



DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

DEC 23 1998

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456


Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient: *Nerium oleander*

Firm: Ozelle Pharmaceuticals, Inc.
Date Received by FDA: December 1, 1998
90-day Date: February 13, 1999

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 February 13, 1999.


Robert J. Moore, Ph.D.

95S-0316

RPT 37



DEC 23 1998

2068 '99 JAN -4 P2:58

Mr. Joseph B. Nester
President
Ozelle Pharmaceuticals, Inc.
11825 IH 10 West
Suite 213
San Antonio, Texas 78230

Dear Mr. Nester:

This letter is in response to your submission to the Food and Drug Administration (FDA) dated November 30, 1998 and received by FDA on December 1, 1998 making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2). Your letter notified FDA of your intent to market a product containing *Nerium oleander* extract.

Under 21 U.S.C. 350b(a), 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 section 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 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 submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing *N. oleander*, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. *N. oleander* is well known to be a poisonous plant. All parts of the oleander plant are poisonous to man and animals and serious adverse effects are associated with ingestion, inhalation, and contact of mucus membranes with oleander or oleander extracts. Adverse effects include, among other things, nausea, vomiting, abdominal pain, diarrhea, cardiovascular symptoms, and peripheral neuritis. The most serious effects that are associated with exposure to oleander result from the cardiotoxic actions of the cardiac glycosides in oleander. The main cardiac glycosides are oleandrin, folinerin, digitoxigenin, and oleandrigenin.

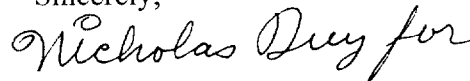
Page 2 - Mr. Joseph B. Nester

Your submission contained data from an intramuscular injection study in dogs of your oleander extract. However, that study is not relevant in establishing the safety of oleander extract for oral consumption, in particular because you provided no toxicokinetic information that would allow for an extrapolation of data of non-oral studies conducted in animals to the safety of oral administration in humans. There also is no information in your submission that bears on the presence (or absence) of the known toxic substances contained in oleander that would enable a conclusion to be reached that this extract is safe; this is a particularly serious limitation of the information contained in the submission given the well documented history of accidental poisonings associated with oral oleander exposure and the extensive scientific literature on its toxicity. Moreover, the risk associated with oral exposure to the cardiac glycosides contained in oleander may be greater in some persons - for example, those who have pre-existing heart disease or arrhythmias, have hypokalemia or renal dysfunction, or who are taking certain drugs (such as digoxin, diuretics, corticosteroids, beta-adrenergic blockers, calcium channel blockers, and others) - than in others. Therefore, the failure of the submission to address the safety of this extract in different consumer demographic populations (particular children, those taking medications, or with underlying diseases) is a serious omission.

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

Please contact us if you have any questions concerning this matter.

Sincerely,

A handwritten signature in cursive script that reads "Nicholas Drey for".

Lynn A. Larsen, Ph.D.

Director

Division of Programs and Enforcement Policy

Office of Special Nutritionals

Center for Food Safety

and Applied Nutrition

OZELLE PHARMACEUTICALS, INC.
11825 IH 10 WEST SUITE 213
SAN ANTONIO, TX 78230
(210) 690-0022 OFFICE (210) 690-3015 FAX

62522

30 November 1998



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

To Whom It May Concern:

Ozelle Pharmaceuticals, Inc. (OPI) located at 11825 IH 10 West Suite 213, San Antonio, Texas 78230, has developed a non-toxic nerium oleander extract product "Oleander Extract Caplets" which is a dietary supplement in caplet form. Recommended dosing is one caplet daily. Each caplet contains 20 mg of the oleander extract. The extract is produced at OPI's wholly owned subsidiary, TexTract Laboratories, Inc. located at 130 West Rhapsody, San Antonio, Texas 78216.

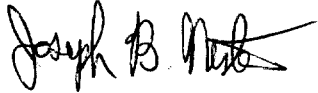
OPI has engaged a number of independent research laboratories to conduct a wide array of tests on the extract to help determine safety and action. These include:

1. A large animal long term toxicity study conducted by Southern Research Institute in Birmingham, Alabama that showed no toxic effects on 32 beagle dogs. (See Attachment A).
2. A "fingerprint" polysaccharide analytical assay for OPI's oleander extract performed by Dr. Robert Newman, Chief of Pharmacology at M.D. Anderson Cancer Center in Houston, TX. demonstrated batch to batch consistency. (See Attachment B).
3. Extensive immunology studies at MDS/PANLABS showed the extract to have immune stimulation properties that helps promote and maintain immune responses. These results confirmed earlier studies showing immuno active polysaccharides in our product (I. Carbik et al. 1990). (See Attachment C).

This information is being submitted to the Center for Food Safety and Applied Nutrition to satisfy informational requirements as described in the Diet Supplement Health and Education Act of 1994 (DSHEA), as finalized in 1997, section 190.6 – requirement for pre-market notification.

Thanking you for your attention to this matter, I remain,

Very truly yours,

A handwritten signature in black ink, appearing to read "Joseph B. Nester". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

JOSEPH B. NESTER
President

Attachments: A – C

**COPYRIGHTED MATERIAL CAN BE
VIEWED IN THE
DOCKETS MANAGEMENT PUBLIC
READING ROOM
5630 FISHERS LANE, ROOM 1061
ROCKVILLE, MD**