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September 21, 2001

Commissioner of Food and Drugs
Food and Drug Administration
c/o Dockets Management Branch (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 01N-0196
Phenylpropanolamine; Proposal to Withdraw Approval of New Drug Applications and Abbreviated New Drug Applications; Opportunity for a Hearing
66 Fed. Reg. 42,665-71 (Aug. 14, 2001)

Dear Commissioner:

As regulatory counsel for American Home Products Corporation ("AHPC"), Arnold & Porter hereby submits comments on the referenced Notice of Opportunity for a Hearing ("NOOH") on behalf of AHPC.

SUMMARY OF AHPC'S REQUEST

1. AHPC requests the withdrawal of its listed New Drug Applications ("NDAs") for products that once contained phenylpropanolamine ("PPA"). Last year, AHPC immediately answered FDA's request to the pharmaceutical industry to discontinue marketing products containing PPA. It has no commercial interest in resuming marketing of such products. Thus, the NDAs cover drug products that are no longer being marketed and may be withdrawn in response to AHPC's request pursuant to 21 C.F.R. §314.150 (c), thereby rendering the NOOH moot.

2. With respect to the proposal to withdraw the NDAs pursuant to 21 U.S.C. § 355 (c) (2), AHPC believes that the NOOH may be misunderstood regarding the strength and conclusions of the Hemorrhagic Stroke Project ("HSP"). The NOOH is an advocacy proposal from the Center for Drug Evaluation and Research (CDER"). Because AHPC has no further commercial interest in the products, it has requested that the NDAs be withdrawn. The company will not request a hearing (and thereby delay withdrawal of NDAs) in order to dispute the contents of the NOOH. In so doing, however, AHPC does not acknowledge the truth of, and does not intend to be bound by, the agency's assertions in the NOOH.

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3. AHPC is concerned that the statements in the NOOH regarding the HSP may have unintended and unwarranted consequences in ongoing product liability litigation. AHPC requests that FDA clarify, in its final order on this matter, that the NOOH and final order are not intended to be used as evidence in a product liability suit. The NOOH's description and interpretation of the HSP have not been examined in an evidentiary hearing and do not constitute adjudicated agency findings.

STATEMENT OF INTEREST

AHPC has cooperated with FDA's request regarding its PPA-containing products. AHPC marketed a number of over-the-counter ("OTC") products that contained PPA before November 6, 2000. Since then, AHPC has, with respect to each product, either reformulated it, withdrawn it from the market pending reformulation, or simply discontinued its sale. AHPC has no plans to reintroduce any PPA-containing product to the market.

The NOOH proposes to revoke approval of a number of NDAs that cover products that contain PPA. Whitehall-Robins Healthcare ("WHR") is the owner of two of these NDAs: NDA 12-436 (Dimetapp Extended-Release Tablet) and NDA 13-087 (Dimetapp Elixir). A. H. Robins Company owns NDA 11-694 (Dimetane-DC Syrup). WHR and A. H. Robins Company are unincorporated divisions of AHPC. Accordingly, AHPC has an interest in whether FDA withdraws those NDAs and the manner in which such a withdrawal is effectuated.

1. REQUEST FOR WITHDRAWAL OF NDA APPROVALS

AHPC formally requests the withdrawal of approval of NDA 11-694, NDA 12-436, and NDA 13-087 under the provisions of 21 C.F.R. § 314.150 (c), because the products covered by these NDA are no longer being marketed.[1] Withdrawal of these NDAs under these circumstances is authorized and, if executed, would obviate further proceedings under the NOOH as to these NDAs.

[1] Whitehall-Robins previously requested that FDA withdraw approval of NDA 13-087 pursuant to 21 C.F.R. § 314.150(c). That request was made on May 27, 1999. By letter dated March 28, 2000, FDA advised Whitehall-Robins that it had begun the requested withdrawal. That process, however, was not completed before the issuance of the NOOH.

2. DESCRIPTION OF THE HSP IN THE NOOH

AHPC recognizes that the NOOH is merely a proposal from CDER. *See* 66 Fed. Reg. at 42,670. CDER is not obligated to assure that an NOOH is complete or properly qualified in its initial presentation of information. The statements in an NOOH are the claims of a proponent, an advocate, in support of a conclusion. Should an interested party present evidence demonstrating a genuine dispute of material fact, the Commissioner would order a hearing in which CDER would have the burden of proof. 21 C.F.R. § 314.200.[2]

Where, as here, an NDA applicant requests withdrawal of its NDA under 21 C.F.R. § 314.150 (c), it and FDA can concur in the result without having to litigate the contents of the NOOH issued under 21 U.S.C. § 355 (e) (2). Public policy should not require an interested party to request a hearing in order not to avoid being bound by statements in an NOOH with which it disagrees. Not only does the request trigger a costly and time-consuming process; it also burdens FDA and diverts taxpayer resources from other matters. Unfortunately, plaintiffs in product liability litigations may argue that the failure to request a hearing represents an admission to the truth of the NOOH and that the NDA holder is bound by the contents of the NOOH. For the record, therefore, AHPC does not acknowledge the truth of any statements made in the NOOH and does not intend that it be bound by the statements contained in the NOOH or any subsequent order relating to it.

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[2] Were an interested party to demand a hearing on the question of safety, it would be entitled to one because the many questions about the limitations of the HSP create a "genuine and substantial issue of fact that requires a hearing." 66 Fed. Reg. at 42,671. The Commissioner may grant summary judgment only where the issue is one covered by particularized regulations such as those governing the standards for an "adequate and well-controlled" study of drug effectiveness. *See Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609, 621 n.17 (1973) (holding that summary judgment could be issued by the Commissioner because certain regulations defining acceptable evidence of efficacy are "precise" and "[a] mere reading of the study submitted will indicate whether the study is totally deficient" with respect to those "precise" parts of the regulations). Such precision is lacking in the safety regulations, and thus it is likely that summary judgment can never be issued where safety is at issue – and certainly not where, as here, there is strong evidence that the evidence relied on by CDER has scientific limitations. *See E. R. Squibb & Sons, Inc. v. Weinberger*, 483 F.2d 1382, 1386 (3d Cir. 1973) ("the standard applied to determine the propriety of summary judgment on the issue of safety has not been made clear by the FDA").

AHPC's concerns stem from the NOOH's description of the HSP and its results. The NOOH does not, in AHPC's opinion, adequately discuss the limitations of the HSP that have been raised by expert epidemiologists. Moreover, the NOOH describes the results in a way that may be interpreted as reaching conclusions that go far beyond what the HSP investigators concluded.

Part of this difficulty may be attributed to the decision of CDER to rely on an unpublished report of the HSP instead of the later published version. The NOOH cites only the unpublished May 2000 report of the HSP and subsequent unpublished (and non-public) analyses of data from this study. Horwitz, *et al.* "Phenylpropanolamine & Risk of Hemorrhagic Stroke: Final Report of The Hemorrhagic Stroke Project" (Reference 1 in the NOOH) (hereafter, "Final Report"). CDER makes no reference to the peer-reviewed version published in December 2000. Kernan WN, Viscoli CM, Brass LM, Horwitz RI. Phenylpropanolamine and the Risk of Hemorrhagic Stroke. *N. Eng. J. Med.* 2000; 343:1826-32 (hereafter, "Kernan 2000"). Nor does CDER refer to a subsequent Letter to the Editor published by the HSP investigators. Kernan WN, Viscoli CM, Brass LM, Horwitz RI. Response to Letters to Editor on Phenylpropanolamine and Hemorrhagic Stroke. *N. Eng. J. Med.* 2001; 344:1095 (hereafter, "Kernan 2001").

Significant differences exist in the conclusions reached in the Final Report and the later published version and related correspondence. The NOOH does not reflect these differences. For example:

> NOOH (August 2001)
>
> "[T]he Yale study [*i.e.*, the HSP] ... ***demonstrated*** that the association between phenylpropanolamine use (as an appetite suppressant and first time use as a nasal decongestant) and an increased risk of hemorrhagic stroke was ***significant*** and was ***most striking in women***." 66 Fed. Reg. at 42670 (emphasis added).
>
> Unpublished Final Report (May 2000)
>
> "In conclusion, the results of the HSP ***suggest*** that PPA increases the risk for hemorrhagic stroke." Final Report at 26 (emphasis added).
>
> Published Report (December 2000)
>
> "Among women between the ages of 18 and 49 years, the use of a product containing phenylpropanolamine as an appetite suppressant was associated with

an increased risk of hemorrhagic stroke. There was also ***a suggestion of an association*** in women with any first use of phenylpropanolamine, which involved only cough or cold remedies. ***No significantly increased risk of hemorrhagic stroke was observed among men*** who used a cough or cold remedy that contained phenylpropanolamine. Because no male subject reported the use of appetite suppressants containing phenylpropanolamine and only two reported the first use of a product containing phenylpropanolamine, ***we could not determine whether men are at increased risk for hemorrhagic stroke under these conditions.***" Kernan 2000 at 1830-31 (emphasis added).

"In conclusion, the results of the Hemorrhagic Stroke Project ***suggest*** that phenylpropanolamine in appetite suppressants, and ***possibly*** also as a cold and cough remedy, is an independent risk factor for hemorrhagic stroke ***in women.***" Kernan 2000 at 1831-32 (emphasis added).

Subsequent Correspondence from the HSP Investigators

"Among women who were 18 to 49 years of age, the first use of any product containing phenylpropanolamine was associated with an increased risk of hemorrhagic stroke (odds ratio, 3.13, $p = 0.08$). ... Although ***this odds ratio did not reach conventional criteria for statistical significance ($p < 0.05$)***, this criterion may be too stringent for evaluating potentially harmful associations." Kernan 2001 at 1095 (emphasis added).

In other words, contrary to what one might interpret from the description in the NOOH first quoted above, the HSP investigators ***do not claim*** that:

- any association was demonstrated (or even suggested) in men between PPA-containing products and hemorrhagic stroke, whether with first use or in cough-cold products or in appetite suppressants, or
- any association was demonstrated between PPA-containing cough-cold products with any use and hemorrhagic stroke in women, or
- the association between PPA-containing cough-cold products with first use and hemorrhagic stroke was "demonstrated" to be statistically "significant."

Similarly, the NOOH states that the study was well-designed and executed successfully; the NOOH mentions only a *single* limitation of the study. Specifically, the NOOH asserts (66 Fed. Reg. at 42,670):

> The case-control design was best suited for this study because the outcome under investigation was rare. All reasonable steps were taken to minimize bias and confounding. Quality control measures were built into the design. Analyses were appropriate for the type of study and were performed according to the protocol. The strengths of the study lie in the clarity of its objectives, the meticulous adherence to sound epidemiological practices in its design and execution, and the consistency of the findings, regardless of the analytic methods. Its only limitation was in the power and sample size....

The NOOH does mention "concerns about the design of the study" raised by industry representatives at the Nonprescription Drugs Advisory Committee ("NDAC") that "industry representatives ... believed made interpretation of the results difficult." The NOOH, however, does not indicate that the "industry representatives" included six expert epidemiologists whom the agency itself has used as consultants. Nor does the NOOH describe those epidemiological concerns about a multitude of limitations in the design and execution of the HSP.[3] AHPC believes that the NOOH could be misinterpreted to mean that no credible scientific issues were raised.

A third example of the way in which the NOOH might be misinterpreted relates to its discussion of the votes of the NDAC. The NOOH potentially creates the misimpression that the NDAC agreed (rather than disagreed) that the HSP supported certain conclusions. For example, with respect to the possible association between hemorrhagic stroke and PPA in ***cough-cold products***, the Committee voted –

[3] In fact, CDER has not included in the list of NOOH references an important document regarding the scientific concerns about the HSP. The Consumer Healthcare Products Association commissioned four experts to review and comment on the HSP. The expert report listing concerns about epidemiological study issues such as selection and matching of controls, confounding, and bias, as well as sample size and robustness of the data, was submitted to FDA. It is not part of the docket of the NOOH. We are attaching it for completeness of the record.

- 8-6 that the HSP was ***not*** conclusive regarding women aged 18-49. Transcript of NDAC Meeting (Oct. 19, 2000) at 238 (hereafter, "Tr.").
- 14-0 that the HSP was ***not*** conclusive regarding men aged 18-49. *Id.*
- 9-5 that the HSP was ***not*** conclusive regarding the general population between ages 18 and 49. *Id.* at 240.

The NOOH does not set forth these votes; rather, it only lists 3 of the 12 votes taken at the meeting. 66 Fed. Reg. at 42,670; Tr. at 231, 232, 238, 239, 240, 253, 264, 265 (the 12 votes).

The advocacy nature of the NOOH is not improper, but it reinforces the need for FDA to clarify that statements in the NOOH are not findings after an adjudication by an evidentiary hearing on the merits. Absent such a clarification, AHPC fears that plaintiffs' lawyers are likely to contend that the NOOH constitutes an official scientific finding by FDA that the HSP is definitive and beyond legitimate scientific discussion. Further, they might also contend that companies, merely by not requesting a hearing, acknowledge the validity of, and are bound by, the agency's statements in the NOOH. Hence, for the record, we repeat that AHPC does not acknowledge the truth of any statements made in the NOOH and does not intend itself bound by the assertions contained in the NOOH or any subsequent order relating to it.

3. REQUEST FOR FDA STATEMENT REGARDING NOOH

AHPC respectfully requests that the Commissioner advise the public that statements made in the NOOH are not intended to be used as evidence in product liability cases. As noted, the NOOH is CDER's advocacy statement of the issues. It does not represent agency findings made after an adjudicated evidentiary proceeding. Nor is the purpose of the notice to affect rights of litigants in private civil cases. Therefore, FDA should clearly state that the NOOH should not be used as evidence in product liability litigations. (In the event that FDA does not proceed to withdraw approval of the AHPC NDAs under 21 C.F.R. § 314.150 (c), but goes forward under 21 U.S.C. § 355 (e) (2), a similar disclaimer would be appropriate for FDA's final order.)

The Agency is aware that its actions may have repercussions in private product liability cases and may create undesirable incentives to contest FDA proposals. In late 1998, FDA proposed to issue a list of drugs withdrawn or removed from the market for reasons

of safety or effectiveness. Notice of Proposed Rulemaking: List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness, 63 Fed. Reg. 54,082 (Oct. 8, 1998). Responding to comments about the risk that the list would be used in product liability litigation, FDA took the position in its Final Order that such use would be improper. List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness, 64 Fed. Reg. 10,944, 10,945 (Mar. 8, 1999). The agency stated that:

> Compounding pharmacists and physicians are the intended audience for this rule. . . . This list is not intended to be used as evidence in a product liability suit, and the addition of language designed to minimize the potential effect of the list in litigation is unnecessary to fulfill its intended purpose.
>
> * * *
>
> The agency wishes to emphasize that the inclusion of a drug product on the list does not mean that the drug product was marketed negligently, was defective, or was marketed in breach of any warranty. Even after exhaustive clinical studies, safety problems may not become apparent until a drug product has been in commercial distribution for a significant amount of time, so the fact that a drug was removed or withdrawn from the market does not mean that the drug was improperly placed in commercial distribution.

Product liability litigation about products containing PPA has already begun. In fact, over 200 suits (including 17 class actions) have been filed in federal and state courts against PPA manufacturers. Plaintiffs will surely attempt to use FDA's statements from this withdrawal proceeding as evidence. Further, in responding to any challenges companies may raise to the HSP in court, plaintiffs may argue that the NOOH should be read as endorsing the HSP or definitively interpreting its results.

Ramon Lopez, a noted plaintiff's lawyer, dispelled any doubt about these possibilities. At a conference about PPA litigation in San Diego on August 16, 2001 – two days following publication of the NOOH – Mr. Lopez described the NOOH as "his birthday present" from FDA.

Accordingly, a statement from FDA paralleling what it has already said with respect to the "List of Drug Products Withdrawn for Reasons of Safety" is consistent and appropriate. (Note that, in the event FDA withdraws approval of the AHPC NDAs as requested under 21 C.F.R. § 314.150 (c), AHPC would expect that PPA will be added to the List, and the statement already made by FDA would apply in that circumstance. Thus, AHPC is not seeking any statement other than one that FDA has already made in this kind of situation.)

CONCLUSION

AHPC respectfully requests that:

1. The Commissioner withdraw the named AHPC NDAs under 21 C.F.R. § 314.150 (c), as the products covered by the NDAs are no longer being marketed, rather than proceed under 21 U.S.C. § 355 (e) (2).

2. The Commissioner formally state that statements made in the NOOH, and any final order if the agency proceeds under 21 U.S.C. § 355 (e) (2), are not intended to – and should not – be used as evidence in product liability cases.

Sincerely,

Arnold & Porter
William W. Vodra
Partner

Exhibit: CHPA Submission to FDA's Nonprescription Drugs Advisory Committee (September 21, 2000).

cc: Sharon Heddish
Vice President
WHR Worldwide Regulatory Affairs

CHPA
FOUNDED 1881

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

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

September 21, 2000

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

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

To Members of the FDA Nonprescription Drugs Advisory Committee
and FDA Consultants and Staff:

The Consumer Healthcare Products Association (CHPA)[1] submits this background document for the October 19, 2000, discussion by the Food and Drug Administration (FDA) Nonprescription Drugs Advisory Committee and invited experts on the final report of the Hemorrhagic Stroke Project (HSP) case-control study of phenylpropanolamine (PPA) and hemorrhagic stroke. You have been asked to review several volumes of information, and with that in mind, we intentionally made this document brief, supplementing material you have received from FDA. We have attempted to highlight important information, particularly the report of an independent panel of epidemiology experts, that you should consider as you review the results from the HSP.

For a number of years CHPA's Phenylpropanolamine Working Group (hereinafter referred to as CHPA members) has been studying, and providing FDA materials on, the safety and effectiveness of PPA as an over-the-counter (OTC) appetite suppressant. CHPA members market all the major national brands and house brands of appetite suppressants and cough/cold products that contain PPA. Submissions to FDA have included reports from effectiveness trials, which led to FDA's approval of PPA as an effective ingredient for weight loss through the OTC Review, and study reports and other information supporting the safe use of PPA as an appetite suppressant. As part of this overall effort, CHPA members agreed in 1992 to FDA's request for additional epidemiologic information on the safety of PPA and funded the HSP study, which was conducted by principal investigators from Yale University.

FDA had concluded at the time the agency asked sought additional information in the form of an epidemiologic study (i.e., the HSP study):

> "The agency does not believe, however, based on information currently available, that phenylpropanolamine used in OTC weight control drug products represents a substantial public health risk. The agency, therefore, does not believe that it is necessary to remove

[1] CHPA is the 119-year-old trade association representing producers of nonprescription medicines and dietary supplements. CHPA has over 200 member companies across the manufacturing, distribution, supply, research, and advertising sectors of the self-care industry.

... P.O. ... • Tel: 202-429-9260 • Fax: 202-223-6835 • www.chpa-info.org

phenylpropanolamine weight control drug products from the OTC market while additional data are being obtained." [emphasis added][2]

Every reasonable effort was made by CHPA members and the principal investigators to incorporate FDA's recommended elements and other suggestions in designing the HSP study. An independent advisory committee was set up to help resolve questions that might arise over the course of the study and its analysis. CHPA members sponsored the study and have been involved in the review and interpretation of the study results. The preliminary study results raised many questions, which the CHPA members thoroughly discussed with the HSP investigators.

CHPA members also spent considerable time and effort reviewing primary data to evaluate the study results and determine how it should be interpreted. They concluded that, despite the best efforts of the investigators, the HSP study results provided no definitive answers. Furthermore, the results raised several questions on the robustness of the study design. As a result of the discrepancies and contradictions in the analyses of the subsets of data and the concerns raised on the soundness of the methods, CHPA members sought input from leading independent epidemiologists and statisticians to help interpret the results. Among those experts are:

- Charles H. Hennekens, MD, DrPH, MPH, Visiting Professor of Medicine and Epidemiology and Public Health, University of Miami School of Medicine
- Robert Hirsch, PhD, Professor of Epidemiology and Biostatistics, George Washington University School of Public Health
- Brian L. Strom, MD, MPH, Chair, Department of Biostatistics and Epidemiology, and Director, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine

CHPA members asked a separate, independent panel of experts in epidemiology and neurology to meet and provide an opinion about the strength of the study and its support of the conclusions made by the study investigators. The panel's report, which is in **Appendix A**, contributes critically important information for the advisory committee's deliberations on the PPA issue.

The members of the expert epidemiology panel are:

- Lewis H. Kuller, MD, DrPH, MPH, Chairman, Department of Epidemiology, University of Pittsburgh
- Philip B. Gorelick, MD, MPH, FACP, Professor of Neurological Sciences, Rush Medical College
- Robert B. Wallace, MD, Chairman of Preventive Medicine, University of Iowa
- Noel S. Weiss, MD, DrPH (Panel Chair), Chairman of Epidemiology, University of Washington

[2] Over-the-Counter Drug Products Containing Phenylpropanolamine; Required Labeling; Proposed Rule [61 F.R. 5912-16 (2/14/96)]

CHPA members urge each of you who are considering the results of the HSP to read the epidemiology expert panel's entire meeting report on its review of the HSP study and the reported results. The report and the curricula vitae of the panel members are included in Appendix A.

The results of the expert reviews are very instructive in considering how to evaluate this study in relationship to the extensive database on PPA, which strongly supports the ingredient's safety as an OTC ingredient. None of the experts that were consulted by CHPA members concluded that the HSP study substantiates a clear association between use of PPA and subsequent development of hemorrhagic stroke. These experts are in general agreement that the HSP study, as large an effort as it might have been over its 5-year span, suffers from significant limitations, many of which are attendant to this type of research. The epidemiology expert panel concludes (see Appendix A for complete report):

> "We emphasize that this study represents a significant undertaking and the investigators made strong efforts to control for many variables. Importantly, there were very few cases of hemorrhagic stroke in PPA users. The small number of cases in conjunction with the large number of potential confounders makes a robust statistical analysis impossible to accomplish. A single, case-control study with results of this type, can, at best, provide a signal of an association. Nonetheless, an alternative conclusion of no association is plausible as well. Although this panel is not qualified to render a public health decision, given that we have not reviewed the entire safety database on PPA, we believe that this study, by itself, does not suggest that use of PPA is creating an imminent public health concern. It could at best be used as only supportive evidence if there are other scientifically valid confirmatory data available. In addition to the ambiguous epidemiological data relating PPA and hemorrhagic stroke, the HSP report offered no plausible pharmacological mechanism that might underlie a causal relationship. . . ."

Hence, the CHPA members, FDA, and the advisory committee members have before them a situation where the principal investigators strongly support their study, which represented a significant investment of time and resources, while leading epidemiologists focus our attention on those aspects of the study that raise fundamental questions about its contribution to an understanding of PPA's safety.

In the view of the CHPA members, 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, even using a one-sided test, does not show a significant relationship between PPA use and subsequent development of 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. CHPA member comments on these and other issues in interpreting the HSP study results are presented in **Appendix B**, a document that was submitted to FDA shortly after the investigators submitted the study report. (The CHPA document was also provided at Tab 20 in the FDA background material sent to you in August.)

Historical Perspective

PPA has been marketed for over 50 years and is currently used in more than 50 OTC medicines as a decongestant to relieve cold and flu-like symptoms and as an appetite suppressant. PPA was reviewed by FDA's cough/cold panel as a nasal decongestant and FDA's miscellaneous internal panel as a diet aid. Both panels found PPA to be generally recognized as safe and effective for its intended uses, when used according to label directions.

Over the years, various putative safety issues have been raised about PPA, and each has been affirmatively addressed through detailed submissions and additional studies by CHPA members. See, for example, CHPA submissions to Docket 81N-002 in May 1989 and on September 6, 1991. The text of the May 1989 submission is **Appendix C** to this document. It includes summaries of clinical studies and independent analyses supporting PPA's safety.

A report of an epidemiologic analysis of the purported association between phenylpropanolamine hydrochloride diet aids with hemorrhagic stroke in the 15- to 44-year-old U.S. female population is **Appendix D**. The results of the analysis, which was conducted by a CHPA member company, "do not suggest or even signal a trend towards an increase in the risk of hemorrhagic stroke associated with PPA single ingredient diet aid use. . . ." The analysis used data from a national cross-sectional study, the National Hospital Discharge Survey (NHDS), to estimate the background rate of hemorrhagic strokes in the U.S. population (i.e., the expected number of strokes). It then compared the observed (reported) number of strokes in the PPA diet aid user population to the expected number of strokes, in a manner similar to a morbidity ratio (i.e., observed reports divided by expected reports, O/E). See the analysis report, which was included in the September 1991 CHPA submission and is **Appendix D** to this document.

Conclusion

CHPA members conclude that, in the context of all the other studies supporting PPA's safety and effectiveness, the inherent limitations of epidemiologic studies, the specific issues and questions about the HSP study raised by a group of leading independent epidemiologists and statisticians, as well as the extensive history of safe use of PPA, the ingredient remains safe and effective as an OTC appetite suppressant and nasal decongestant when used according to label directions. CHPA member companies remain committed to working with the FDA and the academic community to ensure the safety of these products.

Sincerely yours,

R. William Soller, Ph.D.

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

Appendices listed on next page

WS/lct/FDA comments 9-21

List of Appendices

A: Epidemiology Expert Panel Meeting Report
Cirricula Vitae of Panel Members

B: CHPA Comments (May 24, 2000) on the Hemorrhagic Stroke Project Report

C: May 1989 Submission on the Safety of Phenylpropanolamine as an OTC Ingredient

D Epidemiologic Analysis (September 3, 1991)

Consumer Healthcare Products Association

Appendix A

Epidemiology Expert Panel Meeting Report
Review of Yale Hemorrhagic Stroke Project
April 19, 2000

Curricula Vitae of Panel Members

Philip Gorelick, MD, MPH., FACP, Professor of Neuorological Sciences, Rush Medical College

Lewis Kuller, MD, DrPH, MPH, Chairman, Department of Epidemiology, University of Pittsburgh School of Health

Robert Wallace, MD, Chairman of Preventive Medicine, University of Iowa

Noel Weiss, MD, DrPH. (Panel Chair) Chairman of Epidemiology, University of Washington-Seattle

Epidemiology Expert Panel Meeting Report
Review of Yale Hemorrhagic Stroke Project

OVERVIEW:

The Consumer Healthcare Products Association (CHPA) requested that a panel of epidemiologic experts meet to give their opinion on the results of an epidemiology study, The Hemorrhagic Stroke Project (HSP), conducted to determine the relative risk of having a hemorrhagic stroke event coincident with taking phenylpropanolamine either as a cough/cold medication or as an appetite suppressant. CHPA is the trade association that represents the nonprescription drug industry. This panel was convened under the express condition that it would be independent from CHPA and the pharmaceutical industry and be free to express its opinions and conclusions.

The members of the panel represented expertise in the design and conduct of case-control studies involving cardio- and cerebro-vascular diseases, neurology and cardiology. The panel consisted of:

Dr. Philip Goerelick, MD, MPH, FACP (Rush Medical College)
Dr. Lewis Kuller, MD, DrPh, MPH (University of Pittsburgh)
Dr. Robert Wallace, M.D. (University of Iowa)
Dr. Noel Weiss, M.D., Dr. P.H. (University of Washington, Chair of Panel)

Prior to attending the panel discussion, we were provided with comprehensive materials related to the design, conduct, analysis and interpretation of the HSP. These materials included the protocol, interview manual, interim data reports, draft HSP study report, case summaries, and the appendix to the letter sent by CHPA to the investigators in response to their request to industry for comment on the draft report. Also provided was the "Points-to-Consider" document prepared by CHPA epidemiologic and statistical consultants.

Our objective was to discuss the results of the HSP and to present an objective report on our interpretation of the results from this study. It should be noted that the CHPA sponsored the panel in the interest of providing independent expert advice to the manufacturers and distributors of phenylpropanolamine (PPA) containing products.

Although not every member of the panel was in full agreement on every issue, the deliberations are summarized in the attached Appendix. Overall, based on the analyses of the data that were available to us, we did agree that:

- This study had several methodological issues that could have confounded the results.
- Hemorrhagic stroke was a rare event among users of PPA.

- The results of this study, by themselves, are not sufficiently compelling to drive a public health decision regarding reported PPA use and the subsequent development of hemorrhagic stroke.

PANEL DELIBERATIONS:

The following seven questions related to the design, conduct, analysis and interpretation of the study were the focus of the panel deliberations:

1. What is the likelihood that uncontrolled or uncontrollable confounding is a plausible explanation for the study findings?
2. What is the likelihood that uncontrolled or uncontrollable bias is a plausible explanation for the study findings?
3. What is the likelihood of the study findings being affected by information bias?
4. What is the likelihood that chance is a plausible explanation for the study findings?
5. Were the analyses conducted appropriately?
6. Does the study demonstrate a valid statistical association between PPA and hemorrhagic stroke?
7. Are there other aspects that require consideration in evaluating the study report?

(The Appendix provides detailed comments relative to these questions.)

DISCUSSION:

We recognize the difficulty and complexity in carrying out studies of this type and agree that the investigators used best efforts in the conduct of the study. Nonetheless, numerous methodological issues and concerns limit the interpretability of the study. Of concern to us were the marked differences in characteristics between cases and controls. The fact that the small number of exposed cases limited the ability to statistically control for these variables in this study greatly increased the possibility that chance, bias and confounding remain plausible alternative explanations for any apparent association between PPA use and hemorrhagic stroke.

Importantly, the findings demonstrate that, even if real, the population risk associated with the use of PPA and hemorrhagic stroke would be exceedingly small. One might even question the clinical implications of such relative risk values even if they were from a randomized, prospective study. We all agree that the small number of cases precluded adequate controlling in the statistical analysis for known confounding factors. We also have concern that since the overall finding for the primary hypothesis in the study- any PPA exposure- was null, selective emphasis on particular subgroups with smaller numbers might well be misleading

While one cannot eliminate the possibility that the HSP provides a signal, as a stand-alone study, these data are not sufficiently informative to draw any definitive conclusions. It is quite possible that all of the effect could be attributed to confounding and selective emphasis on particular subgroups. Therefore, any presentation of the results should include a detailed discussion of the possible role of confounding, bias, and chance as plausible alternative explanations of the findings.

CONCLUSIONS:

We emphasize that this study represents a significant undertaking and the investigators made strong efforts to control for many variables. Importantly, there were very few cases of hemorrhagic stroke in PPA users. The small number of cases in conjunction with the large number of potential confounders makes a robust statistical analysis impossible to accomplish. A single, case-control study with results of this type, can, at best, provide a signal of an association. Nonetheless, an alternative conclusion of no association is plausible as well. Although this panel is not qualified to render a public health decision, given that we have not reviewed the entire safety database on PPA, we believe that this study, by itself, does not suggest that use of PPA is creating an imminent public health concern. It could at best be used as only supportive evidence if there are other scientifically valid confirmatory data available. In addition to the ambiguous epidemiological data relating PPA and hemorrhagic stroke, the HSP report offered no plausible pharmacological mechanism that might underlie a causal relationship. We remain interested in assisting the investigators, sponsors, or FDA with the review and interpretation of this study, if requested.

Signed:

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(Chairman)

Attachment

APPENDIX I:

Some points to consider relative to the study design, execution and interpretation are summarized below:

I. Rationale for HSP

A. Signal Strength for hypothesis generation

1. The anecdotal case reports that preceded the design of the study should not have biased the design or execution of the study. The decision to use one-sided confidence intervals based on an expectation of risk was not warranted.

II. Methodology Issues

A. Identification of cases and matched controls

1. Cases were enrolled from hospital networks including tertiary care centers, whereas controls were selected by random digit dialing (RDD), which might account for several observed differences between the two populations, including PPA exposure and socio-economic status (SES).

2. The general method of case surveillance employed was reasonable. However, there were a significant number of strokes that could not be studied because of morbidity and mortality.

B. Participation Rates

1. Large differences exist in participation rates between cases and controls. This is a potential bias that was not accounted for in any way in the study report.

2. A large number of potential cases died or for other reasons could not participate. Only 61% of the identified case population were considered eligible and, of these, only 77% were actually enrolled.

3. Control response rate of 30% raises questions about validity and may produce more disparity between cases and controls. A question is whether the RDD procedure was flawed, as 150 needed to be called to get one control (normally expect 25 per enrolled control).

C. Comparability of Cases and Controls

1. RDD matching of controls was ineffective in controlling for SES.

2. Cases differed from controls in race, SES, caffeine exposure, history of hypertension, family history, as well as alcohol, nicotine and caffeine consumption. Inadequate or inappropriate control for these confounders could easily explain any positive association with PPA use. It needs to be emphasized that the small number of cases simply does not allow for appropriately controlling for these variables.

3. SES differences may explain differences in who gets the disease as well as who uses certain products. Particular concern was raised with respect to educational differences that might result in residual confounding sufficient to invalidate the analysis. In other words, we question whether this was truly a population based study.

4. There is some question regarding the geographical diversity of the cases. It would be helpful if the location of the cases by site be identified in the final report to determine if there was heterogeneity by site.

5. Controlling for body mass index (BMI) differences was not adequately addressed in the statistical analysis. While BMI appears to be similar between cases and controls, there may be larger differences in patients with aneurysms and intracerebral bleeds.

6. Heterogeneity in cases may make interpretation more difficult as the risk factors for aneurysm may be different between arterio-venous malformations and intracerebral hemorrhage.

D. Recall Bias/Interview Quality

1. Exposure estimation by self-report is subject to limitations. Cases were asked about drug use immediately prior to a catastrophic event, whereas controls were asked about drug use prior to an arbitrarily chosen day some days beforehand. The fact that cases have had a catastrophic event may bias them towards a greater awareness of previous product use. Controls not only did not have such an event to trigger their recollection, but they also appear to have had different recall periods.

2. Compared to the hospital cases, the non-hospital setting in which controls were interviewed may have influenced their response.

3. A large number of cases (44%) demonstrated some degree of aphasia, possibly limiting their validity and reliability. It appears that the differences in interview quality between the cases and controls could have been substantial. There is also some question regarding the number and quality of assisted interviews. It would be useful to perform an analysis including only subjects who the interviewer considered reliable.

E. Misclassification

1. Because of the small number of PPA users, even a modest degree of misclassification of product use by cases or controls could dramatically alter the findings.

2. The existence of numerous branded and generic products containing PPA could lead to confusion. Furthermore, many of the branded products, while carrying the same trade name, may or may not contain PPA. We all agree that the investigators appeared to have done their best to avoid this confusion; but nevertheless errors could have occurred.

F. Stroke Subtypes

1. Arterio-venous malformations (AVMs) and pressure-related cerebrovascular anomalies are different diseases. Combining them in the analyses may over emphasize a risk.

2. AVMs and intacerebral bleeds should be analyzed separately.

3. 2/3 subarachnoid hemorrhage (SAH) vs. 1/3 intraparenchymal hemorrhage (IPH) distribution in the cases is opposite to the case report experience or the SAH/IPH distribution in the general population (18-49 age group) from various health databases. This finding is difficult to interpret and again brings up the issue of this study being truly population based.

4. Three out of the six appetite suppressant cases had underlying aneurysms. This was not adequately addressed in the study report.

5. Six of eight cases in the "first use" analysis represented subarachnoid hemorrhage leaving only two cases classified as intracerebral. Two cases are truly insufficient to address an effect of PPA in this condition.

G. Prodromal Symptoms

1. Headache should be examined as a potential confounder since all subarachnoid cases were preceded by a headache, whereas controls had no prior headache. It is possible that headache could have contributed to the use of PPA-containing products.

2. Exclusion of cases with sentinel symptoms and alternate index dates changes the outcome events from 8 vs. 6 to 5 vs. 4. The study report should thoroughly discuss the association between sentinel symptoms and product use.

3. Seasonality of cases should be examined as cold/allergy symptoms and associated coughing could be an independent risk factor.

H. Other Drug Use

1. Self-reported cocaine use may be underestimated. Multiple drug use should be examined. Excessive alcohol and illicit drug use are likely to occur concomitantly and to be associated with lower SES and less geographical diversity. As such, geographical representation of cases should be further explored with respect to alcohol and illicit drug use.

2. Caffeine was significantly more prevalent among cases but not controlled for in the analysis.

3. Controls are more likely to use NSAIDs and other non-PPA stimulants than cases. Little consideration has been paid to additional ingredients in cold/allergy products as well as concomitant use of other products. A discussion of the possible role of other drugs in either a protective or detrimental role should be discussed (eg., NSAID effects on coagulation).

4. A higher proportion of controls took PPA-containing products during the 3- to14-day period than cases.

5. All other drug use during the one-day window should be evaluated.

III. Statistical Data Handling

A. Unusual findings with respect to adjusting for confounders

1. In several analyses, the strength of association between PPA and stroke increases when confounders are controlled for. One would expect just the opposite.

B. Residual confounding

1. Confounders could not be adequately controlled for in the analysis because of the small numbers.

2. Chi-squared analyses should be presented by level of confounder to provide a statistically appropriate indicator of the level of such adjustments.

C. Exact rather than asymptotic methods of analysis would have been appropriate.

1. Numbers are too small for asymptotic methods to be used for appetite suppressants.

2. Asymptotic methods were used to analyze data when appropriate methods failed to yield interpretable results.

D. One-sided confidence intervals are not appropriate.

E. The possibility of confounding being responsible for the observed association cannot be eliminated.

F. Association is only observed in subgroup analyses. It is misleading to overemphasize the extremes, particularly when they are inconsistent. For example, the "matched" odds ratio of 3.14 for the "first use" subgroup analysis (based on only eight cases and five controls) involved use of PPA for cough/cold only (and had a two-sided p-value of 2 x 0.029=0.06). By contrast the "any use" subgroup analysis found no consistent association with use of cough/cold PPA (odds ratio 1.23, 1p=0.245), and the apparently extreme ratio of 15.96 was for appetite suppressants, based on 6 cases vs. 1 control.

G. Emphasis on subgroups by time may similarly be misleading. "Current use" on index or prior day (21 cases vs. 21 controls) had a matched odds ratio of 1.61 (1p=.078; 2p=0.16), use on day 2 or 3 had an estimated odds ratio of 1.0 (6 cases vs. 12 controls), and use on days 4 to 14 had a crude odds ratio of 0.67 (11 cases vs. 33 controls). These numbers and matched odds ratios should be given explicitly in the tables (not just available by subtraction and footnotes) and are compatible with differential recall.

IV. Interpretation

A. Overall risks are not significantly elevated. Increased risks are only observed in subset analyses that are limited by small numbers, and not clearly significant when allowance is made for multiple comparisons.

1. The apparent finding that PPA use is protective if not taken within the one-day window is confusing.

2. It is noteworthy that all first-use cases were in cold/allergy products despite higher odds ratio for appetite suppressants.

3. Potential for prodromal symptoms to lead to use of cough-cold/allergy products.

4. Seven of eight "first-use" (cough cold) and five of six appetite suppressant cases were non-black females. Generalization to men or black women might, therefore, be inappropriate.

B. No consistent pattern of use, timing of exposure, or type of product use provides insight into a possible biological mechanism. More emphasis should be placed on physiology and metabolism of the drug in the final report.

C. Data regarding appetite suppressants is difficult to evaluate based on small sample size and lack of biological plausibility.

D. It is unlikely that a transient rise in blood pressure associated with PPA use explains the association seen in the HSP. However, alterations in the vasculature might be expected with chronic alterations in blood pressure.

E. One-sided tests are not appropriate, given the hypothesis being tested. In fact, the one previous analytic study reported a RR=0.59.

F. Lack of consistency in findings and unusual pattern of the data limits interpretability. Nonetheless, the study demonstrates that the population risk of a hemorrhagic event is extremely low.

V. Further Analyses

A. Analysis should be restricted to populations in which data are available.

1. Analysis should be repeated restricting inclusion to white women, as African Americans and men contribute no meaningful data to the overall analysis.

2. Analysis should be restricted to SAH, as there were no cases of intracerebral hemorrhage (ICH), which may be related to high fatality rate of ICH.

B. Stratification based on potential confounders

1. Stratify based on history of prior headache. (Not regression analysis because of small number of cases.)

2. Stratify by heavy versus light caffeine consumption.

Consumer Healthcare Products Association

Appendix B

Comments on the Hemorrhagic Stroke Project Report
CHPA Phenylpropanolamine Working Group
May 24, 2000

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.

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[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/lcv/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									To
	Hospital	Rehab Center	Home	Office	Friend's home	Other	Phone	Not specified	Missing	
Controls	42	0	363	308	4	598	44	2	22	13
	3.0%	0	26.2%	22.3%	0.3%	43.2%	3.2%	0.1%	1.6%	10
Cases	465	66	134	2	3	25	3	0	8	70
	65.8%	9.3%	19.0%	0.3%	0.4%	3.5%	0.4%	0	1.1%	10

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 WITHIING 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 WITHIING 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.