MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: DEC 26 1991

FROM: Medical Officer, HFD-733

THROUGH: Acting Division Director, HFD-730

TO: Director, HFD-210
Division of OTC Drug Evaluation 12-24-91

SUBJECT: Safety of Phenylpropanolamine Hydrochloride (PPA) as an OTC Weight Control Drug Product **(OTC Trac No. 110-05)**

This memo responds to your request for a review of documents: (1) the 17 pertinent items in the summary outline prepared by the staff of HFD-210, (2) the Nonprescription Drug Manufacturers Association (NDMA) comments in response to FDA's reopening of the administrative record (7 volumes - Docket #81N-0022, September 6, 1991), and (3) the Clinical/Statistics Report 90-001 and D'Agostino analysis (2 volumes, October 5, 1991).

Much of the information in these submissions is discussed in my memos dated April 30 and August 6, 1991. In this memo, I will comment on analyses in the submissions that have not been reviewed previously, or that are discrepant with FDA analyses.

Comparison of FDA and NDMA stroke case series:

The difference in the number of stroke case reports between my analysis and NDMA analyses is a potential source of confusion. The discrepancy between the 44 cases in my August 6, 1991 memo and the 46 in the NDMA submission is due to different inclusion criteria for the two case series. Specifically, the case series in my August 6 memo includes reports from health professionals only during 1977-1991, while the NDMA series includes cases from health professionals, consumers, and the National Clearinghouse on Diet Pill Hazard, during 1980-1991. Consumer and National Clearinghouse on Diet Pill Hazard reports were excluded from my series for reasons that were explained in the Methods section of the April 30 memo. The cases reported in the articles submitted to the public record by Kikta and McDowell (items #13 and #14, respectively, of the 17 pertinent items list) were included in both my and NDMA case series, and thus do not represent "new" cases. The case reported in the letter from Dr.Timothy Powers to Congressman Wyden (item #15) is not included in either my or the NDMA case series since a specific event was not identified in the letter. Finally, Poison Control Center cases of cerebral hemorrhage associated with PPA have not been included in either my series or the NDMA series.

Comparison of the FDA and NDMA aggregate analyses of the observed to the expected number of cerebral hemorrhages in PPA-diet pill users:

As suggested by Dr. Temple, an analysis of the number of cerebral hemorrhages in PPA-diet pill users expected by chance alone was included in my April 30 memo, and refined in my August 6 memo to account for under-reporting. NDMA has submitted two variations of this analysis: (1) "Epidemiologic analysis of the purported association of phenylpropanolamine hydrochloride diet aids with hemorrhagic stroke in the 15-44 year old U.S. female population" (CIBA, September 3, 1991), and (2) "Investigation of the relation of hemorrhagic strokes to phenylpropanolamine HCL" (Ralph D'Agostino, October 1, 1991).

The main difference between my analysis and the CIBA/D'Agostino analyses is the inclusion or exclusion of "observed" cerebral hemorrhage cases with caffeine in the diet pill. My analysis includes all PPA-diet pill cases regardless of caffeine content. The CIBA and D'Agostino analyses include only reports with single ingredient (caffeine-free) PPA-diet pills. Exclusion of reports with PPA+caffeine diet pills reduces the number of "observed" cerebral hemorrhage cases from 22 in my series (women $\leq$ 44 years, 1980-1990) to 8 cases in theirs. NDMA has excluded these cases because PPA-diet pills with caffeine were phased out in 1983, and thus are not technically the subject of current regulatory review. It is my opinion that exclusion of the cases of cerebral hemorrhage with the products containing caffeine is not warranted since the amount of caffeine in the PPA-diet pills (200 mg.) was similar to the amount of caffeine in one cup of coffee. Although NDMA adjusted their estimate of the exposed population for their estimate of the proportion of caffeine-free sales from 1980-1984, the FDA has no way to verify these estimates.

The CIBA analysis uses Mediamark^R marketing data to estimate age-specific rates of PPA-diet pill use among 15-44 year old women, and Nielsen marketing data to estimate the percent of use for PPA <u>single ingredient</u> pills. The D'Agostino analyses, by contrast, calculate use in two ways with (1) Mediamark only and (2) combined Nielsen and Mediamark data. D'Agostino noted that the Nielsen and Mediamark surveys give different estimates for the number of diet pill users. The discrepancy between the two surveys amounted to a 64% difference in 1989 (8,436,894 vs. 5,133,000 users, respectively) and is not resolved in the submission.

In several meetings, FDA and NDMA have discussed the most reliable estimate for the incidence of cerebral hemorrhage in the U.S. population. The National Hospital Discharge Survey (NHDS) is the source of age-specific incidence rates for the CIBA and D'Agostino analyses. NDMA adequately justifies use of the survey to address this issue. The incidence of cerebral hemorrhage from the NHDS and the rates summarized in Table 8 of my April 30 memo are very similar. The choice of survey does not alter the overall result of the analysis.

Despite NDMA's exclusion of all cases that occurred with a PPA-diet pill containing caffeine, differences in the estimates of the population of PPA-diet pill users, and minor differences in the estimate of the incidence of cerebral hemorrhage in the population, there is a consistent finding in my analysis and the CIBA and D'Agostino analyses. There are more cases of cerebral hemorrhage on the first day of diet pill use than would be expected by chance, <u>assuming that cerebral hemorrhage events are under-reported</u>. Table 1 provides a comparison of the three analyses. In column 5 of the table, the estimates for the expected number of

cerebral hemorrhages vary according to the estimates of PPA-diet pill exposure (the number of consumers). In column 6, the expected numbers of cerebral hemorrhages have been adjusted (by me) for a conservative estimate of reporting (10%). Despite variation in estimation of the exposed population, the expected numbers of cerebral hemorrhages are similar in their order of magnitude because of the very low probability that a cerebral hemorrhage will occur, by chance, on one of two days during a year when a course of diet pills is begun.

The issue of under-reporting of adverse drug events (ADEs) is discussed in my April 30 memo, but is briefly addressed here because of the inclusion in NDMA's submission of a literature review on under-reporting from Dr. Philip Lavin. Lavin concludes that a reporting rate of 30% is an appropriate estimate of reporting for severe ADEs. Lavin's estimate appears to be based on personal communication with Rogers[1] et al, who surveyed physician's knowledge about the FDA Spontaneous Reporting System. There are several important limitations in this study that Lavin does not address. This survey was designed to assess physician knowledge and attitudes, and did not directly measure the proportion of detected ADEs that were actually reported. As an example, this survey found that 5% of physicians who had detected an ADE in the past year reported it directly to the FDA. This result should not be interpreted as indicating that 5% of <u>all</u> ADEs were reported since the reporting physicians may have detected several ADEs but only reported one. A second major limitation in this study is the low survey response rate (37% of sampled physicians) and the nonrandom sampling of physicians in Baltimore, Baltimore County, Prince Georges, and Montgomery County, Maryland. These two factors (the low response rate, and the geographically homogenous sample of physicians who work in close proximity to FDA headquarters) limit the generalizability of their findings. A third limitation in this study is the broad definition of reporting that included the following places for reporting: the FDA SRS, the drug manufacturer, colleagues, the medical literature, and others including hospital committees. Finally, this study provides no information on patterns of physician reporting with over-the-counter products.

Unfortunately, there is no data to substantiate speculations on the rate of reporting serious adverse events with over-the-counter products.

Discussion

There are several theoretical limitations in interpreting aggregate analyses of spontaneous reports, including incomplete case ascertainment, incomplete information about potentially confounding conditions, imprecise PPA-diet pill exposure information, unstable age-specific rates of cerebral hemorrhage, and the lack of generalizable data on under-reporting. At this time, case reports represent the only available data on this extremely serious and epidemiologically complex issue. Our interpretation of this data suggests an association between PPA-diet pills and cerebral hemorrhage, however we are unable to measure the strength of this association with available information. A population-based case-control study would be necessary in this regard. We are currently in contact with an investigator in the pilot stage of a population-based case-control studies of stroke. He has indicated that it may be feasible to include several questions on PPA-diet pill exposure in the study questionnaire, but he estimates approximately five years to complete this study. Other related questions concerning the prevalence of PPA-diet pill use and misuse (particularly in teens) could be studied in a shorter time frame.

Please contact me with any further questions about the NDMA submission.

Heidi M. Jolson, M.D., M.P.H. H Jolson
Epidemiology Branch
Division of Epidemiology and Surveillance
Office of Epidemiology and Biostatistics
443-2306

Concur:

Chief, Epidemiology Branch RWS 16 Dec 91

c:\h\wp\ppamem.n13

CC:
HFD-100/Temple
HFD-110/Lipicky/Dern
HFD-120/Leber
HFD-150/Burke
HFD-210/Botstein
HFD-700/Anello/Johnson
HFD-710/O'Neill
HFD-733/Stadel/Gross/Burkhart/Jolson/File chron, dru 1.7 phenylpropanolamine
HFD-735/Barash
HFD-737/Gelberg

Table 1
Comparison of the Observed/Expected Ratios of Cerebral Hemorrhage in PPA-diet Pill Users on the First Day of Use According to Analyses by CIBA, D'Agostino, and FDA

Analysis (comment)	Source of estimate of PPA-diet pill users	Single ingredient cases only	Observed	Expected	Expected with adjustment for 10% reporting	O/E ratio with adjustment for 10% reporting
CIBA Tables 6 & 11	Mediamark® and Nielsen surveys 1982, 84 and 89;	Yes	5	14	1.4	3.6
CIBA Table 12 (excluded: cases of overdose +/- contraindicated meds/conditions)	same	Yes	2	14	1.4	1.4
D'Agostino Table A.1.2	Mediamark® and Nielsen surveys - no adjustment to remove proportion of sales due to product with caffeine.	Yes	6	44.89	4.5	1.3
D'Agostino Table A.1.3 (excluded: 2 cases with >3X MRD[1])	same	Yes	5	44.89	4.5	1.3
D'Agostino Table A.1.4 (excluded: 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	44.89	4.5	0.9
D'Agostino Table A.2.2	Mediamark and Nielsen surveys - adjusted to exclude proportion of sales due to product with caffeine	Yes	6	28.53	2.9	2.1
D'Agostino Table A.2.3 (excluded: 2 cases with >3X MRD)	same	Yes	5	28.53	2.9	1.7

[1]MRD denotes maximum recommended dose.

Analysis (comment)	Source of estimate of PPA-diet pill users	Single ingredient cases only	Observed	Expected	Expected with adjustment for 10% reporting	O/E ratio with adjustment for 10% reporting
D'Agostino Table A.2.4 (excluded: 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	28.53	2.9	1.4
D'Agostino Table A.3.2 (1984-1990)	Mediamark and Nielsen surveys 1984-1990 only	Yes	6	27.59	2.8	2.1
D'Agostino Table A.3.3 (1984-1990; excluded: 2 cases with >3X MRD)	same	Yes	5	27.59	2.8	1.8
D'Agostino Table A.3.4 (1984-1990; excluded: 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	27.59	2.8	1.4
D'Agostino Table B.1.2	Mediamark only - no adjustment to remove proportion of sales due to product with caffeine	Yes	6	30.31	3.0	2.0
D'Agostino Table B.1.3 (excluded: 2 cases with >3X MRD)	same	Yes	5	30.31	3.0	1.7
D'Agostino Table B.1.4 (excluded: 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	30.31	3.0	1.3
D'Agostino Table B.2.2	Mediamark-adjusted to exclude proportion of sales due to product with caffeine	Yes	6	21.33	2.1	2.9
D'Agostino Table B.2.3 (excluded: 2 cases with >3X MRD)	same	Yes	5	21.33	2.1	2.4

Analysis (comment)	Source of estimate of PPA-diet pill users	Single ingredient cases only	Observed	Expected	Expected with adjustment for 10% reporting	O/E ratio with adjustment for 10% reporting
D'Agostino Table B.2.4 (excluded: 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	21.33	2.1	1.9
D'Agostino Table B.3.2 (1984-1990)	Mediamark 1984-1990	Yes	6	19.22	1.9	3.2
D'Agostino Table B.3.3 (1984-1990; excluded 2 cases with >3X MRD)	same	Yes	5	19.22	1.9	2.6
D'Agostino Table B.3.4 (1984-1990; excluded 3 cases with >3X MRD or antihypertensive use)	same	Yes	4	19.22	1.9	2.1
Jolson memo 8/6/91 Table 3	Marketing data presented at the May 9, 1991 public meeting by NDMA	No	14	36	3.6	3.9

References:

1.Rogers AS, Israel E, Smith CR, Levine D, McBean AM, Valente C, Faich G. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. Arch Intern Med 1988;148:1596-1600.