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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers lane, Room 1061
Rockville, Maryland 20852

By Federal Express

Re: Dockets No. 81N-0022 and 76N-052N

To Whom It May Concern:

The investigators for the Hemorrhagic Stroke Project (HSP) submit the enclosed response to comments by the Consumer Healthcare Products Association (CHPA) Phenylpropanolamine (PPA) Working Group regarding our recent report.

The CHPA consultants have described several theoretical and practical constraints that may affect the conduct and interpretation of case-control research. We acknowledge that some of these constraints are pertinent to a careful consideration of the HSP, but we believe they do not, alone or combined, weaken the HSP findings. In particular, we believe that neither chance nor the biases cited by the CHPA consultants are likely explanations for the associations we observed between PPA used as an appetite suppressant among women or PPA used as a first dose and risk for hemorrhagic stroke.

On behalf of the HSP Investigators,

Ralph I. Horwitz

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Enclosure: computer diskette

cc: Charles J. Ganley, M.D., Director, Division of Over the Counter Drug Products
Robert DeLap, M.D., Director, Office of Drug Evaluation V

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September 19, 2000
Response to "Comments on the Hemorrhagic Stroke Project Report" by the CHPA Phenylpropanolamine Working Group.

1) The CHPA consultants state that the Hemorrhagic Stroke Project (HSP) did not establish a causal relationship between PPA and hemorrhagic stroke. We agree. A single study is rarely able to establish causation. What the HSP does provide is substantial evidence that PPA is associated with increased risk for hemorrhagic stroke. Causation is one explanation for that association, especially since neither chance nor bias is a likely explanation for the findings.

2) We agree with the CHPA consultants that the results of the Hemorrhagic Stroke Project must be considered in the context of existing safety data on PPA. It was because of deficiencies in the existing data, however, that the HSP was initiated. In particular, prior to the HSP there were no scientifically rigorous data on the association between PPA and risk for hemorrhagic stroke. Our study was designed to provide that data using a case-control format. One of the reasons for choosing the case-control format was because this method is suited to study risk factors for rare diseases, such as hemorrhagic stroke in young persons. Prospective observational research (e.g., clinical trials, cohort studies) would not be practical for examining the association of PPA with hemorrhagic stroke because of ethical objections (for randomized trials) and because too few subjects would have the outcome (for observational studies and randomized trials).

3) We believe that the findings of the HSP suggest that PPA is an independent risk factor for hemorrhagic stroke. We reject the consultants' assertion that "the data are derived from too few cases and controls to allow an unbiased assessment about any relationship between exposure and stroke." The rate of exposure to first use of PPA among female control subjects exceeded the rate we anticipated during design of the study. With the observed exposure rate, the p-values for the association between first use of PPA and stroke among women (0.042) and PPA in appetite suppressants and stroke among women (0.011) met the usual criteria for statistical significance. We address the possible roles for bias and confounding in the report.

4) We disagree with the consultants' contention that conclusions from the study should be based on the odds ratio for any PPA exposure within three days (in men and women) and risk for hemorrhagic stroke. The HSP was designed (in a process that involved the industrial sponsors) with three co-equal specific aims: 1) Among men and women, to estimate the association between any use of PPA and hemorrhagic stroke; and 2) Among men and women, to estimate the association between PPA and hemorrhagic stroke by type of PPA exposure; and 3) Among women, to estimate the association between hemorrhagic stroke and PPA in appetite suppressants and any first use of PPA (appetite suppressants or cough/cold remedies). Contrary to what the consultants state, there was

no "first objective" for the HSP; the aims were always conceived as co-equal. As a historical point, a prime motivation for initiating the HSP was concern specifically regarding use of PPA in appetite suppressants by young women. The sample size was calculated based on the aim to have adequate power to detect a specified odds ratio for the association between PPA used as a first dose among women. The findings referred to by the consultants as "subset findings" were, in fact, findings related to pre-specified aims.

5) In comments regarding confounding variables, the consultants state that confounding factors were not controlled for in the analysis. This is not true. We controlled for confounding variables using two conventional strategies. First, we matched cases to controls on four potential confounders: age, black race, gender, and telephone exchange (a feature that was intended to be a surrogate for socioeconomic status). All cases and controls were matched on gender and telephone exchange. Age matching was successful for 99% of controls and ethnicity matching was successful for 96%. Odds ratios were subsequently derived from conditional logistic regression models for matched sets using exact statistical methods (LogXact Program, v 2.1, Cytel Software Corporation, Cambridge, MA) and accounted for the matching features of age, sex, race, and telephone exchange.

Our second strategy for controlling for confounding variables was to adjust for them in logistic regression models as follows:

A. Adjustment for imperfect matching. Age matching (within 3 years for case subjects less than 30 years old; within 5 years for case subjects 30 years or older) was not achieved for only 9 control subjects and inclusion of age as a term in the models did not affect the estimated odds ratio. Race was not matched for 55 control subjects and this feature was included as a term in all adjusted logistic models.
B. Adjustment for other (non-matching) features. Among demographic features examined, only one (educational level) affected the estimated odds ratio and was retained in the final adjusted model. Among non-demographic features (cigarette smoking, diabetes, alcohol use, cocaine use, oral contraceptive use, and body mass index, specific medication use), none affected the estimated odds ratio. Current cigarette smoking and hypertension were included in the final adjusted models because they were considered a priori potential confounders. They were not matched for in the design due to lack of data supporting an independent relationship to PPA use.

6) The findings of the HSP are based on 27 exposed cases and 33 exposed controls. The consultants suggest that misclassification of these individuals regarding exposure to PPA "could easily and significantly skew the results of the study". We acknowledge that misclassification may affect case-control studies, but we also believe that a major strength of the HSP was successful implementation of procedures to prevent misclassification bias. These procedures are described in our report to the FDA.
The consultants note that telephone interviews precluded the use of visual aids to assist in exposure recall and that more controls (n=44) than cases (n=3) were interviewed by

telephone. As a consequence, the consultants allege, it is more likely for a control subject to be misclassified on reported product use. We believe this criticism is without merit for several reasons. First, the Product Identification Book was not used as an aid to assist in exposure recall. The book was shown to case or control subjects only after they reported a specific exposure to an appetite suppressant or cough/cold remedy. The book was used as a secondary method to verify exposures to brand-name medications. The primary method was examination of medicine containers. Second, among the 44 controls interviewed by telephone call, only one control subject (a male) reported exposure to a brand-name product containing PPA. Because he had discarded the product container, he could not give us a lot number. Accordingly, he was classified as non-exposed. When we re-ran the analysis including him as exposed, none of the findings were changed.

In reply to other comments under the consultants' item 6:

• Case subjects were eligible for enrollment in the HSP up to 30 days after their stroke event. Some patients, therefore, were asked to recall medication exposures that may have occurred up to 30 days before the interview date. We believe a 30 day interval is reasonable because a serious personal event, particularly a health event, is commonly believed to serve as a stimulus to recall for antecedent happenings. For control subjects, we maintained a shorter maximum interval between the index day and the interview (7 days) to improve control subjects' recall of pre-focal time exposures; although this technique may bias our study toward a finding of no association between PPA and hemorrhagic stroke, it was necessary to balance case subjects' greater stimulation for recall of exposures occurring before their stroke.

•The consultants comment that the proportion of aphasic cases could have affected accurate identification and classification of cases reported to have used PPA products. When odds ratios were examined within strata defined by the degree of case-aphasia, the reported associations were increased (with lower p-values compared to the overall results) in the group defined by no significant aphasia (levels 1-3; n=603 cases). This was also true when cases with no aphasia present (level 1; n=388) were examined separately. Therefore, exclusion of cases with some degree of aphasia present would not have affected the conclusions of the study.

•The consultants assert that, because interviewers knew which subjects were case subjects and which were control subjects, they could have inadvertently prompted specific answers and thereby skewed the results. We believe a strength of the HSP was the highly structured and scripted interview that protected the research against this specific problem. Interviewers were trained to adhere to the structured interview.

•The consultants state that differences in interview location for case and control subjects could have skewed results. Interviews for both case subjects and control subjects always took place in a setting that afforded them adequate privacy.

•The consultants state that recall factors, such as those discussed immediately above, may "have a significant and unpredictable impact on the odds ratio in either direction" and refer to the study results as "inconclusive." The consultants also assert

that "no information is provided to give a perspective on how such recall issues affect the study results". Recall bias and exposure classification procedures were discussed in our Final Report of May 10, 2000. We hope that the additional information provided in this letter will help readers draw appropriate inferences from the results of the Hemorrhagic Stroke Project.

7) The consultants suggest that exclusion of dead and non-communicative case subjects from the HSP may have biased the findings. The consultants suggest that the "higher apparent risk of hemorrhagic stroke among PPA users might be due to a lengthening of their survival rather than an increase in disease incidence." Although it seems very unlikely that PPA protects against death and severe disability in stroke patients, we acknowledge that this bias is remotely possible. We excluded dead and non-communicative subjects because, based on other epidemiologic research, we believed that accurate exposure data could not be obtained from proxy respondents.

8) The consultants state that "The study report fails to acknowledge that the findings cannot be entirely generalized to the U.S. Population, as the enrolled cases and controls were not adequately population-based. . ." We make no claim in the report that the findings are generalizable beyond the HSP cohort. However, the case and control subjects are probably fairly representative of their populations, at least in two of the four largest research centers. In both Connecticut and Ohio, we actively surveyed for eligible patients by monitoring admissions and discharges at all major hospitals. In these two research centers, we believe case ascertainment was complete. Across all four centers, we enrolled 76% of eligible subjects (708/930). This percentage actually underestimates the true recruitment percentage of eligible subjects enrolled because 182 of the 930 patients never underwent a full screen for eligibility; had they been fully reviewed some would have been found to be ineligible.

The consultants state that another reason the results of the HSP cannot be generalized to the U. S. population is that the subjects do not represent typical consumers who use PPA drug products. The HSP was never designed to sample typical PPA consumers. Instead, the HSP was designed to sample young men and women with hemorrhagic stroke. We know of no a priori reason why young persons with hemorrhagic stroke would be expected to closely match the demographic features of PPA consumers. Nevertheless, despite our sampling strategy and contrary to statements of the CHPA consultants, HSP participants are actually very similar to typical PPA consumers. Results of a survey provided to us by the Consumer Healthcare Products Association indicates that 62% of PPA users are female, 41% are less than 40 years, and 43% are college educated. These figures are similar to characteristics of case subjects in the HSP (55% female, 42% less than age 40 years, 40% college educated). Control subjects in the HSP were more highly educated than typical users from the industry survey (62% college educated in the HSP), but were otherwise similar (55% female, 43% less than age 40 years).

The consultants comment that the study's case population does not appear to be totally representative of the hemorrhagic stroke population among 18-49 year old persons, especially in terms of the distribution of stroke type (subarachnoid hemorrhage

compared with intracerebral hemorrhage). We believe this criticism is not well-founded. There is surprisingly little research on the relative incidence of SAH or ICH among persons aged 18-49 years of age. Among studies that do report rates by age and gender, estimates vary widely. In The Oxfordshire Community Stroke Study, among persons aged 0-54 years with hemorrhagic stroke 30% had an ICH compared with 71% for SAH(1). In Greater Cincinnati, rates of ICH and SAH are roughly equal up to age 54 years(2). Comparison of rates of ICH and SAH among these and other studies(3, 4) is difficult because diagnostic criteria vary and are not necessarily the same as the criteria used in the HSP. Among persons enrolled in the HSP, 39% had an ICH and 61% had a SAH. We believe there is no basis for saying these proportions from the HSP are not consistent with the range of results reported in the literature.

9) We acknowledge a differential in participation rates between control subjects (36%) and case subject (75%), but we strongly disagree with the comment that "inadequate data are provided to allow independent verification of the findings . . .". The HSP investigators have made available to the study sponsors complete copies of the research data and supporting files (in a format that protects patient confidentiality).

10) Fully adjusted models (including terms for hypertension, smoking, race and education) were not calculable using exact statistical techniques due to computing memory constraints. However, reduced models for the association of PPA use in appetite suppressants and stroke risk in women were estimable using exact methods. For each single-adjustment term model (including hypertension, smoking, race and education alone) and two-adjustment term model (including smoking and race; and education and race) estimated with exact methods, we found minimal changes in the estimated odds ratios (equal to within 0.01 for all measures) and a slight but uniform <u>reduction</u> in all p-values when compared with the asymptotic model results. These comparisons give us confidence that the use of asymptotic methods to report the fully adjusted model was appropriate for these data.

11) The HSP was not designed to provide insight into the biological mechanism for the association between PPA and hemorrhagic stroke. Medical history is replete, however, with examples of important associations that were discovered before their mechanism was understood. Examples include cigarette smoking and coronary heart disease, cigarette smoking and lung cancer, and diethylstilbestrol and clear cell carcinoma of the vagina.

Response to the consultants' concluding point. We agree that the findings of the HSP must be interpreted in the context of existing safety data on PPA. As stated above, however, the HSP was undertaken because of inadequacies in these data. Clinical trials involving PPA, for example, have not enrolled enough patients to be able to detect the occurrence of rare side effects, such as hemorrhagic stroke. Our data suggest that a re-appraisal of the safety of PPA is appropriate.

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