University of Maryland
Medical Center

UNIVERSITY OF MARYLAND
SCHOOL OF MEDICINE

DEPARTMENT OF NEUROLOGY

22 South Greene Street
Baltimore, Maryland 21201-1595
410 328-6484
FAX: 410 328-5899

July 30, 1992

Paula Botstein, M.D.
Acting Director
Office of OTC Drug Evaluation
Food and Drug Administration
HFD-100
Parklawn Building - 14B45
5600 Fishers Lane
Rockville, MD 20857

RE: Phenylpropanolamine Safety Review
OCT Trac No. 206-12

Dear Dr. Botstein:

As a neuroepidemiologist with an ongoing research program related to stroke in young adults, I am pleased to participate in the FDA's review of phenylpropanolamine (PPA). I will address the specific questions raised in your June 22, 1992 letter to me and close with my overall assessment and recommendations.

1. **Issue** - Are the reasons clear and valid in the FDA Epidemiology Branch reports of April 30 and August 6, 1991 for focusing on adverse drug experience reports to the FDA's Spontaneous Reporting System and in the medical literature, and for not using data from Poison Control Centers and the Drug Abuse Warning Network?

Response - I agree that the relevant focus should be on "individuals who take PPA for its intended effects", not on individuals who take PPA for its psychoactive effects, for the purposes of suicide, or accidentally. Thus, reports based on the

FDA's Spontaneous Reporting System and the medical literature are more appropriate than reports based on the Poison Control Centers or the Drug Abuse Warning Network.

2. **Issue** - Is it valid to compare PPA-weight control drugs, PPA-cough/cold products, and all other drugs on the proportion of stroke reports among all adverse drug experience reports in the FDA's Spontaneous Reporting System? To what extent does the comparison of strokes per total adverse drug reactions proportions for PPA-weight control drugs vs. PPA-cough/cold products control for possible reporting bias? Please comment on the explanation for a difference between the number of strokes reported per usage of weight control drugs and cough/cold products with similar doses of PPA.

Response - I agree with the statement in the FDA Epidemiology Branch Report of April 30, 1991 that "comparisons of spontaneously reported data between different drugs need to be cautiously interpreted in light of several potential sources of bias". Strokes per usage rate and strokes per total adverse drug reaction proportion analyses are both influenced by reporting rates for stroke. Stroke reporting by health professionals could have been higher for PPA-diet pills than PPA-cough/cold products if there were greater public awareness of safety issues with diet pills.

"Strokes per total adverse drug reaction" analyses are influenced not only by the reporting rate for stroke but also by the reporting rate for other adverse reactions. This proportion would be reduced for PPA-cough/cold drugs if, as is likely, the antihistamine or antitussive agents in PPA-cough/cold combination products lead to nonstroke adverse drug reactions.

Because of these potential biases, the "strokes per usage" analysis is a relatively weak source of evidence suggesting a

hazard from PPA-diet pills. The "strokes per total adverse drug reaction" analysis is an even weaker source of evidence. However, because of the concurrence of these two lines of evidence, it is necessary to ask why, with similar doses of PPA, diet pills might have a higher stroke risk than cough/cold pills.

One possibility is that PPA-diet pill users differ in systematic ways for PPA-cough/cold users, even when women of similar ages are being compared. For example, there could be a higher rate of obesity among PPA-diet pills users, with an associated higher rate of hypertension. Thus, the higher stroke rates among PPA-diet pills users could be due to confounding by hypertension rather than to PPA per se.

A second possibility is that usage patterns differ for PPA-diet pills and PPA-cough/cold products, with users of PPA-diet pills being more likely than PPA cough/cold users to exceed labelled dosage recommendations. Misuse of PPA-diet pills with resultant exposure to a higher dose of PPA may explain the higher stroke risk of PPA-pill users. Use of an excess dose was observed in two-thirds of strokes associated with PPA-diet pill use.

The most efficient way to distinguish between these alternative explanations would be to conduct a case-control study which would compare use and dose of PPA-containing compounds in young women with a hemorrhagic stroke to a control group without stroke. The design and analysis of such a study could also provide information on the influence of other factors, such as hypertension, on the relationship between PPA and stroke.

3. **Issue** - Please comment on the critical numbers used in the various scenarios for the comparison of the number of observed hemorrhagic strokes in PPA-diet pill users with the number

expected by chance.

Response - I will limit my discussion to the stroke risk among women age 15-44 years of age (scenarios C and D) and will comment on the critical numbers in order of their importance. As recognized in the FDA Epidemiology Branch Report of August 6, 1991, the 2 most important assumptions are the "first dose" effect, which could alter the ratio of observed to expected cases 16-fold, and the reporting rate, which could alter the ratio of observed to expected cases 10-fold. I will also discuss the issue of the cases included in scenarios C and D, and the estimated incidence rate of hemorrhagic stroke in young women. In general, I find these analyses to be reasonable and, in some respects, even conservative in their risk estimates.

First Dose Effect

The evidence that the hypertensive effect of PPA is greatly attenuated after the first dose and the observation that most reported stroke cases follow the first dose are consistent with the hypothesis of a causal relationship between PPA and hemorrhagic stroke. In the context of all the evidence, I believe that it would be unwise to assume that the clustering of reported cases occurring after the first dose is due to reporting bias. Therefore, I find scenario C most persuasive. Even if one withholds judgement about the importance of a "first dose" effect, the calculation of observed to expected cases based on first dose cases (scenario C) remains valid, given an appropriate range of reporting rates.

Reporting rate estimates.

Although few data are available by which to estimate reporting rates, the range of 1% to 10% used in the FDA Epidemiology Branch August 6, 1991 report is reasonable. For

reasons to be described, I believe that the actual reporting rate is more likely to be less than 5%.

In 1988, Rogers[1] published a study of the adverse drug reaction reporting practices of Maryland physicians. Questionnaires were mailed to 3000 randomly selected physicians and 1120 questionnaires were returned. Of the responders, 418 had detected one or more moderate or severe adverse drug reaction and of these 21 (5%) had made a report to the FDA. As pointed out in the Epidemiology Branch Report of December 26, 1991, there are several reasons for believing that this 5% figure is likely to be an overestimate of reporting for strokes associated with PPA-diet pill. First, and most importantly, there was only a 37% response rate. If one assumes that the nonresponders to the questionnaire detected events at the same rate as responders but made no reports to the FDA, then the reporting rate would be 1.9%. The truth probably lies somewhere in between. Second, the result should not be interpreted as indicating that 5% of all adverse drug reactions were reported, since the reporting physicians may have detected several adverse drug reactions but reported only one. Third, this report does not provide information which specifically addresses patterns of physician reporting with over-the-counter products. Use of over-the-counter drug products may not even be ascertained in drug histories. For example, I am conducting a hospital discharge registry of ischemic stroke and intracerebral hemorrhage among men and women 15-44 years of age in the Baltimore-Washington area. Of the 83 charts of patients hospitalized during 1991 reviewed to date, 58 charts (70%) had no recorded information on the use of over-the-counter PPA-containing compounds. Fourth, of the 3 factors which the Rogers report identified as predictors of event reporting, only one, "event severity", would operate to increase reporting of PPA-diet pill related strokes. To the extent that PPA-associated stroke is considered to be a "known and documented" reaction, reporting would be expected to decrease. Finally, the "physician

specialty" factor would tend to reduce reporting, since the neurosurgeons or neurologists who take care of the young stroke patients would be less likely to report adverse drug reactions than primary care physicians.

Selection of cases included in scenario C and D.

I agree with the decision to exclude cases reported by consumers and from the National Clearinghouse on Diet Pill Hazards on the basis that these were "stimulated" reports rather than "spontaneous" reporting.

The inclusion of all cases with duration not specified in the "first day" analyses is probably not justified but does not effect the results appreciably. In scenario C, which I consider to be the most important analysis, only 2 of the 14 cases did not have duration specified.

I believe that any dose of a drug taken for its intended effect should be included as an adverse drug reaction. Again, exclusion of cases taking more than 5 pills would not materially effect the results of Scenario C (only 2 of 14 took over 5 pills).

I agree that it is appropriate to include cases involving all PPA-diet pill cases regardless of caffeine content on the basis the amount of caffeine in these combination products (200 mg) was similar to the amount of caffeine in one cup of coffee.

Estimated incidence rate of hemorrhagic stroke in women age 15-44.

The rate of hemorrhagic stroke was approximately 5/100,000 in Florence, Italy[2] and 15/1000,000 in Stockholm County, Sweden[3]. If the National Survey of Stroke[4] is used, a maximum

estimate of about 4/100,000 can be derived with the following assumptions: 1) the male:female ratio of strokes is 1:1 and 2) all strokes occurring in the age range 0-44 occurred in the age range 15-44. Both these assumptions would tend to inflate the estimated incidence of hemorrhagic stroke among women 15-44 above its true value. Thus, the use of a rate of 10/100,000 by the FDA Epidemiology Branch report of August 6, 1991 would tend to slightly overestimate the rate of hemorrhagic stroke in women age 15-44.

Another important consideration is whether the analyses should be based on cases of intracerebral hemorrhage and subarachnoid hemorrhage, or just on cases of intracerebral hemorrhage. A large majority of the hemorrhagic stroke cases reported to the FDA were intracerebral hemorrhages (12 of 16 in the April 16, 1991 Summary of diet pill cases), while intracerebral hemorrhage accounts for only 1/3 to 1/2 of all nontraumatic brain hemorrhages in young adults[2,3,4]. If the analyses were based only on the observed intracerebral hemorrhage cases and the expected background rate of intracerebral hemorrhage in young women using diet pills, then the observed to expected ratios could approximately double.

Overall Assessment and Recommendations

The analyses presented in the Epidemiology Branch Reports of April 30, August 6, and December 26, 1991 are a careful and evenhanded assessment of the stroke risk of PPA. Although I find the "observed versus expected" analyses more compelling than the "strokes per total adverse reactions" analyses or the "strokes per usage" analyses, the concurrence of these 3 lines of evidence should give a reasonable person cause for concern that PPA-diet pills may be associated with an increased risk of hemorrhagic stroke.

The alternative explanation for the observed cases is that they represent the expected coincidence of a widely used drug and the background rate of stroke in young women. Several points speak against this explanation. First, the reported cases of stroke in association with PPA use are heavily weighted towards intracerebral hemorrhage, the least common stroke type, rather than ischemic stroke, the most common stroke type, or subarachnoid hemorrhage, the second most common stroke type. This specificity of association is more consistent with a causal relationship than with chance co-occurrence. Second, the reported cases often occurred after a first dose and, in particular, within the first 6 hours after ingestion. This is consistent with the time course of the pressor effect of PPA and the marked diminution of this response with repeated doses. Analyses of unusual circumstances associated with reported cases of intracerebral hemorrhage[5] shows that an acute important rise in blood pressure is a common underlying theme. Third, the use of excess doses of PPA (2 or more pills) was commonly seen in reported stroke cases. This is unlikely to be due to coincidence and is consistent with the dose-related blood pressure elevation of PPA. Fourth, the cases of intracerebral hemorrhage were not typical. Reports in the literature include 2 cases of bilateral hemorrhage associated with PPA use and 11 cases showing angiographic features of vasculitis[6]. This suggests that a second potential mechanism, drug induced vasculitis, needs to be considered in PPA-associated stroke[7,8]. PPA has close structural and pharmacological similarities to amphetamine, where drug-induced vasculitis with intracerebral hemorrhage has been well documented as a stroke mechanism[5,7,8,9]. In short, the specificity of the relationship, the presence of first dose and excess dose effects, and the high degree of biological plausibility for a statistical association between PPA and hemorrhagic stroke is perhaps the most persuasive argument in support of the analyses presented in the FDA Epidemiology Branch Reports.

Further epidemiologic studies are needed to resolve the uncertainties in available data about the magnitude of the stroke risk associated with PPA use. Clinical trials or cohort studies have important drawbacks for studying a low frequency event such as stroke in young women. The number of women studied would have to be in the hundreds of thousands to millions, depending on the duration of followup. A much more efficient strategy, both in terms of time and money, would be to conduct a case-control study. Case-control and cohort studies have yielded consistent results in studies of a similar problem, the relationship between oral contraceptive use and stroke risk[10]. Because of the high prevalence of use of PPA products even a small increment in stroke risk attributable to PPA would have important public health consequences.

Respectfully submitted,

Steven J. Kittner

Steven J. Kittner, M.D., M.P.H.
Assistant Professor of Neurology,
Epidemiology and Preventive Medicine

REFERENCES

1. Rogers AS, Israel E, Smith CR, et al. Physician knowledge, attitudes, and behavior related to reporting adverse drug events. Arch Intern Med 1988;148:1596-1600

2. Nencini P, Inzitari D, Baruffi MC, et al. Incidence of stroke in young adults in Florence, Italy. Stroke 1988;19:977-981.

3. Mettinger KL, Soderstrom CE, Allander E. Epidemiology of acute cerebrovascular disease before the age of 55 in the Stockholm County 1973-77: incidence and mortality rates. Stroke 1984;15(5):797-800.

4. Robbins M, Baum HM. Incidence. Stroke 1981;12, suppl 1:I-45-I-55.

5. Caplan L. Intracerebral hemorrhages revisited. Neurology 1988;38:624-627.

6. Forman HP, Levin S, Stewart B, Patel M, Feinstein S. Cerebral vasculitis and hemorrhage in an adolescent taking diet pills containing phenylpropanolamine: case report and review of literature. Pediatrics 1989;83:737-741.

7. Kase CS, Foster TE, Reed JE, Spatz EL, Girgis GN. Intracranial hemorrhage and phenylpropanolamine. Neurology 1987;37:399-404.

8. Glick R, Hoying J, Cerullo L, Perlman S. Phenylpropanolamine: an over-the-counter drug causing central nervous system vasculitis and intracerebral hemorrhage. Neurosurgery 1987;20:969-974.

9. Harrington H, Heller A, Dawson D, Caplan L, Rumbaugh C. Intracerebral hemorrhage and oral amphetamine. Arch Neurol 1983;40:503-507.

10. Stadel BV. Oral contraceptives and cardiovascular disease. New England Journal of Medicine 1981;305:672-677.