TAB 10

Founded 1881

NDMA

NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

Better Health Through Responsible Self-Medication

August 11, 1993

William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration - HFN-810
7520 Standish Place
Rockville, MD 20855

Dear Dr. Gilbertson:

Enclosed with this letter is correspondence to FDA from Dr. Ralph I. Horwitz (Harold H. Hines Professor of Medicine and Epidemiology, School of Medicine, Yale University) which states NDMA's comments concerning FDA's feedback to NDMA regarding a draft protocol of an epidemiologic study on phenylpropanolamine (PPA).

In brief, the detailed comments to FDA from NDMA cover the following points, among others.

1. Definition of PPA exposures will be based on treating PPA products as a single exposure category in order to achieve the primary research objective, which is to examine the association of any PPA use and the risk of hemorrhagic stroke in subjects ages 18-54.

   However, in order to assess an association for each type of PPA product (a secondary aim), the total sample size is augmented with a corresponding change in the power to detect elevated odds ratios separately for cough/cold remedies and appetite suppressants.

2. In order to address a concern that the medication exposure may not be biologically relevant to the stroke event yet recognize that case reports of stroke patients reporting prior PPA use up to a week earlier, the primary exposure window has been redefined as the three-day interval before the index event, with secondary analyses examining one-day and seven-day windows.

3. Because elimination of surrogate interviews could lead to a bias if PPA use were distributed differently among fatal or severe strokes rather than non-fatal or less severe strokes, dead patients or patients with impaired speech should not be excluded from the

. . . continued

1150 Connecticut Avenue, N.W., Washington, D.C. 20036 • Tel: (202) 429-9260 • Fax: (202) 223-6835

study; consequently, data will be collected from surrogates of dead or impaired cases and from surrogates of their matched controls. (note: data from controls, all of whom are alive, will also be assembled by direct interviews).

a. A value of .75 for the sensitivity of interviews with case surrogates is chosen and is reflected in all sample size estimations.

4. For the primary aim, examining the association between any PPA use and the risk of hemorrhagic stroke in subjects ages 18-54, 330 cases and 660 controls will be required. This calculation assumes a 3-day exposure window, 30% surrogate interviews among cases, an alpha level of .05, a beta of .8, and an attenuated Odds Ratio of 1.82.

However, in order to also address several secondary aims, the case sample will be augmented by 50%. Testing the power of the study to detect clinically important odds ratios with 500 cases and 1000 controls assuming a one-day exposure window yields: for any use of PPA, 69% for an OR of 1.82; 82% for an OR of 2.0; and 99% for an OR $\geq$ 3.

A sample size of 500 cases and 1000 controls therefore provides adequate power for the primary aim of any PPA use, at the primary exposure window of 3 days and at secondary windows of 1 day and 7 days.

5. Additional sites could be added to the Yale-Connecticut Hospital Network in order to enroll 500 cases over 42 months.

We look forward to our meeting with FDA on August 25, 1993, at which time we will be prepared to discuss these issues in greater detail.

Sincerely yours,

R. William Soller, Ph.D.

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Enclosure: Letter from Dr. Horwitz to Dr. Gilbertson on Behalf of the NDMA PPA Working Party dated August 9, 1993.

WS/leb\FDAPPACO.811

Yale University

Ralph I. Horwitz, M.D.
Harold H. Hines, Jr. Professor of
Medicine and Epidemiology
School of Medicine
IE-61 SHM
P.O. Box 3333
New Haven, Connecticut 06510-8025

Campus address:
IE-61 SHM
333 Cedar Street
Telephone: 203 785-4152
Fax: 203 785-3461

August 9, 1993

William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research
Department of Health & Human Services
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Gilbertson:

As Principal Investigator for the Yale Hemorrhagic Stroke Project, I am responding to the comments you sent to Dr. William Soller on a draft of the study protocol (dated February 24, 1993). My colleagues and I were grateful to you for your careful review of our protocol. You identified three critical issues for further discussion, including sample size, exposure window, and the use of surrogate interviews. We would add to these issues the definition of Phenylpropanolamine exposure. Although my colleagues and I were delighted by your careful review of the protocol, we fear that certain errors and assumptions led to misleading conclusions in your report. Nevertheless, several of the points you raised were most helpful and have been incorporated in the revised draft protocol. For purposes of clarity, I shall discuss each of the four issues consecutively.

1. <u>DEFINITION OF PHENYLPROPANOLAMINE EXPOSURE</u>

In our draft protocol (February 24, 1993), we defined the primary aim of the study, "to determine whether Phenylpropanolamine users ages 18-54, compared to non-users, have an increased risk of hemorrhagic stroke." Secondary aims included an estimation of the association between Phenylpropanolamine and hemorrhagic stroke separately by the non-prescription indications for Phenylpropanolamine use: appetite suppressant or cough/cold remedy. This distinction between primary and secondary aims is crucial since the study's sample size is necessarily and properly guided by the primary aim. Thus, in estimating sample size, we treated both types of Phenylpropanolamine products as a single exposure category since this tactic fulfilled the primary objective of the research.

Our decision to focus the primary objective (and analysis) on any Phenylpropanolamine exposure was based on the available literature on this subject, the underlying biology, and our own clinical experience. The scientific literature that describes the use of Phenylpropanolamine in patients with stroke considers Phenylpropanolamine, not its other constituents or indications for use, as the potential exposure hazard. Furthermore, despite an exhaustive search, we could find no scientific basis for treating Phenylpropanolamine in appetite suppressants differently from Phenylpropanolamine in cough/cold remedies. Consequently, we believe strongly that the primary aim of the study should remain as stated in the February 24, 1993 draft, and the sample size should be guided by this aim. Nevertheless, because we are interested in estimating the association for each type of Phenylpropanolamine product (secondary aim), in our revised draft protocol and in this letter we augment the total sample size and discuss our power to detect elevated odds ratios separately for cough/cold remedies and appetite suppressants.

2. EXPOSURE WINDOW

In our draft protocol of February 24, 1993, we defined the primary exposure window as the seven day interval before the index event (stroke in cases; corresponding date in controls). In your comments, you consider one day, two day and seven day exposure windows. Although you do not state a preference for the primary exposure window, you do write on page 1, "If only the first day of each course is assumed to be relevant...".

We continue to assert our belief that a one-day exposure window before the index event should not be categorized as the primary exposure interval. We make this assertion because a biological basis for the "first dose" phenomenon has not been established, and because exposure several days before a stroke could not be excluded as possibly related to the risk of cerebral hemorrhage. Furthermore, we know from case reports that some patients with stroke had used Phenylpropanolamine up to a week earlier, leading some investigators to speculate on the possibility of an inflammatory mechanism. Counting patients with Phenylpropanolamine use 2-3 days before the stroke as non-exposed to Phenylpropanolamine would inevitably (and properly) lead to adverse criticisms about the design and analysis of the study. At the same time, we acknowledge that using the seven day window as our primary exposure interval raises concern that the medication exposure may not be biologically relevant to the stroke event. For these reasons, we now propose that the primary exposure window be defined as the three-day interval before the index event, with secondary analyses examining one-day and seven-day windows.

3. EFFECT OF SURROGATE INTERVIEWS

The issue of surrogate interviews among cases occurs because of the natural history of stroke among young patients. Some patients with hemorrhagic stroke die out of hospital without recognition as stroke events. Most patients, however, are admitted to hospital, where a diagnosis of hemorrhagic stroke is confirmed. Our Connecticut Hospital data indicate that about 25% of these men and women ages 18-54 die while hospitalized. Although data are unavailable for accurate estimation, we anticipate that 5% of the survivors will have levels of illness severity or language impairments that make them unable to participate fully with interviews.

We believe that it is scientifically unacceptable to exclude dead patients or patients with impaired speech from the study. Our reluctance stems from our concern for the selection bias that would occur if Phenylpropanolamine use were distributed differently among fatal or severe strokes rather than non-fatal or less severe strokes. Consequently, we believe that we must include fatal strokes and patients with language impairments among the case group.

Once these patients are included, however, we are forced to consider the problems occurring from the use of surrogates to obtain data on exposures and other risk factors. We propose the following plan. For purposes of validity, we will collect data from surrogates of dead or impaired cases and from surrogates of their matched controls. For controls (all of whom are alive), we shall also assemble data obtained from direct interviews. Although the main analysis will use data from interviews with direct controls, the data from surrogate controls will enable us to assess the presence of bias.

For purposes of estimating sample sizes, we assumed a sensitivity of .75 for data on exposure obtained from surrogates of the cases. We chose the value of .75 for the sensitivity of interviews with case surrogates for several reasons. First, we do not believe that the value of 0.5 noted in your earlier letter, which refers to a study of illicit drugs, is applicable to this research which focuses on the use of Phenylpropanolamine. Secondly, the calculations described in your letter assumed that surrogate interviews had a sensitivity of 0.5 and perfect specificity. This latter assumption, which is highly unlikely, severely distorts the effect of surrogate interviews on the calculation of the odds ratio. In fact, even a small reduction in specificity to 0.9 results in many more false positive errors than false negatives. Thus, the selection of a 0.75 sensitivity represents a compromise value. All sample size estimations reflect this adjusted exposure rate occurring as a result of the use of surrogate interviews for cases only.

4. SAMPLE SIZE ESTIMATION

In calculating the sample size, we needed to fulfill several requirements. First, we needed to delineate a definition of Phenylpropanolamine use. Next, we needed to specify and select an exposure window. Finally, we had to obtain the best available estimate for Phenylpropanolamine use in the control population. In making our decisions for estimating sample size, we recognize that we disagree with some of the assumptions specified in your comments and with the ensuing calculations presented in your letter. In this section we describe in detail the assumptions and methods we believe are correct for estimating the sample size needed in the Yale Hemorrhagic Stroke Study.

a. Assumptions

First, we set our sample size to achieve the primary objective of the study which defined exposure as any Phenylpropanolamine use. Second, we selected the primary exposure window as the three-days before the index event. Third, we used data from the MRI survey of the use of diet pills and cough/cold products to estimate the proportion of the eligible population that used Phenylpropanolamine containing products during a three-day exposure interval.

Each of the first two assumptions has been discussed and justified previously. Nevertheless, we recognize the importance of the secondary aims specified in this protocol. For this reason, we describe the power of our study to detect an elevated odds ratio for diet aids and cough/cold products separately and for seven day and 1 day exposure windows. All of our calculations also adjust the sample size for the possibility that surrogate interviews would be needed for up to 30% of the cases. This adjustment requires a change in the detectable odds ratio from the specified 2.0 to the attenuated value of 1.82.

b. Phenylpropanolamine Use in Connecticut Population

We used the MRI market research data to estimate the proportion of subjects in the population who were using Phenylpropanolamine products in the past three days. The MRI conducts a national survey, and data are available on the New England Region generally, and the states of Connecticut and Rhode Island together. Furthermore, data are assembled separately for diet pills and cough/cold products. We restricted the survey data to the recent years 1990, 1991, and 1992, to take account of changes in product availability. During this interval, all of the diet pills available contained Phenylpropanolamine; based on the top 27 brands of cold and sinus products and top 12 brands of cough syrups, we estimate that 30% of sales of cough/cold products contain Phenylpropanolamine.

Because the Connecticut/Rhode Island survey conducted by MRI was based on approximately 500 subjects in each year (1990, 535; 1991, 466; 1992, 448), we repeated the calculations using the larger unweighted sample for New England (approximately 1500 subjects each year). Since our calculations were similar when we used the New England region and Connecticut/Rhode Island alone, we believe the estimations we present are accurate and representative of Phenylpropanolamine users.

The accompanying "work-table" illustrates our method for estimating the proportion of use of Phenylpropanolamine products (diet, cold and cough separately) in any three day interval. We begin with the weighted population data for 1990-92, with the associated proportion of diet pill users at 1.1% in 1990, 3.1% in 1991 and 0.5% in 1992, for an average use of 1.6% (column "a"). We next used the MRI data to estimate the mean number of days Phenylpropanolamine was used in last 30 days (column "b", 13.1 days). These data provide an estimate of the proportion of diet pill users who used the product on any given day (b/30). The quantity, (1-b/30), is the proportion of Phenylpropanolamine users not using diet pills on any given day. To calculate the proportion of users who used a diet pill in any three day period, we next estimated the proportion who had not used the pills for any three days, as $(1-b/30)^3$ (This calculation assumes that non-use on each day is independent of use on the other days). After multiplying this proportion by the probability of being a user, we arrived at an estimated average proportion of use of diet pills in the last three days of 1.4% (range from 0.2 to 3.0%).

We went through a similar set of calculations separately for cold products and cough products. The prevalence of use of these products in a 30 day period was 28% for cold products and 17% for cough products. The mean number of days used in the past 30 days was less for cough/cold than diet pills (8.7 for cold; 5.2 for cough), leading to an overall proportion of users in the past 3 days of 17.6% and 7.6% respectively.

Assuming that 30% of cough/cold products reported in the survey contain Phenylpropanolamine, the proportion of Phenylpropanolamine users is 5.3% for cold and 2.3% for cough products. The overall Phenylpropanolamine use (diet pills and cough/cold) in the last three days is therefore 8.7%.

c. Sample Size Estimate for Primary Aim: Any Phenylpropanolamine Use

For the primary aim, examining the association between any Phenylpropanolamine use and the risk of hemorrhagic stroke in subjects ages 18-54, we require 330 cases and 660 controls. This calculation assumes a 3-day exposure window, 30% surrogate interviews among the case group, an α level = .05, a β = .80, and an attenuated Odds Ratio of 1.82.

Ordinarily, the sample size for the study would be guided by the primary aim of the research. In this study, the investigators, regulators, and manufacturers have a keen interest in several secondary aims. For this reason, we chose to augment the "case" sample size by 50%, and to test the power of the study to detect clinically important odds ratios with 500 cases and 1000 controls. Using similar assumptions, but examining a one-day exposure window, 500 cases and 1000 controls has the following study power: for any use of Phenylpropanolamine, 69% for an odds ratio of 1.82, 83% for an odds ratio of 2.0, and at least 99% for odds ratios of 3 or greater. Thus, a sample size of 500 cases and 1000 controls provides adequate power for the primary aim of any Phenylpropanolamine use, at the primary exposure windows of 3 days, and at secondary windows of 1 day and 7 days.

d. Sample Size Estimate for Secondary Aim: Phenylpropanolamine Use by Product Type

The sample size of 500 cases and 1000 controls also provides sufficient power for analyses of appetite suppressants and cough/cold products separately. For appetite suppressant use, an exposure window of 3 days corresponds to an exposure prevalence in the controls of 1.4%. A study with 500 cases and 1000 controls has a power of 36% to detect an odds ratio of 2.0. When restricting the exposure window to one day, the study has 24% power for an odds ratio of 2.0, 66% for an odds ratio of 3.0, and 84% for an odds ratio of 3.5. For an exposure window of 7 days, the study has ample power to detect an odds ratio of 3.0 for diet pills alone (>90%). Since cough/cold products are used more often than diet pills, the study has ample power (>80%) to detect odds ratios of at least 3 for exposure windows as brief as 1 day.

5. SOURCES OF CASES

As noted previously, the Yale-Connecticut Hospital Network can be expected to generate approximately 200 men and women per year, ages 18-54 with hemorrhagic stroke. Under a conservative assumption that we can recruit 60% of these available subjects, we believe that we can enroll approximately 400 cases over 42 months. We propose recruiting the additional 100 cases by adding additional study sites. The additional sites we anticipate are geographically proximate to Connecticut, and

include Providence, Rhode Island and Worcester, Massachusetts. Discussions are currently underway with investigators at each location.

*** *** ***

As happens so often, case-control studies present substantial challenges to investigators who strive for validity in results while attempting to maintain the generalizability and feasibility of the research. Your previous comments proved helpful to us as we developed further the design of the Yale Hemorrhagic Stroke Study. My colleagues and I look forward to our continuing discussions.

Sincerely yours,

Ralph I. Horwitz

1471L/RIH:cmv
cc: Lawrence Brass, M.D.
Burton Singer, Ph.D.
William Soller, Ph.D.
Catherine Viscoli, Ph.D.

ESTIMATION OF USE OF PHENYLPROPANOLAMINE IN CONNECTICUT/RHODE ISLAND, FOR PAST 3 DAYS (BASED ON MRI MARKET SURVEY)

Type of PPA	Pop. (000)	Prop. of use (a)	Mean uses last 30 dys (b)	Pr used any day (b/30)	Pr users not using on any day (1-b/30)	Prop. not used for any 3 dys $(1-b/30)^3$	Pr used in any 3 days (c)	Overall prop. of use in dys last 3 (a x c)
Appetite Suppressant								
1990	2881	1.1%	13.8	46.0%	54.0%	15.7%	84.3%	1.0%
1991	3285	3.1%	20.6	68.7%	31.3%	3.1%	96.9%	3.0%
1992	4064	0.5%	5.0	16.7%	83.3%	57.9%	42.1%	0.2%
Avg		1.6%	13.1					1.4%
Cold								
1990	2881	21.3%	9.3	31.0%	69.0%	32.9%	67.1%	14.3%
1991	3285	30.3%	9.5	31.7%	68.3%	31.9%	68.1%	20.6%
1992	4064	31.4%	7.4	24.7%	75.3%	42.8%	57.2%	18.0%
Avg		27.7%	8.7					17.6%*
Cough								
1990	2881	14.7%	3.7	12.3%	87.7%	67.4%	32.6%	4.8%
1991	3285	19.9%	6.1	20.3%	79.7%	50.6%	49.4%	9.8%
1992	4064	17.2%	5.7	19.0%	81.0%	53.1%	46.9%	8.1%
Avg		17.3%	5.2					7.6%*

* Assuming 30% of cough/cold products contain PPA, actual proportion of use for PPA products is 5.3% (cold) and 2.3% (cough).

Probability of any use of PPA product = 8.7% (in last 3 days)

- Appetite suppressant = 1.4%
- Cold = 5.3%
- Cough = 2.3%