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

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
Formerly Nonprescription Drug Manufacturers Association

By Federal Express

September 22, 2000

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

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

To Who It May Concern:

Enclosed are three copies of a background document provided by the Consumer Healthcare Products Association (CHPA) for the Nonprescription Drugs Advisory Committee meeting scheduled for October 19, 2000. Copies for distribution to advisory committee members and others were sent directly to the Executive Secretary for the committee, Sandy Titus, Ph.D., on September 21, 2000. No part of the document needs to be treated as confidential.

Please let me know if you need additional copies.

Sincerely,

Lorna C. Totman

Lorna C. Totman, Ph.D.
Director of Scientific Affairs

cc (letter only): Sandy Titus, Ph.D.

Enclosures: CHPA Background for the Nonprescription Drugs Advisory Committee Meeting on Phenylpropanolamine, October 19, 2000

LT/lm/ppa/docketslet

81N-0022 C115

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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.

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> 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. Goerelick, MD, MPH, FACP, Professor of Neuorological 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)