DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Washington, DC

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April 5, 1996

George A. Kargas, M.D.
President
TINOS, L.L.C.
2500 Brownsboro Road
Louisville, Kentucky 40206

Re: Theobromine

Dear Dr. Kargas:

This responds to your letter dated January 18, 1996, concerning the marketing of theobromine as a dietary supplement. This letter addresses the requirements for marketing theobromine as a new dietary ingredient and the requirements for marketing a dietary supplement with certain claims appearing on its label or in its labeling. In addition, the agency is responding to your request for FDA to notify you of any concerns the agency has regarding the marketing of theobromine as a dietary supplement.

Section 413 of the Federal Food, Drug, and Cosmetic Act (the act) requires a manufacturer or distributor of a dietary supplement which contains a new dietary ingredient to submit certain information to the agency. Specifically, the act requires that at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient provide the FDA with information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe. Because you submitted to FDA information which is the basis on which you concluded that the dietary supplement will reasonably be expected to be safe, the agency will consider your submission to be the required 75-day premarket notification of your intent to sell theobromine as a dietary supplement. As required by section 413(a)(2) of the act, we will keep your submission confidential for 90 days from the date of receipt, and thus on April 21, 1996, it will be placed on public display at Dockets Management Branch. Commercial and confidential information in the notification will not be made available to the public.

Nevertheless, you should be aware of the agency's concern over the safety of theobromine as a dietary ingredient. There is a paucity of data on the pharmacological and toxicological effects of the theobromine. However, the use of theobromine has been associated with adverse events, such as nausea, gastrointestinal distress and headache. In addition,

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theobromine, in high enough concentrations, can stimulate the central nervous system. We note that several animal studies raise concern over possible effects, such as inducing anorexia, testicular atrophy and impaired spermatogenesis. These concerns are currently unresolved.

Your letter suggests that you intend to make a claim for the product concerning its craving suppressant activity. Pursuant to section 403(r)(6) of the act, a statement of nutritional support for a dietary supplement may be made if the statement

> (1) claims a benefit related to a classical nutrient deficiency disease and discloses the prevalence of such disease in the United States,
> (2) describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans,
> (3) characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function, or
> (4) describes general well-being from consumption of a nutrient or dietary ingredient.

Section 403(r)(6) permits these statements, however, only under certain conditions. For example, the statement may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases. In addition, a manufacturer of such a product must have substantiation that the nutritional support statement is truthful and not misleading. Furthermore, the nutritional support statement must prominently contain the following disclaimer:

> This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Finally, pursuant to section 403(r)(6), a manufacturer must notify FDA no later than 30 days after the first marketing of a dietary supplement product that bears a nutritional support statement on its label or in its labeling.

Because the information you submitted does not meet these requirements, we cannot consider your letter to be a notification within the meaning of section 403(r)(6) of the act. If you intend to make a nutritional support statement on the label or in the labeling of your dietary supplement product, you must submit to FDA a notification following the requirements listed in section 403(r)(6) of the act. The notification must include the nutritional support statement

that will appear on the label or in the labeling of the dietary supplement.

If it is your intention for theobromine to be evaluated for its use in the suppression of cravings as an over-the-counter (OTC) drug, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Over-the-Counter Drug Evaluation, HFD-800, 7520 Standish Place, Rockville, Maryland 20855.

Be advised that there is no requirement that dietary supplements be approved by FDA prior to marketing. It is the responsibility of the person who introduces a dietary supplement into interstate commerce to ensure that the dietary supplement is safe and properly labeled. Should you have any questions or require additional information, contact Bob Moore of my staff at (202) 205-4605.

Sincerely,

John W. Gordon
Acting Director
Division of Programs
and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

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January 18, 1996

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
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Office of Special Nutritionals
U.S. Food and Drug Administration
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Washington, D.C. 20204

RE: Pre-Market Approval of a New Herbal Dietary Supplement

Dear Dr. Moore:

It was a pleasure talking with you on Tuesday, January 16, 1996. I really appreciate you helping me out with all these regulatory affairs.

As per our conversation, I am enclosing journal articles which pertain to the safety as well as substantiation of the claims of a new dietary supplement we intend to market in the U.S. After an exhaustive review of the literature extending over the past year, we believe we have discovered a compound in the dietary food supply which possesses craving suppressant activity. This chemical, called theobromine, is very well known for decades, and is commonly consumed in a myriad of chocolate containing foods. Furthermore, theobromine is generally recognized as safe in the field. It has not been marketed in the U.S. simply because it was felt to have little, if any, activity.

If you have any concerns or issues regarding the marketing of theobromine as a dietary supplement, please let me know. I can be reached anytime by my digital pager (502) 421-9384.

Thank you very much. With best regards,

Sincerely yours,

George A. Kargas, M.D.

George A. Kargas, M.D.
President
TINOS, L.L.C.