



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

MAR 31 1997

0104 '97 APR 10 P2:55

John Spector, C.E.O.  
Caprice-Greystoke, Ltd.  
1259 Activity Drive  
Vista, CA 92083

Re: Docket Nos. 81N-0022/CP18 and  
76N-052N/CP16

Dear Mr. Spector:

This is in response to your July 25, 1996, letter referring to a December 8, 1995, citizen petition submitted by you on behalf of Caprice-Greystoke, Ltd., requesting that the Food and Drug Administration (FDA) (1) open the administrative record to include certain studies on "Spray-U-Thin," an over-the-counter (OTC) oral liquid immediate-release appetite suppressant containing phenylpropanolamine hydrochloride (PPA); (2) ban all extended-release weight control drug products containing PPA unless certain conditions are met; (3) suspend or reprimand certain Center for Drug Evaluation and Research (CDER) officials; (4) discontinue any protocol written by the Nonprescription Drug Manufacturers Association (NDMA); (5) reject the 1986 Weintraub study; (6) conduct an investigation of Ceiba-Geigy and FDA officials named in the petition, and advise the Attorney General of the ongoing investigation and the possibility of corrupt acts; (7) accept all past petitions submitted by the petitioner; (8) provide an explanation from the Director of CDER concerning the promotions of Drs. Michael Weintraub and William Gilbertson; (9) halt publication of the OTC weight control tentative final monograph (proposed rule) and final monograph (final rule) until investigations are completed and made part of the public record; and (10) extend Category III for PPA to cough-cold medications.

Based on a fair evaluation of all facts and information before it, FDA issued a response to your citizen petition on May 17, 1996. We regret that you are unsatisfied with the agency's findings, as articulated in its response to your petition. However, under FDA regulations (21 C.F.R. 5.20(b) and 10.45(d)), the response is the Commissioner's final decision and constitutes final agency action on issues raised in the petition. Because your July 25, 1996 letter raised no new issues, FDA's May 17, 1996 response to your petition stands as the final reply to your letter.

Sincerely yours,

Jane Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

76N-052N

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MAY 17 1996

John Spector, C.E.O.  
Caprice-Greystoke, Ltd.  
1259 Activity Drive  
Vista, CA 92083

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76N-052N/CP16

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Dear Mr. Spector:

This is in response to your December 8, 1995, citizen petition on behalf of Caprice-Greystoke, Ltd., requesting that the Food and Drug Administration (FDA) (1) open the administrative record to include certain studies on "Spray-U-Thin," an over-the-counter (OTC) oral liquid immediate-release appetite suppressant containing phenylpropanolamine hydrochloride (PPA); (2) ban all extended-release weight control drug products containing PPA unless certain conditions are met; (3) suspend or reprimand certain Center for Drug Evaluation and Research (CDER) officials; (4) discontinue any protocol written by the Nonprescription Drug Manufacturers Association (NDMA); (5) reject the 1986 Weintraub study; (6) conduct an investigation of Ceiba-Geigy and FDA officials named in the petition, and advise the Attorney General of the ongoing investigation and the possibility of corrupt acts; (7) accept all past petitions submitted by the petitioner; (8) provide an explanation from the Director of CDER concerning the promotions of Drs. Michael Weintraub and William Gilbertson; (9) halt publication of the OTC weight control tentative final monograph (proposed rule) and final monograph (final rule) until investigations are completed and made part of the public record; and (10) extend Category III for PPA to cough-cold medications.

Before we address your specific requests, we want to make clear the regulatory status of your product. The labeling concerning the dosage regimen of "Spray-U-Thin" does not meet the levels specified in the February 26, 1982 (47 FR 8466) advance notice of proposed rulemaking (ANPR). As long as your product is in conformance with the labeling provisions of the ANPR, your product can be marketed legally as an immediate-release PPA product until the effective date of the final rule for OTC weight control drug products. This position has been conveyed to you in letters dated November 15, 1995 (enclosure #24(b) of your petition), and March 15, 1996, from CDER's Division of Drug Labeling and Nonprescription Drug Compliance.

76N-052N

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After careful consideration of the issues raised in your petition and the attachments filed thereto, your petition is granted in part and denied in part for the following reasons:

**1. Inclusion of 3 Immediate Release Studies  
in the Administrative Record**

You request that the FDA open the administrative record for the rulemaking proceedings for OTC weight control and nasal decongestant drug products to allow inclusion of the following three studies on immediate-release PPA for weight control: the Bradley Study (1982); the Griffiths, Funderbunk Study (1987); and the Russian Academy of Medical Sciences (RAMS) Study (1995).

In making decisions regarding the tentative final monograph on OTC weight control drug products, the agency has considered all data and information filed in that rulemaking through February 29, 1996 by the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, Maryland 20857. Accordingly, the agency has included the studies and petitions submitted by you in the administrative record to the rulemaking. Upon publication of the tentative final monograph, you will have the opportunity to submit further comments and/or studies supporting the effectiveness of your immediate-release PPA product.

**2. Ban of Extended-Release  
Weight Control Products Containing PPA**

You contend that all extended-release weight control drug products containing PPA should be banned unless certain conditions are met. You argue that such a ban is supported by your concerns regarding the safety of extended-release products and by language contained in the final rule published in the *Federal Register* of August 8, 1991 (56 FR 37792 at 37795).

Based on the available data, the agency believes that extended-release PPA used in OTC drug products does not represent a major public health risk. Therefore, the agency does not believe that it is necessary to remove these products from the market while additional data are being obtained. Furthermore, the language in the August 8, 1991, final rule that may suggest the need for a ban on extended-release PPA is not the agency's position. Rather, the language is from a comment on the rule submitted by

an interested party. The August 8, 1991, final rule concerned 111 weight control active ingredients that were classified as Category II and III by the Panel. Because the agency received no significant comments or new data to upgrade the 111 ingredients to Category I, the rule removed the ingredients from the market, but did not address the two ingredients that the Panel placed in Category I (PPA and benzocaine). Additionally, as noted in the rule, the FDA expressly disagrees with the comment.

With regard to your contention that all extended-release PPA products should be banned because they are unsafe, although the FDA does not believe that all extended-release PPA products are unsafe, the agency's preliminary view is that it will place PPA in Category III (insufficient data) for safety in the proposed rules for OTC weight control drug products and OTC nasal decongestant drug products while additional safety data are being obtained. These two proposed rules will be published simultaneously in the *Federal Register*.

The publication of these proposed rules will not change the marketing status of PPA weight control and nasal decongestant products at this time. Immediate-release and extended-release PPA weight control drug products that comply with the ANPR may continue to be marketed until further notice.

However, all PPA weight control drug products may eventually need an approved new drug application (NDA). Unless new adequate and well-controlled studies demonstrating the effectiveness of immediate-release PPA for weight control are submitted to the rulemaking, immediate-release PPA products will be regarded as new drugs upon the effective date of the final rule. Extended-release PPA weight control drug products contain a quantity of the active ingredient that is not "generally recognized" as safe in a single dose, and these products also are regarded as new drugs (21 CFR 200.31). Extended-release PPA products will need an NDA to demonstrate that they are properly manufactured and controlled to release the total dose at a safe rate. The agency will define the specific requirements necessary for the marketing of extended-release PPA weight control drug products in future proposed rules for OTC weight control drug products and OTC nasal decongestant drug products.

### **3. *Suspension of CDER Officials***

The agency's Office of Internal Affairs (OIA) has completed its investigation of your allegations regarding conflict of interest and has determined that there was no violation of applicable

conflict of interest laws or regulations. Additionally, OIA has determined that your allegations of misconduct and cronyism are so lacking in specificity and factual content that they cannot be responded to in any meaningful fashion.

The FDA takes accusations of this kind very seriously, but you supplied no evidence to support your claim of misconduct by agency officials. Accordingly, your requests for suspension, reprimand, and removal of CDER employees are denied.

#### **4. Discontinuance of Protocols Written by NDMA**

You allege that protocols written by the NDMA constitute a conflict of interest on the part of the NDMA because it is a representative of drug companies.

Manufacturers of drug products routinely submit protocols for new studies to support the safety and effectiveness of their products. The agency carefully reviews these protocols to determine if any revisions are necessary before the studies are conducted. Such dealings with drug companies or their representative trade associations are not considered a conflict of interest, but rather a routine part of the drug development process.

The agency reviewed, modified, and approved the draft protocol for the PPA safety study before the study began in September 1994. The draft and final protocols and the agency's detailed comments on the protocols are on file in the Dockets Management Branch. Because the agency believes that its review of the study protocol helps to ensure the quality of the study, it disagrees with your claim and denies your request.

#### **5. Rejection of the 1986 Weintraub Study**

You also request that the 1986 Weintraub study be rejected based upon your allegations of conflict of interest against Dr. Weintraub. FDA's OIA has completed an investigation concerning your allegations of conflict of interest against Dr. Weintraub and has determined that they are without merit. Accordingly, the agency finds that it would be inappropriate to reject the study for the reasons you suggest and, therefore, denies your request.

**6. Investigation of Ceiba-Geigy and FDA Officials**

You ask for an investigation of Ceiba-Geigy and the FDA officials named in the petition, and for the Attorney General to be advised of the ongoing investigation and the possibility of corrupt acts.

As stated above, the agency has completed its investigation regarding your allegations of conflict of interest, misconduct, and cronyism and finds no evidence to support your claims against agency or industry officials. Accordingly, your request is denied.

**7. Acceptance of Past Petitions**

You further request that the FDA accept all past petitions submitted by your company, arguing that previous petitions were "put on hold or not completely answered." In support of your claim, you state that the FDA responded to your previous petitions asserting that its consideration of them would delay publication of the tentative final monograph.

However, because your petitions have been filed in the Dockets Management Branch and included in the administrative record, the agency has granted your request. This letter formally responds to the petitions previously submitted by your company and constitutes final administrative action taken by the Commissioner subject to judicial review under the provisions of 21 CFR 10.45. Your petitions and the agency's responses are available at the Dockets Management Branch.

**8. Explanation of the Promotions of CDER Officials**

You ask for an explanation from the Director of CDER concerning the promotions of Dr. Michael Weintraub and Dr. William Gilbertson. What you describe as promotions were in fact the result of a CDER reorganization not constituting a promotion. Additionally, as explained in section 3. above, the agency has no evidence to support your claim of misconduct by its officials.

**9. Suspension of the Tentative Final Monograph and Final Monograph**

You request that the FDA suspend publication of the OTC weight control tentative final monograph (proposed rule) and final

monograph (final rule) until investigations are complete and made part of the public record.

Your request is denied. Based on the available data, there is no reason to delay publication of these documents. The agency's tentative view at this time is that PPA will be placed in Category III (insufficient data) for safety in both the proposed rule for OTC weight control drug products and the proposed rule for OTC nasal decongestant drug products while additional safety data are being obtained.

**10. Extension of Category III for PPA  
Cough-Cold Products**

You request that both OTC weight control and nasal decongestant drug products containing PPA be placed in Category III. As discussed above, the agency agrees that both OTC weight control and nasal decongestant drug products containing PPA should be placed in Category III. The FDA expects to propose this change in the upcoming proposed rules. Accordingly, your request is granted.

**Conclusion**

The agency does not believe that there is evidence upon which to base a finding that PPA used in OTC drug products represents a major public health risk. Publication of the proposed rules (placing PPA in Category III for both weight control and cough-cold products) will permit the continued marketing of PPA in weight control and cough-cold products until further studies are completed.

Because present "Spray-U-Thin" labeling is not in compliance with the provisions of the weight control ANPR, the agency considers it a new drug. If the labeling is revised in accordance with all conditions specified in the ANPR, your product can be legally marketed, without preclearance by the agency, until the effective date of the final rule. However, for the reasons stated above, all PPA weight control drug products may eventually need an NDA.

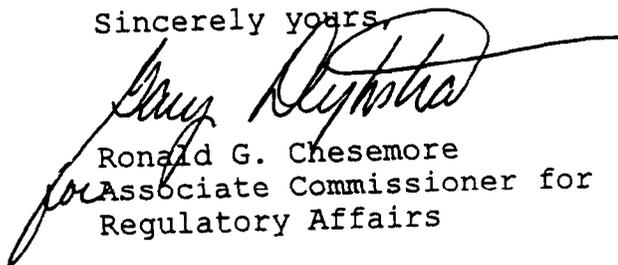
Your petition and this response have been placed in the administrative record for the rulemakings for OTC weight control and OTC nasal decongestant drug products, and the scientific issues will be addressed in the proposed rules. At that time, you will have further opportunity to comment if you so desire.

John Spector, C.E.O.

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I hope that we have addressed the issues raised in your petition to your satisfaction. This response constitutes final agency action concerning requests made in the petition.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Ronald G. Chesemore", with a long horizontal flourish extending to the right.

Ronald G. Chesemore  
Associate Commissioner for  
Regulatory Affairs