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Producers of Quality Nonprescription Medicines and Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Former: Nonprescription Drug Manufacturers Association

OTC-560-2224

May 24, 2000

By Messenger

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

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

To Whom It May Concern:

The Consumer Healthcare Products Association (CHPA) Phenylpropanolamine Working Group summits the enclosed comments on the report recently submitted by Yale University investigators to FDA Docket No. 81N-0022 (RPT 14). These comments were prepared upon our initial review of that Yale final report on the Hemorrhagic Stroke Project. We urge that these CHPA comments be treated as a companion to the Yale study report, as they highlight important issues to be considered in interpreting the study results.

The Hemorrhagic Stroke Project report must be considered in the context of the large existing safety database on phenylpropanolamine (PPA). This evidence from clinical trial and adverse-event tracking, when taken together, overwhelmingly supports the safety and effectiveness of PPA when used as directed on product labeling.

On behalf of the CHPA Phenylpropanolamine Working Group,

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Senior Vice President and
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Enclosures: Comments on the Hemorrhagic Stroke Project Report
(six print copies and an electronic copy on disk)

cc: ✓Charles J. Ganley, M.D., Director, Division of Over-the-Counter Drug Products
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WS/lct

CHPA Phenylpropanolamine Working Group

Comments on the Hemorrhagic Stroke Project Report

May 24, 2000

Introduction

In 1994, members of the Consumer Healthcare Products Association (CHPA) marketing phenylpropanolamine (PPA)-containing appetite suppressants contracted with investigators at Yale University to conduct an epidemiologic study on hemorrhagic stroke.[1] The final report of this study has been provided to the sponsoring companies and the Food and Drug Administration. This document provides commentary on the recently submitted report of the Hemorrhagic Stroke Project.

While even the best-designed and executed epidemiology studies have limitations for reaching definitive conclusions, the nature and complexity of the Yale study make drawing any meaningful conclusions particularly difficult, primarily due to inadequate controlling for bias and confounding. Also of particular concern are the scientific limitations of interpreting results from small numbers of cases and controls who were exposed to PPA. Important confounders and biases, which are likely to have had a profound impact on the study results and conclusions, have been overlooked in the study report.

Our core concern relates to the overall strength of the study, and we believe the study data do not support a serious challenge to the safety of phenylpropanolamine in over-the-counter medicines. We strongly disagree with any broad-sweeping statements and conclusions about the results of the Yale study that explicitly state or imply it represents strong epidemiologic evidence applicable to the general population. Numerous factors limit the ability of this study to support these conclusions.

These comments summarize our overall conclusions and specific concerns about the Yale study report. Important methodological and analytical issues of relevance in interpreting the study results are identified in the Attachment, which is entitled "Points to Consider in Review of The Hemorrhagic Stroke Project: Case-Control Study of Phenylpropanolamine (PPA) and Hemorrhagic Stroke."

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[1] The five-year case-control study began in 1994 and involved interviews of 702 patients between the ages of 18 and 49 who had been hospitalized with hemorrhagic strokes and a total of 1,376 controls matched to cases on the basis of age, gender, race and geographic location. The cases were identified from a network of 20 hospitals in Connecticut and from participating hospitals in Providence, Rhode Island; Cincinnati, Ohio; and Houston, Texas.

Summary Comments

1. The Hemorrhagic Stroke Project did not establish a causal relationship between PPA use and hemorrhagic stroke.

2. The findings of the Hemorrhagic Stroke Project must be considered in the context of existing safety data on PPA. This evidence overwhelmingly supports the safety and effectiveness of PPA when used according to label directions.[2]

3. The study findings of an apparent "association" between stroke and PPA exposure should not be relied upon as conclusive. Important biases and inadequate controlling for confounding factors (see below) could account for the reported association. A more appropriate conclusion is that the data are derived from too few cases and controls to allow an unbiased assessment about any relationship between exposure and stroke.

4. Conclusions from the study should be based on overall PPA exposure, which is the study's first objective (i.e., "Do PPA users have an increased risk?"). The overall analysis based on this endpoint resulted in an odds ratio that does not demonstrate increased risk [i.e., OR=1.49 (p=0.084)] of PPA use and hemorrhagic stroke. No meaningful conclusions can be derived from analyses of very small, selected subsets. There are too few cases and controls in the subgroups who reportedly took PPA to allow for effective controlling for confounding factors.

5. Confounding factors, which are independent risk factors that are associated with both PPA product use and the occurrence of stroke and include lifestyle habits and pre-existing medical conditions that could independently contribute to stroke, such as hypertension and cigarette smoking, were not controlled for in the study analyses. Cases and controls were not adequately matched for confounding factors, which is a deviation from the study protocol.
   - Some examples of confounders that were not adequately controlled for include the following:
     - Educational level and socioeconomic status were quite different between the cases and the controls, and cases were more likely to be black than were controls. Lower socioeconomic status and a lower educational level are known risk factors typically associated with greater morbidity and mortality in a number of diseases, including stroke. Those and several other risk factors for stroke are significantly more prevalent among cases than among controls. Cases were more likely to be current smokers, consume more alcoholic beverages, be illicit drug users, be reported to have hypertension, and/or have a family history of stroke.

[2] Submissions by CHPA [then named Nonprescription Drug Manufacturers Association] to FDA Docket No. 81N-0022: October 17, 1990, letter to William E. Gilbertson, Director, Division of OTC Drug Evaluation; September 6, 1991, "Overall Statement on the Safety and Effectiveness of Phenylpropanolamine as an OTC Appetite Suppressant"

- Hypertension is a risk factor for hemorrhagic stroke and for an increased risk of aneurysm formation and rupture, and is associated with obesity. Obese persons might be expected to be more likely to use PPA-containing appetite suppressants, but notably few persons in the study had taken PPA appetite suppressants. Although the use of antihypertensive medication and degree of blood pressure control are potentially important risk factors, they were not assessed nor, therefore, controlled for as confounders.

- The reported apparent "association" of hemorrhagic stroke and PPA in this study could arise from the comparison of a high-risk group for hemorrhagic stroke (hypertension, cocaine and alcohol abuse, caffeine consumption, family history of hemorrhagic stroke, obesity) with controls drawn from the general population, with limited control of confounding.

6. Because of the small number of cases of hemorrhagic stroke reportedly associated with PPA use identified in this five-year study, errors in classification of exposure could easily and significantly skew the results of the study. This could be caused by errors in participant recall and/or product misclassification. The apparent association between PPA appetite suppressant use and stroke reported by the Yale investigators would not be apparent if only four controls were misclassified as unexposed to PPA.

   - Since there are cough/cold products and appetite suppressants that do not contain PPA, a participant could incorrectly recall that they took product A (with PPA), when in fact they took product B (with no PPA).

   - Telephone interviews preclude the use of visual aids to assist subjects in their recall of exposure. More than twice as many controls as cases were interviewed over the telephone, suggesting it was more likely for an exposed control to be misclassified on reported product use.

   - Many other factors could also affect the accuracy of exposure classification. For example:

     - Study participants were asked to recall the specifics of medicine taken more than two weeks before, a substantial time between reported use and time of interview.

     - Forty percent of the interviewed cases had a degree of aphasia. (Aphasia is the loss of ability to speak or understand spoken or written language due to disease or injury of the brain.) The proportion of aphasic cases could have affected accurate identification and classification of cases reported to have used PPA products.

     - Interviewers knew which subjects were cases and which were controls, and could have inadvertently prompted specific answers and thereby skewed the results.

     - The difference in the severity of the event for cases versus controls and in the location of the interviews (hospital versus home) could also have contributed to skewing the results.

- Because such factors as those suggested above may have a significant and unpredictable impact on the odds ratio in either direction and virtually no information is provided to give a perspective on how such recall issues affect the study results, the scientific documentation supporting a putative exposure is, at best, inconclusive.

7. The study was based on prevalent cases. Cases who died before interview and those who were unable to communicate within 30 days (i.e., 34%) were excluded. Studies based only on prevalent cases could be misleading. A 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, and excluded cases may differ in their exposure to PPA and other risk factors for hemorrhagic stroke that would likely be confounders of the association of interest. Exclusion of the most severe patients could have affected the results, overestimating the risk associated with the use of PPA. This bias does not allow any posterior control for confounding factors associated with survival from hemorrhagic stroke.

8. 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 and differ in sociodemographic characteristics from typical U.S. consumers who use PPA drug products. Furthermore, the study's case population does not appear to be totally representative of the hemorrhagic stroke population among 18- to 49-year-olds in the United States (i.e., the study shows a different distribution by stroke type), as well as excluding fatal strokes.

9. The large differential in participation rates between cases and controls could affect the findings and is not adequately explained in the report. Likewise, inadequate data are provided to allow independent verification of the findings or to verify that sensitivity analyses do not alter the confidence limits or p values for the findings.

10. Choice of analytical methodology is also of concern. Inappropriate statistical methods were used, given the small numbers of exposed cases. Likewise, inappropriate and/or inadequate methods were used to control for confounding.

    - The number of subjects exposed to appetite suppressants is too few to meet the criterion for the use of asymptotic statistical methods. These methods require a minimum of five observations in each exposure-disease category. Seven exposed subjects divided between cases and controls does not satisfy this criterion. Therefore, analysis of exposure to appetite suppressants should use exact, rather than asymptotic, statistical methods.
    - The attempt to control for confounding by including confounders in the exact method of analysis was unsuccessful due to the few exposed subjects. Therefore, interpretation of the results of the exact analysis must include confounding as a very likely explanation for the observed association. Further, these confounders cannot be considered controlled in the asymptotic analysis, since the assumption for this analysis is violated.
    - A reflection of the inappropriateness of the asymptotic statistical analysis is the fact that the strength of the association between exposure and disease (i.e., the magnitude of the

odds ratio) increased when confounders were "controlled." This is contrary to what is usually observed in control of confounding variables, where the adjusted odds ratio is expected to be smaller than the unadjusted odds ratio.

11. The study provided no insight on a biologically plausible mechanism for any relationship between use of PPA and hemorrhagic stroke. Although recommended doses of PPA have been shown to cause small, transient, but clinically insignificant, changes in blood pressure,[3] these minor changes are within the range of usual increases associated with such daily activities as climbing stairs or mowing a lawn. Hence, alteration of blood pressure is not a clear underlying mechanism for a putative association between PPA and stroke, nor is any other biologically plausible mechanism known.

Concluding Points

The Hemorrhagic Stroke Project report must be considered in the context of the large existing safety database on PPA. This evidence from clinical trial and adverse-event tracking, when taken together, overwhelmingly supports the safety and effectiveness of PPA when used as directed on product labeling. PPA-containing products have been used by millions of consumers over the past 50 years with a very low incidence of reports of serious side effects.

The CHPA PPA Task Group and expert consultants continue to review the reported results and additional data from the study. The group expects to submit all of its findings to the Food and Drug Administration.

Attachment: Points to Consider in Review of The Hemorrhagic Stroke Project: Case-Control Study of Phenylpropanolamine (PPA) and Hemorrhagic Stroke

WS/LT/lct/PPA/Comments to FDA:5-23-00

[3] Blackburn et al. 1989. *Journal of the American Medical Association* 262(22):3267-72; Morgan and Funderbunk 1992. *American Journal of Clinical Nutrition* 55:2065-2105

POINTS TO CONSIDER IN REVIEW OF THE HEMORRHAGIC STROKE PROJECT: CASE-CONTROL STUDY OF PHENYLPROPANOLAMINE (PPA) AND HEMORRHAGIC STROKE MAY 9, 2000

Statisticians and epidemiology consultants to the study sponsors (hereafter referred to as the "expert statistical review group") reviewed the materials obtained from Yale regarding the Hemorrhagic Stroke Project. The expert statistical review group's goal was to identify important methodological and analytical issues of relevance in interpreting this study's findings. Some descriptive analyses (detailed in Analysis Plan of February 11, 2000) were performed to supplement the information provided by Yale and to highlight some of the methodological issues. Several analytic issues are addressed qualitatively at this time (e.g. confounding), and others (e.g., sensitivity analyses) are addressed quantitatively. Appendix 1 contains data tables that support the analyses discussed here and Appendix 2 contains descriptive data on the exposed cases and controls. Finally, we provide a series of study interpretation issues that should be considered in placing this study in perspective. *{Note: the additional data provided in this report were computed using the datasets provided by Yale in December 1999. The total numbers of cases and controls differ from those in the final report.}*

I. Methodology Issues in Case-Control Study of PPA and Hemorrhagic Stroke
   - A. Identification of cases and matched controls
     1. The population from which controls are selected should be as similar as possible to the population from which the cases were identified
     2. Different sampling processes were used for acquiring cases and controls
        - a. Cases were identified through hospital networks
        - b. Controls were selected by random digit telephone interview, and matched by age, gender, race, and socio-economic status (using telephone exchange as a surrogate)
   - B. Selection of Cases
     1. Cases were identified through two population-based hospital networks (OH/KY and CT/MA and two tertiary care hospitals (RI and TX)
        - a. Limited information is presented to indicate that the population-based hospitals cover the entire cachement area
        - b. Patients aged 18 and 19 may be treated in pediatric hospitals
     2. Cases included in study may not represent all cases in the population
        - a. Only 61% of the original identified cohort was considered eligible, and only 77% of the eligible were enrolled in the study
        - b. Exclusions removed the following subjects:
          - (1) Persons who died before interview (N=378, 23%)
          - (2) Persons who could not communicate within 30 days (N=186, 11%)
          - (3) Persons who refused or their physician refused to allow contact (N=48, 3%)
     3. Basing the study on only prevalent cases could be misleading; a 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.

4. Excluded cases may differ in their exposure to PPA and other risk factors for hemorrhagic stroke that would likely be confounders of the association of interest.
5. Exclusion of cases does not allow any posterior control for confounding factors associated with survival from hemorrhagic stroke.
6. Exclusion of deceased or disabled cases (i.e., no surrogate interviews) was discussed with FDA and investigators with subsequent decision that the potential bias due to non-differential imprecision (by use of surrogate respondents) was a greater threat to validity than sampling bias resulting from exclusion of sickest patients.
7. While the expert statistical review group understands that some pilot investigations were conducted to evaluate the validity of surrogate interviews, no information has been identified to document a potential change in the protocol. The protocol specifies that a sensitivity analysis of 50% was assumed for surrogate determination. This is no better than a coin flip.
8. Nondifferential imprecision by the use of surrogates in determining exposure would have the effect of biasing the results toward the null hypothesis (i.e., underestimating the odds ratio).
    a. In light of statistically significant odds ratio, nondifferential imprecision is not an issue.
    b. The expected direction of the sampling bias resulting from exclusion of the sickest patients is to overestimate the odds ratio.
    c. Thus, the sampling bias could explain the observed associations.
9. Through the validation of cases, patients who had known arterio-venous malformation (AVM) or vascular aneurysm prior to the index event were excluded. However, 3 of the 6 female cases who took appetite suppressants were noted to have had AVM or aneurysm in the narrative histories:
    a. Aneurysm and AVM are the most commonly identified causes of subarachnoid hemorrhage (SAH).
    b. AVM is associated with most intracerebral hemorrhages.
    c. Usually cerebral aneurysms and AVMs are diagnosed during the course of a hemorrhagic stroke, and SAH occurs more frequently in women than in men.
    d. The inclusion of SAH susceptible cases would more likely affect women than men, and could, to some extent, explain the results between PPA and hemorrhagic stroke.
10. Potential impact on study findings is unknown; further evaluation of the included and excluded stroke cases could provide more insights.

C. Selection of controls

1. The protocol does not specify what method of RDD was used to enroll controls. If selection stopped upon filling a quota, then there may be an over-selection of individuals who stay at home more (and hence answer the telephone more) than the population as a whole.

D. Comparability of cases and controls

1. Controls were matched by telephone exchange to approximate control for socio-economic status.
2. Cases were significantly different from controls in several important confounders. A number of risk factors for stroke are significantly more prevalent among cases than among controls. These include: race, social economic status, caffeine exposure, hypertension, family history, alcohol consumption, and cocaine use. The imbalance of these confounders would, if uncontrolled, be more than sufficient to explain the observed association between PPA in appetite suppressants and stroke.
   a. Two of the 4 demographic characteristics were different between cases and controls.
      (1) race
      (2) education
   b. Five of the 9 clinical characteristics were different between cases and controls.
      (1) cigarette smoking
      (2) hypertension
      (3) family history of stroke
      (4) alcohol use
      (5) cocaine use
   c. Three of the 10 pharmacologic exposures were different between cases and controls.
      (1) NSAIDS
      (2) caffeine
      (3) nicotine

E. Description of Study Population

1. Appendix 1 Table 1 shows the distribution of cases and controls by region.
2. Appendix 1 Table 2 shows the distribution of *exposed* (in the 3-day window) cases and controls by region.
   a. The largest subject-contributing site (CT/MA, the base of the coordinating center) produced 0 subjects exposed to appetite suppressants, where as the next largest contributor produced 5 (5/7=71%) subjects exposed to appetite suppressants.
   b. This leads to questions concerning possible interview bias:
      (1) Were the interview methods described in the protocol adhered to as strictly in other sites as at the coordinating site?
      (2) Is there truly a factor or factors that make OK/KY so different from CT/MA that could account for these differences?
3. Appendix 1 Table 3 shows the age and gender distribution of cases and controls.

F. Precision of exposure estimation and possible recall bias

1. Appendix 1 Table 4 shows the distribution of cases and controls by

method of verification of PPA exposure.

a. 32% of all exposures were not verified using protocol specified means, such as the Product ID Book, Drug Container, or Pharmacy at which the drug was purchased.
b. A larger proportion of control exposures than case exposures were not verified (43% of control exposures and 19% of case exposures).
c. This could lead to possible misclassification of exposure status. (15 control patients did not have their exposure verified and it only takes 4 misclassifications to diminish the association between PPA and stroke).

2. Exposure is estimated by self-reported interview, with verification using pictures and obtaining medicine bottles, when available. In some instances, verification was done by telephone interview.
3. Since cases know that they have the disease, they are likely to be thinking about exposures before asked to report on them.
4. Cases have more interest in the study than do controls, so they might make a greater effort to recall exposure.
5. Exposure estimation is influenced by the length of the recall period and the amount of precision required.
6. Exposure estimation may be influenced by the setting in which the interview occurred (e.g., hospital, home). (Appendix 1 Table 5 shows the distribution of cases and controls by interview location).
   a. 34% of cases were interviewed in places other than the hospital.
   b. 43% of controls were interviewed in some unspecified "other" location.
      (1) Why were so many controls interviewed in a location that was not anticipated by the protocol?
      (2) Were adjustments made in the interview process?
      (3) Were interviewers trained to handle this deviation from the original expectations cited in the protocol?
      (4) Were the interviewers more prepared to handle the case interviews than the control interviews?"
7. Assignment of index dates
   a. Assignment of primary index date is based on physician assessment.
      (1) 75 cases had sentinel symptoms prior to primary index date; in 80 cases, timing of symptom onset was classified as unclear.
   b. Alternate index date is based on patient narrative of symptoms and assigned if sentinel symptoms occurred prior to physician assessment.
      (1) For those 75 cases with an assigned alternate index date, alternate index dates were noted for 58 cases. In these cases, the alternate index dates were generally from 1 to 4

days earlier than the primary index date.

(2) Use of an alternate index date could alter the exposure status, and the resulting odds ratio.

c. Comments in some questionnaires indicate symptoms prior to primary or alternate index date but not assigned as sentinel symptoms.

(1) Case descriptions and/or questionnaire data may indicate that the subject had a headache prior to the index date, yet alternate dates are not always assigned. [e.g., See Cases # 18-0025(cough-cold first use), # 71-0026 (cough-cold first use), and # 46-0201 (appetite suppressant)]

d. In the first dose analysis that excludes all 155 cases and associated controls, the number of cases is reduced from 8 to 6, and the number of exposed controls is reduced from 5 to 4.

e. When alternate dates are used as the primary date, cases classified as exposed in the original analysis might become unexposed and some new cases might be considered exposed.

f. "Current use" (all exposure within 24 hours of focal time) is the most biologically plausible OR, based on the pharmacologic and pharmacodynamic properties of the drugs. This OR = 1.61 (p=0.078). The number of exposed cases is this analysis is reduced form 27 overall, to 21.

g. When considering appetite suppressants, only 3 of the 6 exposed cases remain as "current use". [as per the November 4, 1999 report, this unadjusted OR, based on 3 cases and 0 controls, is estimated to be 7.70 (p=0.037). The unadjusted OR for cough cold current use is 1.70 (p=0.073)].

G. Assessment of interview quality

1. Recall period (difference between index date and interview date)

a. Protocol indicates cases and controls should have comparable recall periods but this was not achieved.

b. All but 3 controls were asked to recall a focal date that was no more than 7 days prior to their interview date. In contrast, more than 50% of the cases were asked to recall a focal time that was at least 11 days prior to their index date, and more than 25% were required to recall events at a time that was between 19 and 30 days prior to their stroke event.

c. Recall period for cases was greater than for controls (Appendix 1 Table 6 shows the distribution of elapsed time between focal date and interview date).

2. Interviewer observations

a. 44% of cases have some degree of aphasia; 10% were considered to have a communication burden, fragmentary expression, or no useable speech (Appendix 1 Table 7 shows the distribution of degree of subject aphasia as rated by the interviewer).

b. 0.4% of controls spoke languages other than English; 6% of cases spoke languages other than English (Appendix 1 Table 8 shows the distribution of languages spoken by the subjects during the interview).

c. 11% of controls and 20% of cases had assisted interviews; potential for increased stimulated recall in cases. (Appendix 1 Table 9 shows the distribution of individuals present to assist the subjects during interviews).

d. 6% of cases and less than 2% of controls were considered to have some or great difficulty in language during the interview (Appendix 1 Table 10 shows the distribution of language ability of subjects during the interview, as rated by the interviewer).

e. Interviewer confidence (rating performed by interviewer)

(1) Interviewer confidence was rated as fairly or very confident for about 95% of controls, and for 72% of cases.

(2) The two lowest ratings (somewhat, little or no confidence) were assigned to 1% of controls and 12% of cases.

(3) There is an association between increased severity of aphasia and reduction in interviewer confidence.

(4) Appendix 1 Table 11 shows the distribution of interviewer confidence rating in the subject's ability to give an accurate history.

f. Appendix 1 Table 12 shows the distribution of the subjects' level of certainty regarding PPA exposure by day, on days 0 and -1.

g. Taken together, it appears that the control interviews are of higher quality than the cases.

H. Interview issues and possible observation bias

1. Interviewers were blinded as to the specific hypotheses being tested; it is unknown if the blinding was preserved during the conduct of the study.

2. Interviewers could distinguish cases from controls.

a. Cases often interviewed in hospital, but controls were usually at home.

b. Hospital date indicated on calendar used to help person recall events.

3. "Stimulated recall" used at the end of the interview to help persons remember medications taken during exposure window.

a. Picture book and examination of medicine cabinet used to modify original report of drug exposure.

b. Likely to be applied differently between cases and controls.

(1) Use of picture book not possible during phone interview.

(2) Controls interviewed at home have more access to medicine cabinet than cases interviewed in hospital.

4. There is evidence to suggest that greater probing of the cases may have taken place.

a. The Procedure Manual instructs interviewers to "probe" for

information on exposures.

b. The Procedure Manual instructs interviewers to "allow the subject sufficient time to think about [exposure]" when recording information on exposures.
   (1) This suggests that the interviewer had authority to deviate from script when it appears necessary.

II. Data analysis issues
   A. Assessment and control for confounding
      1. Precision of measurement
         a. Overall, the adjusted and unadjusted ORs are very similar. For example, unadjusted OR=1.67 vs. adj OR=1.49 (overall risk estimate). This indicates either that
            (1) these factors are not risk factors in this population, or
            (2) the measurement of these risk factors is too crude.
         b. Imprecision in representation of a confounder results in incomplete control of confounding.
            (1) Results in "residual" confounding.
            (2) The magnitude of the effect of residual confounding depends (inversely) on the level of precision.
         c. Important confounders were represented with a minimum of precision in the analyses; for other confounders, more detailed data were collected but they were not used in the adjusted analyses.
            (1) Race
               (a) black
               (b) not black
            (2) Self-reported hypertension history
               (a) history
               (b) no history
            (3) Tobacco smoking
               (a) current use
               (b) past use or no use
            (4) Cocaine
            (5) definite or probable use during 3 days preceding event (e.g., stroke)
               (a) no or unlikely use during 3 days preceding event
            (6) Oral contraceptives
               (a) used within 3 days preceding event
               (b) not used within 3 days preceding event
            (7) Others
               (a) BMI
               (b) Family history of hemorrhagic stroke
         d. For example, while a history of hypertension was evaluated by subject interview, no measurement of blood pressure was made nor was there an attempt to evaluate whether blood pressure was well-controlled at the time of the stroke (or index date).

2. Each potential confounding risk factor was considered independently in the model. Many of the risk factors are interrelated, yet there is no discussion of interaction, or that a step-wise process was followed in the model.
3. Inclusion in analyses
    a. Not all important confounders could be included in statistical models due to infrequent exposure (e.g., family history of stroke).
    b. Examples
        (1) confounding by cocaine use could not be controlled in models for women and any exposure to PPA.
        (2) confounding by race could not be controlled for men.

B. Appropriateness of asymptotic methods of analyses vs. exact methods
1. Use of asymptotic methods of analysis make more assumptions than do exact methods.
    a. The number of subjects exposed to appetite suppressants is too few to meet the criterion for the use of asymptotic methods.
    b. These methods require a minimum of 5 observations in each exposure-disease category; seven exposed subjects divided between cases and controls does not satisfy this criterion.
    c. Therefore, analysis of exposure to appetite suppressants should use exact, rather than asymptotic, statistical methods.
2. If exact methods disagree with the results of asymptotic methods, it is the asymptotic methods that are misleading.
3. Asymptotic methods were used to analyze these data when the exact methods did not yield interpretable results.
    a. Asymptotic methods were substituted for exact methods when controlling for cigarette use and oral contraception use in all models that included women.
    b. Asymptotic methods were substituted for exact methods when controlling for cocaine use in all models that included men.
    c. Asymptotic methods were substituted for exact methods when controlling for history of hypertension in all models that included both men and women.
    d. A reflection of the inappropriateness of the asymptotic analysis is the fact that the strength of the association between exposure and disease (i.e., the magnitude of the odds ratio) increases when confounders are "controlled." Instead, the adjusted odds ratio is expected to be smaller than the unadjusted odds ratio.
4. The attempt to control for confounding by including confounders in the exact method of analysis was unsuccessful due to the few exposed subjects.
    a. Interpretation of the results of the exact analysis must include confounding as a very likely explanation for the observed association.
    b. Further, these confounders cannot be considered controlled in the

asymptotic analysis, since the assumption for this analysis is violated.

C. Stability of estimates
   1. Infrequent exposure causes or may cause small differences in measurements to create substantial changes in estimates.
   2. An important example of this instability is in determination of exposure status in the control group.
   3. Sensitivity analyses using both exact and asymptotic methods were carried out whereby the exposure status of randomly selected control patients was changed from unexposed to exposed, one at a time, and the odds ratio recalculated.
   4. Example in subgroup of women only using **exact methods**
      a. Instability in the estimates of association between PPA exposure and hemorrhagic stroke was seen in the primary protocol specified aims (exact procedures; no control for confounding).
      b. If five controls who were exposed to any form of PPA were misclassified as unexposed, there would not be a statistically significant difference between cases and controls (odds ratio = 1.69, lower confidence limit = 0.98).
      c. If three controls who were exposed to PPA in appetite suppressants were misclassified as unexposed, there would not be a statistically significant difference between cases and controls (odds ratio = 3.7, lower confidence limit = 0.94; see Appendix 1 Table 13 for depiction of sensitivity analysis results using exact methods).
   5. Example in subgroup of women only using **asymptotic methods**
      a. In the sensitivity analyses of women only, risk of hemorrhagic stroke was estimated while controlling for race, hypertension, and current smoking status, using asymptotic methods.
      b. If three controls who were exposed to any form of PPA, were misclassified as unexposed, there would not be a statistically significant difference between cases and controls (odds ratio = 1.69, lower confidence limit = 0.98).
      c. If four controls who were exposed to PPA in appetite suppressants, were misclassified as unexposed, there would not be a statistically significant difference between cases and controls (odds ratio = 2.90, lower confidence limit = 0.95; see Appendix 1 Table 14 for depiction of sensitivity analysis results using asymptotic methods).
   6. In order to validate the above findings, sensitivity analyses were repeated whereby exposure status of *different* randomly selected controls was changed for the exact and asymptotic analyses limited to women and appetite suppressant use.
      a. Repeated sensitivity analysis using **exact** procedures: if as few as three controls were misclassified as unexposed, there would not be a statistically significant difference.
      b. Repeated sensitivity analysis using **asymptotic** procedures: if four

(and sometimes as few as three) controls were misclassified as unexposed, there would not be a statistically significant difference.

7. Presentation of results in relation to stated objectives
   a. The overall risks are not significantly elevated. Increased risks are seen only in subset analyses of appetite suppressant use and first use (in 3 day window).
      (1) Table 4: Any PPA OR=1.49 (p=0.084)
      (2) Table 5: Current use OR=1.61 (p=0.078)
      (3) Table 5: Prior Use OR=1.16 (p=.391)
   b. In terms of the stated study objectives,
      (1) Objective 1: Do PPA users have an increased risk: OR=1.49 (p=0.084)
      (2) Objective 2: Association of PPA and stroke by type of PPA exposure:
         (a) Cough-cold: OR=1.23 (p=0.245)
         (b) Appetite suppressants: OR=15.96 (p=0.013)
      (3) Objective 3 – Association of PPA and risk in women
         (a) Appetite suppressant use OR=16.56 (p=0.011)
         (b) First dose use OR=3.13 (p=0.042)

III. Interpretation issues in Case-Control Study of PPA and Hemorrhagic Stroke

A. PPA provides a health benefit through its inclusion as an ingredient in diet drugs and cough/cold remedies. Any possible risk associated with PPA use should be considered in context of these benefits.
   1. PPA is a Category I ingredient (safe and effective) for appetite suppression and nasal decongestion.
   2. PPA is the active component in over-the-counter (OTC) weight management products.
   3. No other Category I ingredients exist for weight management; hence reclassification would effectively remove a therapeutic category from the OTC marketplace.
   4. Numerous OTC and prescription cold/allergy products (both monograph and NDA) contain PPA.
   5. PPA-containing products are marketed throughout the world and have been so for many years.
   6. New PPA-containing products have been approved via NDA in US as recently as one year ago.
   7. PPA is drug of choice in some cold/allergy products due to formulation issues.

B. History preceding Case-Control Study of PPA and Hemorrhagic Stroke
   1. Suspicion of a possible link to hemorrhagic stroke was raised in early 1990s as a result of review of spontaneous reports.
   2. Industry (CHPA, which was then named the Nonprescription Drug Manufacturers Association) submitted data from review of spontaneous reports, hospital discharge summaries, poison control annual reports,

clinical and literature database in 1991.

3. Argument at that time and to this date focused on lack of a biological mechanism.
4. FDA requested additional data.
5. Industry and FDA worked with investigators at Yale School of Medicine to design a case control study to examine the possibility of an association (understood limitations of design).
6. Study was sponsored by Industry at a cost of approximately $5 Million.

C. Findings from this study must be considered in context

1. Absolute numbers of stroke cases identified, found to be eligible, and then enrolled over the 5-year period of the study surveillance demonstrate the hemorrhagic stroke associated with PPA exposure is an extremely rare event.
2. Small numbers could lead to misleading conclusions. Misclassification of exposure in as few as five controls could remove significance.
3. It is possible that the findings could be explained by a combination of bias and chance.
4. No plausible biological mechanism can describe the association described in this study between PPA exposure and hemorrhagic stroke.
5. No consistent pattern of use, timing of exposure, duration of exposure, or concomitant factors provides any insight into a possible biological mechanism.
6. Clinical evidence demonstrates that any rise in blood pressure in response to the therapeutic use of PPA is transient and not clinically relevant. Life events, such as stress, are likely to be associated with similar degrees of blood pressure elevation.
7. The plasma half-life of PPA is between 4-6 hrs. Pharmacologic studies demonstrate that tolerance develops to the blood pressure rising effects of PPA.
8. There is no evidence, clinical or otherwise, to suggest that chronic therapeutic exposure to PPA is associated with cerebrovasculature damage (vasculitis).
9. Findings represent a single data point and need to be considered in the context of all other data.

D. Implications of FDA and Industry reactions to the study findings

1. Careful review of methods and results will be necessary before findings can be used as the basis for regulatory policy. FDA should seek all data (not only manuscript) as part of their review.
2. Rapid communication of findings and resulting publicity may force FDA to react prior to thorough review. As such, posting on FDA website may be damaging.
3. FDA restraint and careful review will minimize consumer fear and industry needs to reformulate their products.

Appendix 1.
TABLES AND FIGURES

Table 1.
DISTRIBUTION OF CASES AND CONTROLS BY REGION

Region	Cases	Controls	Total
CT/MA	249	491	740 (35.4%)
OH/KY	229	448	677 (32.4%)
RI	99	194	293 (14.0%)
TX	129	250	379 (18.1%)
Total	706	1383	2089 (100%)

Table 2.
DISTRIBUTION OF EXPOSED
(IN 3 DAY WINDOW) CASES AND CONTROLS BY REGION

Region	Cases			Controls		
	Cough-Cold	Appetite Suppressants	Total	Cough-Cold	Appetite Suppressants	Total
CT/MA	10	0	10 (33.3%)	13	0	13 (33.3%)
OH/KY	9	4	13 (43.3%)	18	1	19 (48.7%)
RI	2	1	3 (10%)	2	0	2 (5.1%)
TX	3	1	4 (13.3%)	5	0	5 (12.8%)
Total	24	6	30 (100%)	38	1	39 (100%)

Table 3.
AGE AND SEX DISTRIBUTION OF CASES AND CONTROLS

Age Group	Cases			Controls		
	Females	Males	Total	Females	Males	Total
< 20	5	3	8	9	6	15
20 –24	14	14	28	27	28	55
25 – 29	27	15	42	52	29	81
30 – 34	53	36	89	105	72	177
35 – 39	73	59	132	142	115	257
40 – 44	99	85	184	194	167	361
45 – 49	114	109	223	224	213	437
Total	385	321	706	753	630	1383

Table 4.
LEVEL OF VERIFICATION OF PPA EXPOSURE DAYS 0 THROUGH –3

Verification Method	Cases	Controls
Container & ID book	4 (12.9%)	4 (11.4%)
Container only	5 (16.1%)	2 (5.7%)
Pharmacy	2 (6.5%)	0
Telephone & ID book	9 (29.0%)	10 (28.6%)
ID book only	5 (16.1%)	4 (11.4%)
Telephone only	5 (16.1%)	13 (37.1%)
No verification*	1 (3.2%)	2 (5.7%)
Total reported exposures	31	35

Note: subjects may report more than one PPA exposure

Table 5.
CASES AND CONTROLS BY INTERVIEW LOCATION

Study Group	Location of Interview									Total
	Hospital	Rehab Center	Home	Office	Friend's home	Other	Phone	Not specified	Missing	
Controls	42	0	363	308	4	598	44	2	22	1383
	3.0%	0	26.2%	22.3%	0.3%	43.2%	3.2%	0.1%	1.6%	100%
Cases	465	66	134	2	3	25	3	0	8	706
	65.8%	9.3%	19.0%	0.3%	0.4%	3.5%	0.4%	0	1.1%	100%

Table 6.
DISTRIBUTION OF ELAPSED TIME BETWEEN FOCAL DATE AND INTERVIEW DATE

	Cases	Controls
Mean Difference	12.8 days	3 days
Median Difference	11 days	3 days
Maximum days difference	30 days	9 days

Table 7.
DEGREE OF SUBJECT APHASIA AS RATED BY INTERVIEWER

Study Group	Aphasia Rating								TOTAL
	No deficits	Minimal handicap	Loss of fluency	Little/No assistance	Familiar topics possible	Fragmentary expression	No usable speech	Missing	
Controls	14 1.0%	2 0.1%	0	0	0	0	0	1367 98.8%	1383 100%
Cases	383 54.2%	148 21.0%	63 8.9%	25 3.5%	29 4.1%	25 3.5%	1 0.1%	32 4.5%	706 100%

Table 8.
LANGUAGE SPOKEN BY SUBJECT DURING INTERVIEW

Study Group	Language of Interview					Total
	English	Spanish	Portuguese	Other	Missing	
Controls	1360 99.6%	5 0.4%	0	0	18 1.3%	1365 100%
Cases	656 93%	32 4.5%	3 0.4%	7 1.0%	8 1.1%	706 100%

Table 9.
IDENTIFICATION OF INDIVIDUALS PRESENT DURING INTERVIEW

Study Group	Relationship of Individual Present							Total
	None	Spouse	Child	Other Relative	Friend	Other	Missing	
Controls	1209 87.4%	32 2.3%	59 4.3%	10 0.7%	8 0.6%	41 3.0%	24 1.7%	1383 100%
Cases	556 78.7%	21 3.0%	12 1.7%	32 4.5%	4 0.6%	63 8.9%	18 2.5%	706 100%

Table 10.
LANGUAGE ABILITY OF SUBJECT DURING INTERVIEW,
AS RATED BY THE INTERVIEWER

Study Group	Ability				Total
	No problem	Some difficulty	Great difficulty	Missing	
Controls	1350 97.6%	16 1.2%	1 0.1%	16 1.2%	1383 100%
Cases	642 90.9%	18 2.5%	31 4.4%	15 2.1%	706 100%

Table 11.
RATING OF INTERVIEWER CONFIDENCE IN SUBJECT ABILITY TO GIVE ACCURATE HISTORY

Study Group	Confidence Rating						Total
	Very confident	Fairly Confident	Confident	Somewhat Confident	Little/no confidence	Missing	
Controls	919 66.4%	370 26.8%	47 3.4%	25 1.8%	4 0.3%	18 1.3%	1383 100%
Cases	283 40.1%	221 31.3%	104 14.7%	61 8.6%	26 3.7%	11 1.6%	706 100%

Table 12.
LEVEL OF CERTAINTY OF PPA EXPOSURE BY DAY FOR DAYS 0 AND -1

Cough and Cold Preparations				
Day-0				
	Definite	**Probable**	**Uncertain**	**Total**
CASE	15	0	2	17
Control	15	1	1	17
Day –1				
CASE	15	0	4	19
Control	18	2	2	22
Appetite Suppressants				
Day -0				
CASE	2	1	0	3
Control	0	0	0	0
Day –1				
CASE	2	1	0	3
Control	0	0	0	0

Table 13.
SAMPLE SENSITIVITY ANALYSIS OF EXACT METHODS:
RISK IN WOMEN ONLY,
EXAMINING PPA EXPOSURE IN APPETITE SUPRESSANT ONLY

Number of unexposed controls changed to exposed controls	Odds Ratio	Lower Confidence Limit
0	12.19	1.87
1	10.7	1.61
2	5.5	1.19
3	3.7	0.94

Table 14.
SAMPLE SENSITIVITY ANALYSIS OF ASYMPTOTIC METHODS: RISK IN WOMEN ONLY, EXAMINING PPA EXPOSURE IN APPETITE SUPRESSANT ONLY

Number of unexposed controls changed to exposed controls	Odds Ratio	Lower Confidence Limit
0	14.5	2.17
1	8.0	1.82
2	5.0	1.39
3	3.5	1.09
4	2.9	0.95

Appendix 2.
DESCRIPTION OF CASES AND CONTROLS EXPOSED TO PPA

Table 1.
CURRENT* PPA USERS: DESCRIPTION OF CASES
FIRST USE WITHIN 3 DAY WINDOW (ALL ARE COUGH-COLD EXPOSURES)

CASES											
ID No.	**Race Sex**	**Age**	**Wt.**	**Stroke Date & Type**	**Dose Date**	**PPA Product Amount**	**Other Exp.**	**Smoker**	**Stroke Hx**	**Other**	**Caffeine**
18-0025	NBF	42	150	1/25/97 SAH	1/25 1 hr Day 0	2 tab cold med	2 tab Tylenol Day –1 Ocs for 2 months	No	None	Prior headaches	N/A
20-0092	NBF	48	140	10/23/95 IPH	10/23 Day 0	Tavist D 2 tab	ABAP/ASA	Yes 20/day	None	Prior headaches	8.5cups coffee/day
20-0297	NBF	45	105	7/3 IPH	7/3 Day 0	2 T cold med	Exedrin 2 tabs	Ex 10/day	None	-	-
35-0109	NBM	21	200	2/21/SAH	2/21 Day 0	2 "big gulps" liquid cough med	NyQuil 4 tbs	Yes 35/day	None	Heavy Drinker, illicit drugs	10 glasses soda/day
45-0008	NBF	42	112	7/3 SAH	7/3 Day -1	1 tab for nasal congestion	Nuprin 3/tab/day Claritin 1 tab/day	No	None	Headache	8 glasses soda/day
46-0093	NBF	34	148	12/25 SAH	12/25 Day 0 & Day -1	2 tab cold med	Revco Children's Pain Rel. Cold Zoloft 1 tab Tranzodone	Yes 20/day	None	4 beers/week	10 cups coffee/day
71-0026	NBF	31	115	7/29 SAH	7/29 Day -1	Entex 1 tab	Indocin Bacterium	Yes 30/day	Yes	Moderate Drinker. HTN (no meds) prior headache diabetic	6 glasses soda/week
71-0039	NBF	30	103	11/5 SAH	11/5 Day 0	Antihist. 1 tab	OC	No	Yes	Prior headache	1 glass soda/week

Table 2.
CURRENT* PPA USERS: DESCRIPTION OF CONTROLS
**FIRST USE WITHIN 3 DAY WINDOW (ALL ARE COUGH-COLD EXPOSURES)*

CONTROLS											
ID No.	**Race Sex**	**Age**	**Wt.**	**Stroke Date & Type**	**Dose Date**	**PPA Product Amount**	**Other Exp.**	**Smoker**	**Stroke Hx**	**Other**	**Caffeine**
06-0140B	NBF	25	195	-	Day 0 & Day –1	Cough 1 swallow/day	None	No	None	Gestational Diabetic	1 cup tea/day
20-0205B	BM	34	225	-	Day 0 & Day –1	Alka Seltzer + Cold 2 tabs ID, 4 tabs Day -1	None	No	Yes	Heavy drinker 42 beers + 3 mixed drinks	2 cups coffee/day
46-0244B	NBF	40	?	-	Day 0 & Day -1	Cold med 2 effervescent tabs/day	NyQuil ES Tyl. Augmentin Darvocet	Yes 6.5/day	Yes	Cerv. Cancer	5.6 glass soda/day
71-0038A	NBF	36	125	-	Day -1	Antihist 1 tab	Advil	Yes 20/day	None	Light drinker	6 cups coffee/day coffee 2 cups tea/day tea 1 glass soda/day
71-0349A	NBF	41	190	-	Day -1	Sinus 1 tab	None	Ex 20/day	Yes	Light drinker	2 cups coffee/day 1 glass soda/day

Table 3.

CURRENT* PPA USERS: DESCRIPTION OF CASES

**FIRST USE WITHING 3 DAY WINDOW (ALL APETITE SUPPRESANT USERS)*

CASES											
ID No.	**Race Sex**	**Age**	**Wt.**	**Ht.**	**BMI**	**HTN**	**Current Smoker**	**Cocaine (3 Day)**	**Oral Contraception**	**Desire to Lose Wt.**	**Desired Amt. (lbs.)**
31001	BF	22	160	64	27.49	No	No (Ex)	No	Yes	Yes	20
33059	NBF	46	120	66	19.38	Yes (1yr; no meds)	No (Never)	No	No	No	
460080	NBF	32	155	65	25.81	No	No (Never)	No	No	Yes	40
460201	NBF	38	200	67	31.35	No	No (40/d)	No	No	Yes	50
620094	NBF	26	105	62	19.22	No	Yes (30/d)	No	No	Yes	10
710398	NBF	38	126	59	25.47	Yes (10 yrs. no meds)	Yes (20/d)	No	Yes	Yes	10

Note: No history of MI, Angina, CHF, heart surgery or diabetes in any of these patients.

Table 4.

CURRENT* PPA USERS: DESCRIPTION OF CONTROLS

**FIRST USE WITHING 3 DAY WINDOW (ALL APETITE SUPPRESANT USERS)*

CONTROLS											
ID No.	**Race Sex**	**Age**	**Wt.**	**Ht.**	**BMI**	**HTN**	**Current Smoker**	**Cocaine (3 Day)**	**Oral Contraception**	**Desire to Lose Wt.**	**Desired Amt. (lbs.)**
350043	NBF	44	223	64	38.31	No	No (Never)	No	No	Yes	50

Note: No history of MI, Angina, CHF, heart surgery or diabetes in any of these patients.