DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date SEP 24 1997

From Acting Director, Division of Programs & Enforcement Policy, Office of Special Nutritionals, HFS-455

Subject 75-Day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

97N-0754 '97 SEP 26 A9:43

New Dietary Ingredient:	Pokeweed lectins from *Phytolacca americana*
Firm:	Advanced Plant Pharmaceuticals, Inc.
Date Received by FDA:	August 1, 1997
90-Day Date:	October 29, 1997

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after October 29, 1997.

James Tanner

James T. Tanner, Ph.D.

Attachment

95S-0316

RPT 13

SEP 24 1997

Mr. Sam Berkowitz
Advanced Plant Pharmaceuticals, Inc.
17 John Street, 3rd Floor
New York, New York 10038

Dear Mr. Berkowitz:

This is in response to your letter to the Food and Drug Administration (FDA) dated July 29, 1997, making a submission pursuant to section 413(c) of the Federal Food, Drug, and Cosmetic Act (the act) for a new dietary ingredient. Your letter notified FDA of your intent to market a dietary supplement containing a new dietary ingredient that is a mixture of proteins of the type known as lectins from the pokeweed plant, *Phytolacca americana.*

Section 413 of 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.

You have not provided 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. Your submission does not provide information about the quantity of the new dietary ingredient in the dietary supplement nor about the conditions of use recommended or suggested in the labeling of the dietary supplement. In the absence of such information, it is not possible to determine whether a dietary supplement containing this new dietary ingredient will reasonably be expected to be safe. A dietary supplement that contains a dietary ingredient that is 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 is adulterated under section 402(f)(1)(B) of the act.

FDA fundamentally disagrees with your determination that a dietary supplement containing a mixture of lectins from the pokeweed plant *(Phytolacca americana)* will reasonably be expected to be safe. Pokeweed is a well-characterized poisonous plant. Toxicity to humans and animals is associated with exposure to all parts of the pokeweed plant and the lectins are believed to be one of primary biochemical contributors to pokeweed toxicity. Oral, ocular, and dermal exposure to pokeweed plant have been shown to result in human poisonings.

Signs and symptoms of pokeweed include stomach cramping; nausea, bloody, persistent, and debilitating vomiting and diarrhea, dyspnea, spasms, hypotension, heart block, convulsions, and death.

Since you have not complied with section 413 of the act and shown that the dietary supplement that is the subject of your notification is safe, introduction of this product into interstate commerce is prohibited under section 301(u) of the act. Moreover, the dietary supplement is subject to regulatory action pursuant to section 402(f)(1)(B) of the act.

Sincerely yours,

James T. Tanner, Ph.D.
Acting Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

cc:
HFA-224 (w/incoming)
HFA-305 (Docket No. 95S-0316)
HFS-22 (CCO)
HFS-456 (r/f, Miles, Moore)
HFS-450 (r/f, OSN w/ control slip)
r/d:HFS-456:CMiles:9/22/97
Revised:HFS-456:RMoore:9/23/97
Init:GCF-1:PDerfler:9/24/97
f/t:rjm:HFS-456:9/24/97:docname:53972.osn:disc22

rec'd
8/1/97
HFS-450

Advanced Plant Pharmaceuticals, Inc.
17 John Street 3rd Floor
New York N.Y. 10038
212 964-5863

July 29, 1997

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W.
Washington, D.C. 20204

Pokeweed Mitogen
Section 413 (c) Notification

In accordance with the requirements of section 413(c) of the Food Drug and Cosmetic Act, Advanced Plant Pharmaceuticals, Inc. herewith notifies the FDA of its intent to market a dietary ingredient not marketed prior to October 15, 1994

The product intended for sale is a mixture of proteins of the type known as lectins from the pokeweed plant, *Phytolacca americana.* Lectins are a general class of proteins that bind to carbohydrates, the specific sugar bound depending on the lectin in question (1). Those from *Phytolacca Americana* bind to N-acetyl glucosamine (2).

The information below supports the use of pokeweed lectins as a product for human consumption under the category of food supplement.

1. Pokeweed lectins can be defined as a "dietary supplement" because they are a botanical product. It can be provided in tablet, capsule or softgel form, and cannot be represented as a meal replacement or conventional food.

IIa. Pokeweed lectins do not represent "a significant or unreasonable risk of illness or injury", "an imminent hazard to public health or safety" or a "poisonous or deleterious substance which may render it injurious to health" in any animal or human exposed to them. This is according to rodent experimentation and human case studies (3-8).

IIb. Pokeweed lectins are in the category of "new dietary ingredient". Although parts of the pokeweed plant have been marketed in the past, the product described here represents a purified extract, without noxious quantities of toxic pokeweed components, such as triterpenes (9). The process of extracting pokeweed lectins does not chemically alter the lectins (I0, 11)

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IIc. The history of use of pokeweed lectins and of exposure to these proteins provides evidence that pokeweed lectins are expected to be safe. Descriptions of human consumption and exposure to pokeweed lectins include stimulation of the immune system as the only observed effect (7, 8). Stimulation of the immune system was described in rodents, as well, without any other toxic effects being found in spite of close examination (3-6). A recent paper describing chronic treatment of mice with a dose of pokeweed lower than used in previously published studies found no tissue damage on gross organ examination and no avoidance responses by the animals themselves during the course of receiving pokeweed lectins (12). The length of treatment was 16 days in that report. A single human subject ingested the same pokeweed lectin preparation at a dose of 61 ug/kg, and experienced no metabolic effects except the intended result - temporary loss of appetite (DD Lazarus, personal communication).

References

1. Chrispeels MJ, Raikhel NV. Lectins, lectin genes and their role in plant defense. Plant Cell 3-.1-9, 1991.
2. Waxdal MJ. Isolation, characterization, and biological activities of five mitogens from pokeweed. Biochemistry 13,3671-3676, 1974.
3. Lozzio BB, Comas FV. Biological effects of pokeweed mitogen. Int Arch Allergy 36:266-281, 1969.
4. Zazula BM, Fikrig SM. *In vivo* effects of pokeweed mitogen on mouse spleen cells. Proc Soc Ex Biol Med 133:1088-1092, 1970.
5. Saito K, Markey SP, Heyes MP. Effects of immune activation on quinolinic acid and neuroactive kynurenines in the mouse. Neuroscience 51:25-39, 1992.
6. Hamilton RJ, Shih RD, Hoffman RS. Mobitz type I heart block after pokeweed ingestion. Vet Human Toxicol 37:66-67, 1995.
7. Barker BE, Fames P, LaMarche PH. Peripheral blood plasmacytosis following systemic exposure to *Phytolacca Americana* (pokeweed). Pediatrics 38:490-493, 1966.
8. Barker BE, Lutzner MA, Fames P, et al. Effect of Phytolacca on human hemic cells in vivo. Clin Res 15:271, 1967. (abstract)
9. Kang SS, Woo WS. Triterpenes from the berries of *Phytolacca Americana.* J Nat Prod 43:5-13, 1980.
10. purification
11. purification
12. Lazarus OD, Trimble LA, Moldawer LL. The metabolic effects of pokeweed mitogen in mice. Metabolism, in press, 1997.

Sincerely,

Sam Berkowitz