Health Organization, Geneva, Switzerland, 1989, p. 12.

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 November 27, 2002, you may wish to identify for FDA in writing the specific information in the 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