

THOMPSON MEDICAL COMPANY, INC.

919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 688-4420

August 9, 1984

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Dockets Management Branch
Food and Drug Administration
Department of Health and
Human Services
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

CITIZEN PETITION

Thompson Medical Company, Inc. submits this petition under 21 CFR 10.30 to request the Commissioner of Food and Drugs to open the administrative records in the Over-the-Counter Drug Reviews of Weight Control Drug Products (Docket No. 81N-022) and Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Docket No. 76N-0052N) to accept the enclosed letter to Dr. Harry M. Meyer, Jr., Director of the Center for Drugs and Biologics.

A. Action Requested

The undersigned respectfully requests that the administrative record be opened to permit the enclosed materials to be considered in the referenced OTC Drug Reviews.

B. Statement of Grounds

The grounds on which the petitioner relies are that phenylpropanolamine hydrochloride (PPA) is one of the ingredients of weight control products and nasal decongestants which are the subjects, respectively, of the above-referenced proposed OTC Drug Products Monographs. The Panel Monographs concluded that PPA and its salts are safe and effective for OTC weight control and oral nasal decongestant use in the specified dosages. The Tentative Final Monograph has not yet been published in either Review. In the preamble to the Advance Notice of Proposed Rulemaking in the Weight Control Drug Products Review (47 Fed. Reg. 8466, et seq., February 26, 1982), the Commissioner requested further studies regarding the safety of PPA for use in weight control products.

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The enclosed letter and attachments contain new information and studies demonstrating the safety of PPA in weight control products. Since the same ingredient is involved in both types of products, the enclosed materials are highly significant to the agency's OTC Drug Reviews of both weight control and cough/cold drug products. Therefore, these materials should be considered in both Reviews at the earliest possible time.

C. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Edward L. Steinberg, M.Sc., O.D.
Vice Chairman of the Board



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Dr. Harry M. Meyer, Jr.
Director
Center for Drugs and Biologics
Food and Drug Administration
Room 13B-45
5600 Fishers Lane
Rockville, Maryland 20857

Attention: Dr. Robert Temple
Director, Office of
Drug Research & Review

Re: Documentation of Safety of
Phenylpropanolamine Hydrochloride
(PPA): Follow-up on July 19, 1984
Meeting

Dear Dr. Meyer:

We were most appreciative of the opportunity to meet with you and your colleagues on July 19, 1984, to discuss the new information on PPA safety which has come to our attention. This letter is in response to your request at the end of our meeting for documentation of the statements we made to you during the meeting and for a summary of all the research data which has earlier been submitted to FDA during the three OTC reviews of this drug, for weight control, cough/cold, and topical oral cavity uses.

Our principal point was that FDA's safety concerns are based on an Australian product which we now know did not contain the American PPA and most likely contained a much more potent isomer of 85 mg in immediate-release form. It is this fact which explains why the elevated blood pressure readings reported by Dr. Horowitz in 1979-1980 in Australia have never been replicated in this country in more than 60 clinical trials

of the U.S. drug. Because of this, the adverse reaction reports based on the Australian product are entirely irrelevant in evaluating the safety of PPA products sold in the U.S..

I. Meeting of July 19, 1984

As we stated at the meeting, we understand that FDA has recommended to HHS Secretary Heckler that PPA be down-graded from Category I to Category III in the Tentative Final Monographs on OTC Weight Control and Cough/Cold Drugs. We believe that, based on precedents such as the Alka-Seltzer case, a down-grading may have a devastating effect on consumer confidence in all PPA products. These products have been marketed for some 50 years in this country and have been extraordinarily free from adverse reaction reports, especially considering the approximately 5 billion doses taken annually by millions of consumers.

Most importantly, we understand that the proposed down-grading is based upon FDA's concern about possible adverse blood pressure effects, a concern which was expressed in the agency's preamble to the ANPR publication of the Panel Report on OTC Weight Control Drugs (47 FR 8466, February 26, 1982). The preamble referred to a handful of published reports on the blood-pressure effects of an Australian product, "Trimolets", conducted in Australia by Dr. J.D. Horowitz, et al.

II. The Trimolets Product Studied by Horowitz Did Not Contain the PPA Marketed in the U.S.

At the time of the Horowitz studies, in 1977-1979, the Trimolets appetite suppressant was an 85-mg product then being marketed in Australia by Rorer (Aust.) Pty. Limited, Chatswood, New South Wales, a subsidiary of an American company, William H. Rorer, Inc., Fort Washington, Pennsylvania. The product line was sold by Rorer in 1979 to The Boots Company (Australia), which proceeded to re-formulate and relabel it. Boots has since marketed Trimolets in 25-mg and 50-mg immediate release forms.

1. Rorer's Trimolets Labeling. The "before and after" Trimolets package labels themselves document the change. Attached as Exhibit 1 is the original Rorer Trimolets label, which designated the 85-mg ingredient as "D-Phenylpropanolamine." The "D" is a reference to a significantly different stereochemical molecular structure from the phenethylamine which is marketed as PPA in the United States. The PPA used in this country is a racemic mixture identified as "dl-norephedrine U.S.P.." Exhibit 2 is a

chart showing the molecular structures of eight different phenethylamines. Only the racemic mixture of the two at the lower left, dl-norephedrine, is properly designated as "phenylpropanolamine", and that mixture is the only one marketed in the United States. The German "pharmazeutische Stoffliste" (Exhibit 2a) uses phenylpropanolamine as an incorrect synonym for d-norpseudoephedrine.

2. Boots' Trimolets Labeling After Reformulation. Exhibit 3 is the "after" portion of the Australian product: it is the box label of the current, reformulated Trimolets marketed since 1980 by Boots. It shows "Phenylpropanolamine Hydrochloride HCl B.P.", which is a racemic mixture. Exhibit 4 is the relevant British Pharmacopeia reference. In addition we have now learned that in parts of Australia Boots is also marketing a Trimolets product containing d -pseudoephedrine, 85 mg.

3. Rorer Statement. Since the Australian Rorer subsidiary is no longer in existence, we contacted the Rorer parent company in Pennsylvania. Enclosed as Exhibit 5 is their letter confirming that the Trimolets manufactured for their Australian subsidiary was "d-Phenylpropanolamine." Again, the reference is not to "dl", establishing that a different isomer from PPA sold in the U.S. was contained in Rorer's Trimolets product.

4. Other Rorer Australian Labeling. During the late 1970's, at the same time that it was marketing Trimolets with the label shown in Exhibit 1, Rorer's Australian subsidiary was also marketing, under the corporate name "Biochem", another weight control product, trade-named "TeradecS." The TeradecS label, enclosed as Exhibit 6, identifies the racemic mixture that is used in the United States: "dl-2-amino-1-phenyl-1-propanol hydrochloride." Clearly, where Rorer used the racemic mixture, it labeled it properly and quite differently from the way it labeled its 85-mg Trimolets product, used by Dr. Horowitz in his study.

5. Results with Rorer's Trimolets Never Replicated with U.S. Products. As noted above, FDA's preamble cited two clinical studies and a handful of anecdotal reports of adverse blood pressure effects from Rorer's Trimolets. These effects have never been replicated in the United States with the U.S. products containing PPA, in more than 60 controlled clinical studies of dose levels as high as 200 mg per day, involving more than 4,000 patients and for periods as long as six months. Most of these studies have already been submitted to FDA in Comments and Reply Comments on the February 26, 1982 ANPR by The Proprietary Association (Exhibits 7 and 8, respectively) and in subsequent filings by Thompson Medical

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Company, Inc. (Exhibits 9 through 13). More recent studies demonstrate the same conclusion, that PPA U.S.P. in currently approved doses is indeed safe and that the Horowitz results have never been replicated in this country (Exhibits 14 through 19). These most recent studies are herewith offered for the record on the Weight Control and Cough/Cold Monographs.

This mass of positive data demonstrates that PPA, as used in American weight control, cough/cold and topical oral cavity products, produces no adverse blood pressure effects. The U.S. studies also demonstrate that PPA does not aggravate pre-existing hypertension at the currently-marketed dose levels (Exhibit 7, pp. 12-13), does not stimulate the central nervous system (Exhibits 18 and 19 and Exhibit 8, p. 7), does not have any drug abuse potential (Exhibit 8, pp. 8-11), and does not interact with aspirin (Exhibit 7, pp. 13-16).

It should be noted particularly that among the new studies cited above as showing no adverse reactions is an epidemiological study commissioned by the FDA itself. It is also one of the largest studies ever conducted on any drug, involving 216,189 prescriptions filled for PPA-containing products from 1977 to 1981 at the Group Health Cooperative of Puget Sound. Exhibit 15 is the first published report of that study's results, concluding "that the risk of cerebral hemorrhage requiring hospital admission and attributable to taking PPA-containing cough and cold remedies, if present at all, is very small." We have been advised by Dr. Hershel Jick of the Boston Collaborative Drug Surveillance Program, who is analyzing the data from this study for the FDA, that, when published, the data will also show similar favorable results with regard to blood pressure effects and other adverse reactions.

The agency's February 26, 1982, preamble raised the question, based upon the Horowitz study and the other reports of the 85-mg Rorer Trimolets, whether the adverse blood-pressure effects reported by those investigators may have been dose-response related. Again, no such relationship has ever been demonstrated in U.S. tests of PPA-containing products. Exhibit 7, at pages 9 and 10, catalogues six studies of PPA in immediate-release doses ranging from 36 mg (the current maximum immediate release dose in the U.S. is 37.5 mg), to 50 mg, 75 mg, 100 mg, and 150 mg. Clinically significant increases in blood pressure were detected only following administration of 150 mg immediate release PPA, and only in five of the 35 volunteers who received 150 mg. Similarly, Exhibit 7 at pp. 15-16 documents a study in which patients received 200 mg per day in individual 50-mg immediate-release doses for a period of 30 days, and no evidence of drug-related

toxicity was observed or determined. Finally, Exhibit 15 documents a recent study of 75-mg immediate-release doses of PPA, again showing no elevation in blood pressure. These results are entirely incompatible with Dr. Horowitz's results.

To conclude on our basic point here, it is quite clear that the 85-mg Rorer Trimolets product, which reportedly produced substantial blood pressure effects, did not contain the racemic mixture of PPA which is used in this country. This conclusion is inevitable, based on:

- 1) Rorer's Trimolets label, which identified a non-racemic chemical form;
- 2) Rorer's statement that the product manufactured for Rorer (Australia) was the non-racemic form;
- 3) Rorer's labeling of another anorectic product which it sold contemporaneously in Australia, labeling which clearly identified the racemic mixture;
- 4) Boots' subsequent reformulation of the product and relabeling to show the racemic mixture; and
- 5) the fact that the Horowitz study results have never been replicated in more than 60 controlled studies in this country of the U.S. racemic phenylpropanolamine.

III. There are Significant Pharmacological Differences Between the Racemic and Non-Racemic Phenylethylamines.

As Exhibit 2 shows, there are several different isomers of phenethylamines. Only an analysis of the product which was studied by the Australian investigators five and six years ago could produce an exact identification of the active ingredient or ingredients in that product. What makes it especially difficult to obtain an exact identification at this point is that the usual certificate of analysis of the product studied is not available now and was not reviewed by the investigators at the time of the study. This would have provided information on the exact dosage, product formulation, date of manufacture, source of imported raw material, and batch number. In the absence of this information, the only certainty at this point is that the drug studied was not the racemic mixture used in U.S. PPA-containing products.

Moreover, the other isomers of ephedrine are known to have a number of adverse effects. For example, 1-norephedrine

and d-norpseudoephedrine produce central nervous system and/or blood pressure effects at conventional dosage levels. In a major study in 1967 of the entire eight-membered series of ephedrine and norephedrine stereoisomers as compared with amphetamines, Fairchild and Alles showed that d-norpseudoephedrine was the most potent stimulant, following d-amphetamine and l-amphetamine. These in turn were followed by l-ephedrine and l-norpseudoephedrine. (Exhibit 19)

We conclude that, whatever other stereoisomer of ephedrine was used in the Rorer 85-mg Trimolets product, the side effects observed by the investigators with that product were understandable. In this connection it is particularly important to note that the 85-mg Trimolets product was in immediate-release form. The old Trimolets label statement, "One capsule gives up to 12 hours effective control of appetite," implied that the product was in timed-release form (Exhibit 1). However, as was documented in Exhibit 7 at p. 5, when samples of the Trimolets 85-mg product were subjected to laboratory analysis, the product was found to be immediately soluble in water and not in a sustained-release form. This has recently been confirmed by Dr. William J. Louis, the principal researcher in the Horowitz studies, during his presentation at a seminar on PPA held at The New York Academy of Medicine on June 10-11, 1984.

As a result, whatever non-racemic isomer was in the product tested by Dr. Horowitz, it was in a delivery form which presented the subjects with an 85-mg bolus dose. Considering the toxicity associated with other isomers of ephedrine, it is hardly surprising that Dr. Horowitz's adverse results have never been replicated in the massive number of tests of the U.S. racemic mixture which, as documented in II above, showed no blood pressure, CNS, or other side-effects up to a 150-mg immediate-release dose.

IV. Conclusion.

The agency's safety concerns with PPA are based primarily on Australian reports of side-effects from the 85-mg product formerly marketed by Rorer's Australian subsidiary. It is now clear, from Rorer's labeling of this and its other anorexiant product, from Rorer's own statement, from Boots' subsequent labeling of its re-formulated Trimolets, and from the vastly different test results that Rorer's Trimolets produced compared with the U.S. racemic mixture, that the Australian adverse reaction reports involved a non-racemic stereoisomer.

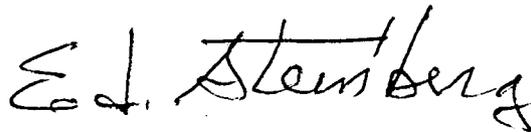
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It is difficult at this point, some five to six years after the Australian studies, for us (or even Dr. Horowitz and his colleagues) to determine with any certainty what the active ingredient was in the product they studied. However we are convinced by the labeling, the Rorer confirmatory statement, and the reported adverse reactions, that the product tested was not the racemic U.S. phenylpropanolamine.

It is respectfully submitted that the Australian adverse reaction reports, based on a different drug from the U.S. active ingredient, are entirely irrelevant in evaluating the safety of PPA products used in the U.S.. Since the clinical data on the drug used in the U.S. uniformly confirms safety and since the drug has been used safely in this country for more than 50 years, the American drug should not be down-graded to Category III on the basis of tests conducted abroad with a different active ingredient. To do so would unjustifiably denigrate the U.S. drug and severely weaken the confidence of millions of Americans who use PPA-containing cough/cold and weight control products. In the case of weight control products, it might cause millions of overweight Americans to avoid these products and thereby contribute to one of the greatest health hazards, obesity.

Pursuant to your request at our July 19 meeting, we are sending copies of this letter to the Dockets Management Branch for inclusion in the official records of the Weight Control and Cough/Cold Monographs.

Sincerely,



Edward L. Steinberg, M.Sc., O.D.
Vice Chairman of the Board