TAB 12

Founded 1881

NDMA

NONPRESCRIPTION DRUG MANUFACTURERS ASSOCIATION

Better Health Through Responsible Self-Medication

October 14, 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, HFD 810
7520 Standish Place, Room 201
Rockville, Maryland 20855

RE: Docket Number 81N-0022

Dear Dr. Gilbertson:

Please find enclosed ten (10) copies of our response to the feedback meeting of August 25, 1993 on the subject of the protocol for the Yale Hemorrhagic Stroke Study.

Our response is based on the vigorous and productive discussion concerning the protocol and summarizes the current status of the protocol, identifying points of agreement and also presenting new analyses to resolve points of uncertainty. We have organized our response according to the following sections:

1. Overall Objective and Specific Aims;
2. Definition of Phenylpropanolamine Exposure;
3. Exposure Window;
4. Use of Surrogate Interviews;
5. Sample Size Estimation;
6. Interim Analysis.

81N-0022 C110

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

We thank you for your valuable input and look forward to your early response to this letter, so that we may finalize the protocol incorporating FDA's input and then initiate this study as soon as possible.

Sincerely yours,

R. William Soller, Ph.D.

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

Enclosure: As stated

cc: Docket Management Branch (3 copies)

WS/jq
ppa\rspltr

Nonprescription Drug Manufacturers Association

Response to the NDMA/FDA Feedback Discussion of August 25, 1993 on the Protocol for the Yale Hemorrhagic Stroke Study

The following remarks represent the collective response from the Yale investigators to the feedback discussion of August 25, 1993, pertaining to the protocol for the Yale Hemorrhagic Study. These comments have the endorsement of the NDMA Phenylpropanolamine Working Party.

1. Overall Objective and Specific Aim

From the August 25, 1993 feedback meeting, we believe there is agreement (i.e., between FDA and NDMA) that the overall objective of the Yale Hemorrhagic Study is to determine whether use of phenylpropanolamine is associated with an increased risk of hemorrhagic stroke. As a result of the NDMA/FDA discussion, we now understand the specific objectives of FDA and their relationship to the objectives originally formulated by the Yale investigators. Accordingly, we propose that we outline a series of specific aims of equal importance, and size the study to ensure sufficient statistical power to detect clinically important risks associated with each aim. The aims are:

a. To determine whether phenylpropanolamine users, ages 18-49, compared to non-users, have an increased risk of hemorrhagic stroke

b. To estimate the association between phenylpropanolamine and hemorrhagic stroke separately by the nonprescription indications for phenylpropanolamine use: appetite suppressant or cough/cold remedy; and by the use of appetite suppressants in women ages 18-49

c. To estimate the association between "first dose" use of phenylpropanolamine (either cough/cold or appetite suppressant) and hemorrhagic stroke in women ages 18-49.

2. Definition of Phenylpropanolamine Exposure and Timing of Exposure Window

We agreed during the FDA/NDMA discussion of August 25, 1993, that the definition of phenylpropanolamine exposure for this study will depend upon the analysis being conducted. To answer the first and third specific aims, we shall examine all use of phenylpropanolamine. The second aim requires that phenylpropanolamine exposure be classified separately by its nonprescription indication for use.

...continued

This simple principle of tailoring the exposure definition to the specific aim also applies to the timing of phenylpropanolamine use. The analyses for the first and second specific aims will be based on a three-day exposure window, while the analysis for the third specific aim depends only on first dose/first day exposure. Under this first dose/first day specification, a patient would be counted as "exposed" only if the index event (stroke in cases or corresponding date in the controls) occurred within 24 hours of the first dose of phenylpropanolamine used by the patient. Patients are counted as "non-exposed" whenever the first dose occurred more than 24 hours before the index event (regardless of continued use of phenylpropanolamine).

As noted in earlier drafts, we intend to conduct a series of additional analyses to explore the impact of dose and timing of use on the association between phenylpropanolamine and hemorrhagic stroke. In these planned analyses, we shall look at differences in recency (time of last use), latency (time of first use), and pattern of use.

3. Use of Surrogate Interview

When FDA initially proposed limiting the cases and controls to subjects who were alive at the time of the interview, NDMA dissented because of our concern that selection bias might distort the measured association between phenylpropanolamine use and hemorrhagic stroke. At that time, we suspected that the effects of misclassification bias were less worrisome than the effects of selection bias. Modeling the effects of misclassification bias convinced us otherwise -- that the cases and controls should be limited to living subjects. The following illustrates the basis for our position.

Assume that the true odds ratio between phenylpropanolamine and hemorrhagic stroke is 3.0; that the true exposure prevalence in controls is 0.502% and in cases is 1.492% (these exposure prevalences will be used for the first-dose analysis in planning sample size). Assume that 30% of the cases are dead or impaired, requiring surrogate interviews for these cases and their matched controls. Assume also that surrogate interviews have a sensitivity of 50% and a specificity of 90%. In the final analysis, the study will be comprised of two strata, one with direct interviews of living subjects, the second with interviews of proxy subjects. The direct stratum will yield a measured odds ratio of 3.0, which faithfully reflects the true odds ratio. However, the proxy stratum has a measured odds ratio of 1.04 that misrepresents the true value for the odds ratio. When the two strata are combined, the measured odds ratio is 1.25. These two subgroups defined by distinctive sources of data are highly heterogeneous, yield different estimates of the odds ratio, and are non-combinable on the basis of methodologic and statistical principles. For that reason, we now believe that only living subjects should be included in the main analyses for this study, accepting the theoretical possibility for some selection bias.

...continued

The quantitative evidence for the unexpectedly large impact of misclassification bias is presented in the accompanying Table 1. This table displays the effects of the bias on a range of true odds ratios varying from values of 3.0 to 6.0. The measured odds ratio for the direct interview stratum are identical to the true values, since we assume that direct interviews have perfect sensitivity and specificity. The measured odds ratios for the proxy or surrogate interview stratum assume a sensitivity of 50% and specificity of 90%. The final odds ratio for the combined strata is based on using proxy interviews for 30% of cases and controls. In all instances, misclassification bias leads to severe attenuation of the combined measured odds ratio (from 1.25 to 1.62).

4. Sample Size Estimation

The most extreme set of assumptions for calculating sample size arises from the need to estimate the risk of hemorrhagic stroke associated with the first dose/first day use in women 18-49 years of age. For that reason, we shall begin by calculating the sample size needed to detect this first dose effect and then examine the study's power to detect clinically important increases in the odds ratio for the other study aims.

a. First Dose/First Day Effect

In calculating the sample size, we employed a series of assumptions that were agreed upon at the August 25, 1993 meeting. First, we restricted the subjects to women ages 18-49. Second, we used any type of phenylpropanolamine (cough/cold or appetite suppressant). Third, we set the desired odds ratio at a value of 5.0. Fourth, we set $\alpha = .05$ and $\beta = .20$. Finally we used a one-tailed test of significance.

As presented previously, using data from the MRI survey of Connecticut and Rhode Island, we can estimate the proportion of subjects who used phenylpropanolamine in the last 30 days. Since we are interested only in the first use each month, we divided the proportion of users by 30 to estimate the proportion of first dose users. For appetite suppressants, the proportion of users in the last 30 days was 1.6%, yielding an estimate of first-dose users of 0.05%. The estimates for cold and cough preparations were 0.92% and 0.58%, respectively. We used the conservative estimate of 30% to calculate the proportion of cough/cold users with phenylpropanolamine-containing products (based on sales figure), to yield values of 0.28% and 0.17%, respectively. Thus the overall first dose exposure in controls is 0.502%.

Table 2 displays the sample sizes required for a one-tailed test ($\alpha = .05$), at odds ratios from 4 to 6, and with beta error varied from .1 (90% power) to .3 (70% power). For the one-tailed test with 80% power to detect an odds ratio of 5.0, for the association of first dose phenylpropanolamine to stroke, 324 women ages 18-49

...continued

are required (assuming two controls per case). At 80% power, the required sample size ranges from 240 to detect an odds ratio of 6.0 to 483 to detect an odds ratio of 4.0. Table 3 displays the sample size estimates using a two-tailed test ($\alpha = .05$). For the two-tailed test with 80% power to detect an odds ratio of 5.0, 404 women ages 18-40 are required.

Accepting the one-tailed test and assuming 350 cases and 700 controls comprised of women ages 18-49, the study has the following power: 95% to detect an odds ratio of 6.0; 90% for an odds ratio of 5.5; 83% for an odds ratio of 5.0; 74% for an odds ratio of 4.5; and 63% for an odds ratio of 4.0. For all of these calculations, the estimated sample size refers to subjects alive and able to communicate at the time of the interview (no surrogate interviews)

b. Any Phenylpropanolamine Use

This analysis includes men and women ages 18-49, using phenylpropanolamine in appetite suppressants or cough/cold products. In this analysis, exposure is defined as three days before the index event. To have equal numbers of men and women with hemorrhagic stroke, we would add 350 men and 700 male controls, for an overall study sample of 700 alive cases and 1,400 alive controls. Assuming an exposure rate in the controls of 4.52%, the study has exceedingly high power to detect clinically meaningful odds ratios as follows: 98% for an odds ratio of 2.0; and 99% for an odds ratio of 2.5.

c. Phenylpropanolamine Use by Indication

For the association between phenylpropanolamine used in cough/cold preparations and the risk of hemorrhagic stroke, all subjects are included in the analysis. We estimate an exposure control rate (for 3-day window) of 3.90% (for ages 18-49), leading to the following level of statistical power: 96% for an odds ratio of 2.0; 99% for an odds ratio of 2.5.

For the association between phenylpropanolamine in appetite suppressants and the risk of hemorrhagic stroke, only women ages 18-49 are included in the analysis. Assuming an exposure control rate (for 3-day window) of 0.64% results in the following levels of statistical power: 36% for an odds ratio of 2.0; 79% for an odds ratio of 3.0; 98% for an odds ratio of 4.0.

...continued

d. Monitoring Exposure Rates in Controls

We recognize that the control exposure rates used to calculate the required sample sizes are based on survey estimates. To ensure that the study is suitably sized for our objectives, we propose to monitor the control exposure rate after 100 and 200 controls are enrolled. No attempt will be made at this point to conduct any analyses or effect size or statistical significance. The purpose of the monitoring is only to inform us whether sample size planning was based on sound estimates of phenyl- propanolamine use among control subjects.

5. Interim Analysis

We propose one interim analysis, conducted after half of the sample has been enrolled (350 men and women cases, 700 men and women controls), which would be anticipated in April, 1996, assuming a January, 1993 start-up date and uniform monthly enrollment of cases and controls over the course of the study. The interim analysis will focus on the first (any phenylpropanolamine use, 3-day window, men and women) and third (appetite suppressant phenylpropanolamine use, first day/dose window, women only) objectives. To preserve the specified sample sizes, we intend to use the O'Brien-Fleming method for testing the significance of effect estimates. The O'Brien-Fleming significance level is 0.005 for the first look and 0.048 for the second and final look. As you know, the O'Brien-Fleming boundary is not a decision rule but rather an indication that further evaluation of early stopping is needed. The rule ensures that, if early termination is not done, the final look will be at the .05 significance level.

WS:jq
rspnse

TABLE 1: EFFECT OF 30% PROXY RESPONDENTS ON MEASURED ODDS RATIO*

True Odds Ratio	Odds Ratios For: Direct Interviews Stratum	Surrogate Interview Stratum	Combined Strata Odds Ratios
3.0	3.0	1.04	1.25
3.5	3.5	1.05	1.31
4.0	4.0	1.06	1.37
4.5	4.5	1.08	1.43
5.0	5.0	1.09	1.50
5.5	5.5	1.10	1.56
6.0	6.0	1.11	1.62

* Sensitivity of proxy respondents = 50%
Sensitivity of provy responendts = 90%
Control exposure = .502%

TABLE 2: NUMBER OF REQUIRED CASES*
BY ODDS RATIO AND POWER OF TEST
(ALPHA = .05, 1-TAILED)

	Odds Ratio				
Power	4.0	4.5	5.0	5.5	6.0
70%	360	289	240	205	178
75%	412	331	275	235	204
80%	483	389	324	276	240
85%	572	461	384	328	286
90%	696	562	469	401	349

*Assumes 2 controls per case

TABLE 3: NUMBER OF REQUIRED CASES
BY ODDS RATIO AND POWER OF TEST
(ALPHA = .05, 2-TAILED)

	Odds Ratio				
Power	4.0	4.5	5.0	5.5	6.0
70%	465	373	310	264	229
75%	524	421	350	298	259
80%	604	485	404	344	300
85%	703	566	471	402	350
90%	840	677	564	482	420