TAB 9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

RS

Food and Drug Administration
Rockville MD 20857

JUN 17 1993

R. William Soller, Ph.D.
Senior Vice President and Director
of Science and Technology
Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 81N-0022
Comment No. PR7

Dear Dr. Soller:

This letter relates to your submission dated March 4, 1993, and coded PR7 under Docket No. 81N-0022 in FDA's Dockets Management Branch. Your submission contains a final draft protocol for a population-based, case-control study of the relationship between the use of over-the-counter (OTC) weight control drug products containing phenylpropanolamine hydrochloride (PPA) and the risk of hemorrhagic stroke.

The Office of OTC Drug Evaluation has reviewed the draft protocol. Although the document appears to be well prepared, several of the procedures proposed in the protocol are based on unverified assumptions. Three critical issues that need to be resolved before a study is conducted are sample size, exposure window, and the use of surrogate interviews. We have the following specific comments:

Marketing data from the Nonprescription Drug Manufacturers Association indicate that use of PPA weight control drug products is predominantly in women under age 44 (Ref 1). The exposure prevalence in men is only about 25 percent that in women. Thus, it appears that limiting the study to women only (perhaps under age 45) would be most efficient.

In the protocol, the sample size estimation was calculated under the assumption of a 10 percent exposure rate in controls. However, the 10 percent exposure rate appears to be based on the annual (or, perhaps, 6-month) exposure rate, an exposure window much larger than the 1 to 7-day window defined in the protocol. Based on the assumption that an individual is only at increased risk of experiencing a cardio-vascular accident (CVA) during the first seven days of a course of treatment, and assuming two courses of treatment per year, the probability that a control is exposed on any given day of the year is 14 days / 365 days x 10% = 0.38%. If only the first day of each course is assumed to be relevant, then the probability that a control is exposed on any given day of the year is 2 days / 365 days x 10% = 0.055%. If the first two days are assumed to be relevant, then the probability is 0.11%.

Because of the lack of data concerning PPA-containing cough-cold products (i.e., number and length of courses of medication per year), estimation of the prevalence of use of these products is more difficult. In the protocol, it is estimated that 30 percent of PPA use is in weight control products and 70 percent of PPA use is in cough-cold products. Using these figures, we can estimate the exposure in the population. There are an estimated 9 million users of PPA weight control drug products annually (Ref. 1). If we assume (for purposes of estimation) that there were 8 million users age 54 or younger (the proposed age range in the protocol), then there were approximately 19 million users of PPA cough-cold products under age 55. In the 1990 census, the U.S. population aged 18-54 was about 132,000,000, yielding an annual prevalence of use of 14.4 percent. For initiation of use of a PPA cough-cold product within 1, 2, or 7 days of an event, the exposure prevalence in men and women would be 0.0004, 0.0008, and 0.0028 respectively.

The power of a case-control study is determined by: 1) the number of cases, and 2) the size of the odds ratio to be detected. If sample sizes required with a given type I error (0.05) and a given power (0.80) for a 2-sided test are calculated, and a 24-hour exposure window is used, the study would need 3,630 cases and 7,260 controls (two controls per case) in order to detect a 2-7 fold odds ratio. If the study is designed to rule out large odds ratios, then 1,281 cases are required to rule out a 10-fold or larger odds ratio, and 199 cases to rule out a 50-fold or larger odds ratio.

When a 7-day exposure window is used, the study would require 531 cases and 1,062 controls to detect a 2-7 fold odds ratio, 191 cases to rule out a 10-fold or larger odds ratio, and 34 cases to rule out a 50-fold or larger odds ratio. The 7-day window, of course, could reduce the size of a PPA effect. It should also be noted that, when confounding variables are considered, the power of the study may be significantly reduced.

The crucial parameter required to determine both the sample size and power of a case-control study is the exposure rate of the controls. The three major reasons that this protocol miscalculates the exposure rate are: 1) the difference between the exposure to PPA weight control and PPA cough-cold products, 2) use of the wrong exposure window, and 3) misclassification of the exposure status. Although the protocol proposes to consider exposure to both PPA weight control and PPA cough-cold drug products in the study, the exposure rate used for the controls is the exposure rate for PPA weight control drug products only. Another factor that makes the sample size calculation even more difficult is the seasonal use of cough-cold drug products.

The protocol states that PPA has a short half-life lasting about 4 hours, and should be eliminated from the body within 24 hours. The protocol also states that concerns regarding a possible first-dose effect have been expressed. Considering these facts, the reasons for choosing a 7-day exposure window for the main analyses in the study are unclear. This issue needs further discussion.

We believe that the proposed study should not include surrogate respondents as part of the sample. The inclusion of surrogate repondents will have a negative effect on the ability to detect an increased relative risk or odds ratio if it exists. Misclassification of exposure status by surrogate respondents will have the effect of reducing the observed odds ratio in a given study. The lower the background exposure rate among controls, the greater the effect of driving the observed odds ratio towards 1.0, the no effect level. The degree of the effect of misclassification due to surrogate respondents can be calculated if the sensitivity and specificity of exposure classification among the cases and controls is known.

In a recent case-control study of subarachnoid hemorrhage (SAH) and smoking and alcohol use, conducted in Washington State (Stroke 1992; 23:1242-9), surrogate respondents were used for both cases and controls, allowing the level of agreement between subjects and surrogate respondents to be determined. One of the exposure variables studied was the use of "stimulant" drugs, including cocaine, amphetamine, and PPA. Exposure status was classified as "never" versus "ever" use of a stimulant drug. The sensitivity of surrogate responses for stimulant drug use was about 0.5 (i.e., of SAH cases who self-reported ever using stimulant drugs, surrogates answered correctly only half the time). The specificity of surrogate responses was about 0.9 (i.e., of SAH cases who self-reported never having used stimulant drugs, surrogates answered correctly about 90 percent of the time). Similar sensitivity and specificity were observed among control subjects and their surrogates.

In addition, data from the study described above showed that the number of surrogate respondents increased as the age of the case increased. Among cases under 45 years of age, about 30 percent required a surrogate. Among subjects up to 54 years of age, the use of surrogate respondents increased to 40-45 percent. The effect of misclassification due to surrogate respondents will be to drive the observed odds ratio strongly towards a value of 1.0. The net effect of these observations on the proposed PPA study is that the information provided by surrogate respondents will not contribute toward determining the true level of risk. Therefore, we believe that, in order to assure the power of the proposed study, the study should be based only on subjects who are able to respond for themselves. In order to compensate for the loss of

subjects unable to participate (30% for weight control drugs and 40% for cough-cold drugs), the actual sample size must be 43% (for weight control) and 67% (for cough-cold) larger than the sample size calculated when one assumes no losses at all.

The estimated sample sizes needed to detect a relative risk of 10 in the study of PPA diet-pills and PPA cough-cold preparations are shown in the table below for 1, 2, and 7-day intervals prior to hemorrhagic stroke. The 7-day interval is provided for purposes of comparison with the protocol.

	Exposure Rate	Exposure Period	Theoretical Adequate Sample Size	Actual Required Sample Size
Weight Control	0.00055	1 day	1281	1832
	0.00110	2 days	645	922
	0.00385	7 days	191	273
Cough-Cold	0.0004	1 day	1758	2936
	0.0008	2 days	884	1476
	0.0028	7 days	259	443

The theoretical adequate sample size is the number of cases required to detect a relative risk of 10, provided the exposure rate is as estimated and there are no losses due to misclassification. The column labeled "Actual Required Sample Size" has factored in the predicted effect of misclassification due to surrogate responses.

In assessing the feasibility of the proposed study, several points need to be considered. In the study of PPA weight control drug product use beginning within the 24-hour period preceding brain hemorrhage, eligible cases should be restricted to women under 45 years of age. Although the protocol did not describe the age composition of hemorrhagic stroke cases in Connecticut, data from the Washington State study suggest that about 20 percent of strokes will occur in this group of women. Thus, based on a 24 hour exposure window, about 1800 cases of hemorrhagic stroke in women under age 45 would be needed. We estimate that the Connecticut system would provide about 40 cases per year in women under age 45. In the study of PPA cough-cold products, about 50 percent of strokes will occur in subjects under age 55. Thus, about 2900 cases per year would be needed compared to about 100 cases per year available from Connecticut.

It is important to note that not all patients who are eligible will wish to participate in the study. In addition, there will be losses due to other factors as the study progresses. Neither of these points have been considered in the sample size

estimation, but each would require that the sample size be increased.

There are two ways to properly determine the power and sample size of the proposed study. First, a pilot interview survey should be conducted in order to estimate the exposure rate in controls. If the 7-day exposure rate of 10 percent assumed in the protocol is accurate, then it can be verified by interviewing no more than 800 controls. However, if, as we believe, the 7-day exposure rate is about 0.38 percent, then more than 16,000 controls would have to be interviewed. It would require almost another 100,000 controls to verify the 1-day exposure rate, if it is about 0.055 percent. If a large sample pilot survey is impractical, the survey can be conducted sequentially to insure the appropriateness of the sample size. As proposed in the protocol, interim analyses are planned and these analyses may be used for modification of the sample size estimate.

In conclusion, there are several issues that need to be resolved prior to beginning the proposed case-control study of the relatioship between the use of PPA drug products and the risk of hemorrhagic stroke. Because of concerns regarding sample size estimates, the proper exposure window, and possible misclassification due to surrogate respondents, we believe a pilot interview survey should be conducted to determine the exposure rate in controls. Once this rate is determined, the other issues discussed above can be considered in determining the feasibility of the proposed study.

We will be glad to meet with you to discuss these issues regarding the proposed study on PPA. Any comment you wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,

William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

REFERENCES

(1) Derived from testimony by William Soller, Ph.D. at the FDA public meeting on the safety, effectiveness, and possible misuse of phenylpropanolamine for over-the-counter weight control use, May 9, 1991.