

Memorandum

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Date:

JUL 28 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: ACAPHA

Firm: Global Cancer strategies

Date Received by FDA: February 3, 2006

90-Day Date: May 4, 2006

Please append this letter dated July 12, 2006, to the notice above, Report 337.

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—

1995S-0316

SUP 16



JUL 12 2006

Dr. T. P. Chiang, C.E.O.
Global Cancer Strategies Ltd.
113-990 Beach Avenue
Vancouver, British Columbia V6Z 2N9
Canada

Dear Dr. Chiang:

This is to inform you that the notification, dated January 31, 2006, that you submitted 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 February 3, 2006. Your notification concerned the substance that you identified as "ACAPHA" which you prepare from *Sophora tonkinensis* Gagnep., *Sonchus brachyotus* DC., *Prunella vulgaris* L., *Polygonum bistorta* L., *Dioscorea bulbifera* L. and *Dictamnus dasycarpus* Turcz. You intend to market "ACAPHA" as a new dietary ingredient in a dietary supplement product called "ProhibitRx".

According to your notification, "The recommended daily dose is 1.8g, 3 x 600 mg tablets/day.... The tablets should be consumed three times, one tablet at a time orally with water or liquid before meals." As to conditions of use, your notification states that "[t]he product is intended for use by health adult males and females who are seeking to supplement their diet with herbal supplement to support the health of their epithelial tissues such as the oro-pharyngeal and respiratory tissues, i.e. support normal respiratory function in a smoke-rich environment, support respiratory health for those exposed to second hand smoking, support body's ability to cope with a polluted environment, may help minimize the risk to long-term health posed by exposure to environmental toxins.

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 21 U.S.C. 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 "ProhibitRx" will reasonably be expected to be safe.

FDA was unable to determine the identity of your new dietary ingredient, "ACAPHA". For example, according to your notification, the product will be standardized to the content of the alkaloid, matrine, which is described as being present only in *Sophora tonkinensis*. Since the other five botanical starting materials are extracted separately in the manufacturing process described in your notification, it is unclear how the constituents of the other botanicals contribute to the composition of your ingredient. In addition, information in your notification describes the existence of multiple varieties of *Dioscorea bulbifera*, some of which are described as being cultivated for food use whereas other, uncultivated varieties are described as "slightly poisonous" and "bitter and even poisonous". It is unclear to FDA whether the "ACAPHA" that is the subject of your notification contains poisonous constituents extracted from the *Dioscorea bulbifera* used to manufacture the ingredient.

In addition, the relationship between "ACAPHA" and the botanicals described in your notification are unclear. For example, your notification contains information about the history of use as food or for medical treatments for each of the botanical starting materials used to manufacture your "ACAPHA". However, this history of use information does not describe the amounts consumed, the parts of the plants used and/or the manner in which the plants were processed prior to consumption. It is unclear how the constituents of your "ACAPHA" are qualitatively or quantitatively similar to the botanical materials described in the history of use information that you rely on as a basis for the safety for your new dietary ingredient.

In addition, your notification provides information from studies of "ACAPHA" in mice, rats and mongrel dogs. However, the information provided from those studies raises concerns about hepatotoxicity of "ACAPHA" and was inadequate to allow FDA to evaluate the basis for the safety of your product. For example, the notification does not address the degeneration of liver cells and abnormal levels of liver enzymes described in the studies of rats that were included in your notification. These signals of liver toxicity are of even more concern to FDA due to information in the published literature concerning liver toxicity associated with *Dictamnus dasycarpus*¹ and *Dioscorea bulbifera*². In addition, the small sample sizes, lack of data from individual animals, and lack of separate data for male vs. female animals in the mongrel dog studies prevent those studies from demonstrating the safety of ACAPHA at the tested doses.

¹ C.A. McRae et al. (2002) Hepatitis associated with Chinese herbs. *Eur. J. Gastroenterol. Hepatol.* 14: 559-62.

² H.Q. Tan et al. (2003) [Studies on liver-toxicity in rhigoma of *Dioscorea bulbifera*] *Zhongguo Zhong Yao Za Zhi.* 28:661-3. L. Su L et al. (2003) *Fa Yi Xue Za Zhi.*;19:81-3. [Experimental pathological study of subacute intoxication by *Dioscorea bulbifera* L]

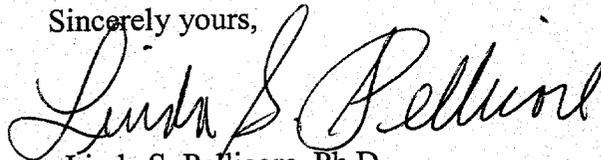
In addition, your notification provides information about a clinical study of administration of "ACAPHA" to 8 individuals over 4 weeks. This study was inadequate support the safe chronic human consumption of "ACAPHA".

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that ACAPHA when used under the conditions recommended or suggested in the labeling of "ProhibitRx", 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).

This letter supersedes the April 17 April 17, 2006 response letter.

If you have any questions concerning this matter please contact Victoria Lutwak at (301) 436-1775.

Sincerely yours,



Linda S. Pellicore, Ph.D.
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