



Food and Drug Administration
Rockville MD 20857

DEC 22 1994

John Spector
Caprice-Greystoke, Ltd.
1259 Activity Drive
Vista, California 92083

Re: Docket No. 81N-0022
Comments No. CP17, AMD1, C112,
LET96, and PRC1
Re: Docket No. 76N-052N
Comments No. CP15, AMD1, AMD2,
LET116, and C227

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Dear Mr. Spector:

This letter concerns your citizen petition, coded CP17 under Docket No. 81N-0022, and filed in FDA's Dockets Management Branch on August 26, 1994, amendment AMD1 (dated September 20, 1994), and comments No. C112 (dated October 7, 1994), LET96 (dated October 10, 1994), and PRC1 (dated October 19, 1994). The petition requested that FDA: (1) Reopen the administrative record for the rulemaking for over-the-counter (OTC) weight control drug products to consider your company's submission, and (2) reassess the agency's position and its actions regarding your company's product, an oral liquid metered spray containing phenylpropanolamine hydrochloride (PPA).

As stated in my letter to you dated October 12, 1994, because FDA is nearing completion of the tentative final monograph (proposed rule) for OTC weight control drug products, the agency cannot formally reopen the administrative record to consider your citizen petition at this time. However, even though the record is closed, we are able to respond to your petition. The tentative final monograph (proposed rule) includes all data and information filed through June 17, 1994. Reopening the record to include subsequent data would cause a delay in publication to occur. Our feedback procedures (see enclosed copies of the FEDERAL REGISTER notices of September 29, 1981 (46 FR 47740) and April 1, 1983 (48 FR 14050)) provide that any "feedback" communication, such as your petition, that is submitted before a proposed rule is published, but which is not used by the agency in preparing the proposed rule, will be placed in the administrative record and addressed when it is opened during the comment period following publication of the proposed rule. In addition, communications between the agency and industry may continue outside the formal comment period and will be a part of the public record. Accordingly, the agency has reviewed the information in your citizen petition and your subsequent submissions, and we are responding to your concerns at this time.

76N-052N

LET117

We have the following comments:

In your October 19, 1994 letter, you stated that your citizen petition was received by the Dockets Management Branch (DMB) on August 2, 1994. However, DMB records for both the OTC weight control and nasal decongestant dockets indicate that the petition was received and filed on August 26, 1994.

In your petition and subsequent submissions, you state that the agency has completely reversed its position from initially proposing to "ban" controlled-release and "approve" immediate-release PPA for weight control, to now approving controlled-release and not approving immediate-release PPA. Based on these and other statements in your submissions, it appears to us that you may have misinterpreted the scope and intent of the OTC drug review. Let me more fully explain the process by providing some background information.

The OTC drug review is a three-phase public rulemaking process, with each phase requiring publication in the FEDERAL REGISTER (21 CFR 330.10). The OTC drug review determines whether ingredients in nonprescription drugs are "generally recognized" as safe and effective and not misbranded (Category I), or not safe or effective (Category II). During the course of the review, there is an interim status (Category III), if insufficient data are available to permit classification in Category I or II. The process culminates in regulations (final monographs) establishing standards for both the active ingredients and the labeling in each OTC therapeutic drug class. I must point out that the review encompasses all OTC drug products in the marketplace as of May 11, 1972 (date of final regulations establishing the review). At that time, as even today, some marketed products were controlled-release. Because the review is an ingredient and not a dosage-form review, data on marketed controlled-release products containing PPA could be submitted. The understanding was that, if PPA were found to be Category I, only an immediate-release dosage form could be included in the monograph. The monographs for internal drug products apply only to immediate-release oral dosage forms. Controlled-release dosage forms are considered "new drugs," and are not included in OTC drug monographs. These dosage forms require approved new drug applications (NDAs) as a condition of marketing, pursuant to FDA regulations in 21 CFR 200.31.

During the first phase of the OTC drug review, the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (the Panel) reviewed ingredients in OTC weight control drug products. The Panel was composed of experts from outside the federal government. The Panel's independent recommendations were published in the FEDERAL REGISTER of February 26, 1982 (47 FR 8466), as an advance notice of proposed rulemaking (ANPR) for OTC

weight control drug products. The agency published the Panel's report to stimulate discussion and comment on the entire scope of the Panel's deliberations.

Based on studies available at that time, the Panel recommended that PPA be placed in Category I for weight control at single doses of 25 to 50 milligrams (mg) and a total daily dose not to exceed 150 mg of PPA. The Panel also recommended that the single and daily doses for any timed-release preparation not exceed those for immediate-release preparations (47 FR 8475). To clarify the Panel's statement above concerning timed-release preparations, the agency noted that, "under 21 CFR 200.31, timed-release formulations that contain a quantity of an active ingredient that is not generally recognized as safe as a single dose are regarded as new drugs" (47 FR 8468). In addition, the agency pointed out that "an approved NDA will be necessary at the time of a final monograph to demonstrate that phenylpropanolamine in a timed-release dosage form is properly manufactured and controlled to release the total dose at a safe rate." These statements were intended to alert manufacturers that, in order to continue to market controlled-release PPA weight control drug products, they would need to submit an NDA before publication of a final monograph (final rule).

In the FEDERAL REGISTER of August 8, 1991 (56 FR 37792), the agency published a final rule regarding certain active weight control ingredients that were classified in Category II and Category III by the Panel. These 111 ingredients included all of the active ingredients reviewed by the Panel, other than PPA and benzocaine. Because the agency received no significant comments or new data to upgrade the status of these 111 ingredients to Category I, the final rule removed these ingredients as active ingredients in OTC weight control drug products from the marketplace. Because data had been submitted for PPA and benzocaine, these ingredients were deferred and are the subject of the upcoming tentative final monograph.

The statements in the FEDERAL REGISTER notices of February 26, 1982 (47 FR 8466) and August 8, 1991 (56 FR 37792) should not be misconstrued to mean that FDA proposed to "ban" controlled-release PPA weight control drug products. This was never the intent. The FDA discussion indicates that controlled-release PPA weight control drug products are regarded (for the reasons explained above) as new drugs and are not "generally recognized" as safe and effective under an OTC drug monograph. All controlled-release PPA weight control drug products will require an approved NDA for continued marketing after publication of the final rule covering PPA and benzocaine for weight control use.

In the second phase of the OTC drug review, FDA evaluates the Panel's findings, public comments that are received, and new data

that may have become available. The agency publishes its tentative conclusions in the FEDERAL REGISTER as a proposed rule or tentative final monograph. The tentative final monograph for PPA and benzocaine for weight control use is the document that is now nearing completion.

In my letter to the Nonprescription Drug Manufacturers Association (NDMA) dated May 20, 1994 (Docket No. 81N-0022, Comment No. LET92), I notified NDMA that, after reviewing the Panel's report, submitted data, and other available information, our Office had determined that the data showed that PPA is effective, at a daily dosage of 75 mg in a controlled-release dosage form. As discussed in my letter, this determination was based on four recent, well-controlled clinical studies using controlled-release PPA combined with a reduced-calorie diet. As Dr. Rhodes pointed out, those studies were completed between 1986 and 1991. The agency's review of all of these data was completed within the last year. This review has also led to a determination that the existing data are inadequate to support immediate-release doses of 25 to 37.5 mg PPA because adequate clinical studies were not submitted to support the effectiveness of these doses.

My letter also stated that, unless additional studies or supportive data provide evidence that an immediate-release PPA dosage form is safe and effective for weight control use, PPA will not be included in a final monograph. (Controlled-release PPA products could still be marketed as new drugs with an approved NDA.) Another purpose of my letter was to urge manufacturers to begin preparing and submitting their NDAs for controlled-release PPA weight control products. Those data (e.g., release profiles, drug plasma concentration time profiles, manufacturing controls information) could then be evaluated before the publication of a final rule. Until the publication of a final rule (third phase of the OTC drug review) in the FEDERAL REGISTER on OTC weight control drug products containing PPA and benzocaine, immediate-release PPA dosage forms that meet the conditions of the Panel's report (discussed above) may still be marketed without additional safety and efficacy data, and controlled-release dosage forms (also meeting the conditions of the Panel's report) may still be marketed without an approved NDA. However, as you are aware, there are unresolved safety concerns regarding a possible increased risk of stroke associated with the use of PPA-containing drug products. Manufacturers of some OTC PPA weight control drug products are sponsoring a case-control study to resolve this issue. Therefore, FDA's final decision on the continued availability of PPA as an OTC drug product in either dosage form will depend on the results of the case-control study.

You also submitted a simulated blood serum level test to verify the lack of toxicity of PPA in your product. These data consist

of two graphs comparing the concentration of PPA (nanograms per milliliter) resulting from 1 spray every 1 and 2 hours, 2 sprays every 2 and 4 hours, and 4 sprays every 4 hours. No other information is included. Your submission also contains an engineering test report on the spray pump designed to demonstrate that this system will deliver a consistent dosage. Although these data seem to indicate that the pump will deliver a consistent dosage, they do not demonstrate the safety and effectiveness of your product's dosage regimen for weight control use. In addition, you submitted the United States Pharmacopeia (U.S.P.) dissolution specifications for extended-release PPA, and comparative safety tests on Spray-U-Thin versus Dexatrim to determine the forces required to open these products. The testing laboratory concludes that your product is safer than Dexatrim because "it appears that it would be easier for a child to dislodge a Dexatrim tablet than to apply a Spray-U-Thin solution." After evaluating the information contained in your submission, our review scientists conclude that these data are helpful, but are not adequate to establish the safety and effectiveness of your product for OTC weight control use.

As stated in § 330.10(a)(4)(i) and (ii) of the OTC drug review procedures (21 CFR 330.10(a)(4)(i) and (ii)), proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety will ordinarily be based upon published studies which may be corroborated by unpublished studies and other data. Proof of effectiveness shall consist of controlled clinical investigations, which may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

As I stated earlier, our determination that 75 mg controlled-release PPA is effective for weight loss was based on an evaluation of four well-controlled clinical studies using controlled-release PPA combined with a reduced-calorie diet. As will be discussed in the upcoming tentative final monograph, this remains an agency proposal that is subject to comment upon publication in the FEDERAL REGISTER. We would need similar relevant data for your product. In turn, a summary of your data and the agency's evaluation of these data would be included in a future FEDERAL REGISTER publication for public comment prior to a final agency action.

Your petition states that an oral liquid metered spray containing 12.5 mg of PPA taken every two hours is just as effective as 25 mg every four hours, yet much safer. However, your petition includes no supportive clinical data. Because the Panel did not review any data on the safety or effectiveness of such a dosage regimen for PPA, and the agency is not aware of such a product ever having been marketed for OTC weight control use, you would need to submit well-controlled clinical studies to support the safety and effectiveness of such a dosage regimen. In addition, your petition includes a report by C. T. Rhodes, Ph.D., stating that your product, containing 5 mg per metered spray, and administered as three sprays at 0, 4, 8, 12, and 16 hours, complies fully with the U.S.P. dissolution specifications for extended-release PPA. Dr. Rhodes further states that your product "can reasonably be regarded as pharmacokinetically and therapeutically equivalent" to timed-release PPA (such as Acutrim) already on the market. However, the report includes no supportive data, other than several theoretical calculations. It is our view that alternative dosage schedules discussed by Dr. Rhodes would require appropriate supporting data. Clinical data are needed to support the safety and effectiveness of the alternative dosage schedules that Dr. Rhodes discussed.

Your petition states that the appointment of Dr. Michael Weintraub as Director of the Office of OTC Drug Evaluation in 1993 is a "glaring conflict of interest," because Dr. Weintraub conducted one of the studies (published in 1986) supporting the effectiveness of controlled-release PPA. The agency's conclusions regarding the safety and effectiveness of PPA as an OTC weight control ingredient are based on a review of the available data by three components of FDA's Center for Drug Evaluation and Research: (1) the Office of Drug Evaluation I (ODE I), (2) the Office of Epidemiology and Biostatistics, and (3) the Office of OTC Drug Evaluation. In addition, Dr. Weintraub's study report was submitted by a drug manufacturer in 1989 and reviewed by the Division of Neuropharmacological Drug Products (part of ODE I) before Dr. Weintraub was affiliated with FDA. Further, to avoid any possible appearance of a conflict of interest, Dr. Weintraub has disqualified himself from the efficacy decision-making process regarding PPA for weight control. Other FDA medical and scientific staff has been assigned to evaluate this drug.

Finally, your petition refers to a warning letter dated February 11, 1994, issued to you by the Los Angeles District Compliance Branch following an inspection by FDA investigators. The issues in the agency's warning letter are outside the scope of the OTC drug review and need to be addressed separately by the Division of Drug Labeling Compliance. We have forwarded a copy of this letter to the OTC Compliance Branch.

In conclusion, I hope that the additional information I have provided clarifies the agency's complex regulatory process concerning OTC drugs. I have tried to respond to your specific requests as follows:

1. Although the administrative record has not been formally reopened, we have reviewed the data contained in your petition.
2. While your statements that smaller dosages administered more frequently are safer and as effective have merit, they are not supported by the data submitted. A clinical study is necessary.
3. GMP and related issues concerning specific products are not part of the OTC drug review and will be addressed by other parts of the agency.
4. The agency has conducted an impartial review of the data concerning the safety and effectiveness of PPA for weight control use.

As noted in my letter of October 12, 1994 to you, you will have the opportunity to submit comments on the agency's proposed regulation and to submit additional data following publication of the tentative final monograph, in a future issue of the FEDERAL REGISTER.

I hope this information is helpful.

Sincerely yours,



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Enclosures 