



**Memorandum**

**JUN 30 2004**

Date: \_\_\_\_\_  
From: Interdisciplinary Scientist/Pharmacist, 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: *Hypoestes rosea* dried leaf powder

Firm: Quinta Naturaceuticals, Inc.

Date Received by FDA: April 1, 2004

90-Day Date: June 30, 2004

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 Webster*

95S-0316

RPT239



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, Maryland 20740

Howard B. Cottam, Ph.D.  
Director of Scientific Affairs  
Quinta Naturaceuticals, Inc.  
5390 Little Uvas Road  
Morgan Hill, California 95037

JUN 15 2004

Dear Dr. Cottam:

This is to inform you that the notification, dated March 26, 2004, you submitted pursuant to 21 U.S.C. 350 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 April 1, 2004. Your notification concerns the substance called *Hypoestes rosea* (P. Beauv.) that you intend to market as a new dietary ingredient.

You describe your substance as a botanical herb with the Latin binomial of *Hypoestes rosea* given by the botanist P. Beauv. You state that your substance will be marketed as a dry leaf powder contained in gelatin capsules, with no additives. Under conditions of use, you state that "A recommended dose is 1 gram per day, taken orally with or without food, for individuals 18 years of age or older would be indicated on the label. Also indicated on the label would be the warnings: Keep out of reach of children. Not for use in women who are pregnant or nursing mothers."

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 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 considered 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 *Hypoestes rosea* will reasonably be expected to be safe.

Page - 2 - Howard B. Cottam, Ph.D.

According to your notification, you intend to market the dry leaf powder prepared from the plant, *Hypoestes rosea* (P. Beauv.). Your notification states that there is a history of use of the plant for medicinal purposes by West African natives. However the documentation provided in your notification indicates that the medicinal preparations are used for topical skin disorders. Your notification did not provide any information on the oral ingestion of the plant, *Hypoestes rosea* (P. Beauv.), for medicinal purposes by West African natives.

In addition, your notification failed to provide adequate information on the chemical composition of the material that is the subject of your notification. No active components are identified and no specifications for your product are provided in your notification. Thus, FDA is not able to evaluate your conclusion that your product containing the substance *Hypoestes rosea* is reasonably expected to be safe.

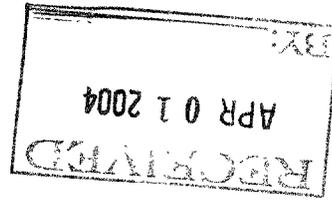
For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that *Hypoestes rosea* when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated 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 an 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).

Your notification will be kept confidential for 90 days after the filing date of April 1, 2004. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

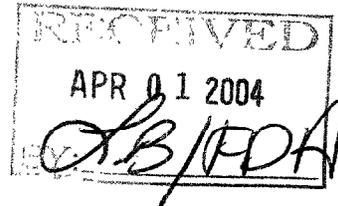
Sincerely yours,

  
for Susan J. Walker, M.D.  
Director  
Division of Dietary Supplement Programs  
Office of Nutritional Products, Labeling  
and Dietary Supplements  
Center for Food Safety  
and Applied Nutrition



March 26, 2004

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-80)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835



To Whom It May Concern:

Enclosed herein are documents pertaining to the Premarket Notification of a New Dietary Ingredient (Supplement), pursuant to Section 413b of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350b), submitted by Quinta Naturaceuticals, Inc. The subject of this notification is the registration of the botanical herb *Hypoestes rosea*.

Respectfully submitted,

A handwritten signature in cursive script that reads "Howard B. Cottam".

Howard B. Cottam, Ph.D.  
Director of Scientific Affairs  
Quinta Naturaceuticals, Inc.  
5390 Little Uvas Road  
Morgan Hill, CA 95037

hcottam@ucsd.edu

87898

## Premarket Notification of a New Dietary Ingredient

The undersigned, Howard B. Cottam, Ph.D., submits this premarket notification of a new dietary ingredient pursuant to Section 413b of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 350b) and as codified in the FDA regulations (21 CFR 190.6), with respect to the botanical herb *Hypoestes rosea*, and is submitted on behalf of Quinta Naturaceuticals, Inc. Attached hereto, and constituting a part of this notification, are the following:

- A. General manufacturer information.
- B. Botanical name and classification of the new dietary ingredient.
- C. Description of the dietary ingredient including history of use and evidence of safety.
- D. Signature of manufacturer designee.
- E. Attachments

A. Howard B. Cottam, Ph.D., Director of Scientific Affairs  
Quinta Naturaceuticals, Inc.  
5390 Little Uvas Road  
Morgan Hill, California 95037

Email: [hcottam@ucsd.edu](mailto:hcottam@ucsd.edu)

**B. Botanical Name.** The dietary supplement which is the subject of this notification is a botanical herb currently produced in the state of California. It is a member of the family Acanthacea and has been given the Latin binomial name of *Hypoestes rosea* by the botanist P. Beauv according to the late Professor L.S. Gill of the University of Benin, Nigeria (see reference 1).

**C. Description and History.** The botanical herb *Hypoestes rosea* is indigenous to the West African areas of Cameroon and Nigeria. It was first registered with the Department of Forestry of Nigeria in Ibadan in 1929 as a native plant of British

Cameroon and then in 1946 as found in the city of Onitsha of the locality Oshakuma, Nigeria, and again in 1948 as found in the province of Benin. In 1982, Professors Adesomoju and Okogun of the University of Ibadan, Nigeria isolated and characterized several diterpenes from this plant species growing in that region (see references 2-4). Their interest in this plant was generated by inquiries made to native traditional medicine practitioners about various indigenous plants used in folklore medicine. This plant was reported to be used topically by natives as a remedy for skin infections (see reference 1) and as a food source as an ingredient in soups (see reference 5).

**Evidence of Safety.** Application was made to the United States Department of Agriculture (USDA) to import into the U.S. cuttings from *Hypoestes rosea* plants growing in Nigeria. A permit was granted and cuttings were procured, inspected, and imported to California. It should be noted here that *Hypoestes rosea* does not appear on the USDA Federal Noxious Weed List (see Attachment item 1). The cuttings were established and propagated under greenhouse conditions in Northern California more than two years ago. Manufacturing presently continues under GMP-like conditions at our California greenhouses. During this time, several individuals began consuming the dry leaf powder of *Hypoestes rosea* as a food supplement for its potential beneficial effects in inflammation, blood lipid regulation, and as a cancer prevention agent. Preclinical evidence for efficacy of this herb for these indications is based on studies published on one of the active ingredients found in *Hypoestes rosea* known as hypoestoxide (see references 6-7). Hypoestoxide is present in *Hypoestes rosea* in an abundance of approximately 0.1% by weight of dry leaf powder. Studies associated with these publications showed that a maximum tolerated oral dose could never be reached with either the dry leaf powder or purified hypoestoxide in laboratory animals (rodents) and in canine, even up to 2 grams per kilogram dosage (see Attachment item 2). Thus, no animal has ever died in studies of oral dosing even up to 2 grams per kilogram of this herb or the diterpene derived from it (hypoestoxide). Indeed, no adverse side effects have ever been observed in animal studies even at these levels by oral administration over an extended period of time (several months). Due to the perceived safety of this herb in connection with its traditional native uses in humans and our own preclinical studies in

animals, individuals in California began consuming the herb as a food supplement as mentioned above. Table 1 depicts a summary of individuals consuming *Hypoestes rosea* dry powder relative to the length of time of consumption and general health status. In at least one individual, clinical laboratory blood analysis was evaluated after 1 year of uninterrupted daily consumption of the herb. As can be seen, the values reported for the various panels are within normal ranges (see Attachment item 3). Of note is the value for triglycerides in the lipid fractionation panel. This value is very good and correlates with observations noted earlier in the laboratory animal studies wherein high values for this blood lipid were brought into the normal range within one week of oral dosing (dog study, see Attachment item 4). Also of note in the human blood analysis are the liver enzyme values in the liver panel. Generally, a toxic substance given orally, especially over an extended period of time, will lead to abnormally high liver enzyme values, indicating liver damage. Here, values are normal after 1 year of herb consumption. Finally, no bone marrow toxicity is noted as evidenced by the normal blood counts (CBC and differential).

**Proposed Dose and Use of *Hypoestes rosea*.** Given our experience with *Hypoestes rosea*, it is proposed that this herb be marketed as a dry leaf powder product contained in gelatin capsules, with no additives. A recommended dose of 1 gram per day, taken orally with or without food, for individuals 18 years of age or older would be indicated on the label. Also indicated on the label would be the warnings: “Keep out of reach of children. Not for use in women who are pregnant or nursing mothers.” These warning are only to satisfy the requirement to be extremely conservative until more data is collected regarding the long term use of the product. There is no data to indicate that this product would be harmful in children or pregnant women or infants of nursing mothers, or in any subset of the population.

In summary, the use of *Hypoestes rosea* in humans as a food supplement should generally be recognized as safe for the proposed oral dose and use based on:

1. Traditional use of the herb by African natives in medicine and as a food source.

**TABLE 1**

**Effect of oral ingestion of dried leaf powder of *Hypoestes rosea* as a dietary supplement on general well-being in human subjects**

<u>Subject #</u>	<u>Dose (grams)</u>	<u>Duration (months)</u>	<u>Health Status</u>
1	1 g x bid	2	Excellent
2	1 g x qd	24	Excellent
3	1 g x qd	24	Excellent
4	1 g x qd	12	Excellent
5	1 x qd	12	Excellent
6	1 x qd	12	Excellent
7	1 x qd	12	Excellent
8	1 x qd	12	Excellent
9	1 x qd	12	Excellent
10	1 x qd	12	Excellent

As shown in Table 1, daily intake of 1 g capsules of dried leaf powder of *Hypoestes rosea* did not cause any untoward effects over a two-year period in ten human subjects.

2. Data generated in laboratory animals in an attempt to establish a maximum tolerated dose by oral administration.
3. Experience in at least 10 humans consuming the herb for extended periods (as long as 2 years at 1 gram per day) with no adverse effects and manifesting normal liver and blood test values.

**D. Signature of manufacturer designee:** I certify that the information contained in this notification is true and accurate to the best of my knowledge.

  
\_\_\_\_\_

Date 3-26-04

Howard B. Cottam, Ph.D., Director of Scientific Affairs  
Quinta Naturaceuticals, Inc.

**E. Attachments (see items 1-4 attached)**

**F. References**

1. Gill, L. S., *Ethnomedical Uses of Plants in Nigeria*, Uniben Press, Benin City, Nigeria, 1992, p. 135.
2. Okogun, J. I., Adesomoju, A. A., et al. Roseanolone: a new diterpene from *Hypoestes rosea*. *Z. Naturforsch.*, 37c: 558-561, 1982.
3. Adesomoju, A. A., Okogun, J. I., et al. Hypoestoxide: a new diterpene from *Hypoestes rosea* (Acanthaceae). *Heterocycles*, 20: 2125-2128, 1983.
4. Adesomoju, A. A., Okogun, J. I., et al. *Phytochemistry*, 22: 2535-2536, 1983.
5. Professor Joseph Okogun, personal communication).
6. Ojo-Amaize, E. A., et al. Hypoestoxide, a novel anti-inflammatory natural diterpene, inhibits the activity of I $\kappa$ B kinase. *Cell. Immunol.*, 209: 149-157, 2001.
7. Ojo-Amaize, E. A., et al. Hypoestoxide, a natural nonmutagenic diterpenoid with antiangiogenic and antitumor activity: possible mechanisms of action. *Cancer Res.* 62: 4007-4014, 2002.

## ATTACHMENTS

- Item 1      USDA Noxious Weed List.
- Item 2      Published papers on Hypoestoxide derived from Hypoestes rosea (see References 6,7).
- Item 3      Human clinical laboratory report.
- Item 4      Canine clinical laboratory report.