APPENDIX B

STATISTICAL REVIEW OF EPIDEMIOLOGICAL REPORT

DATE: **September 26, 2000**

STATISTICAL REVIEWER: Yi Tsong, Ph.D., Mathematical Statistician
Quantitative Methods Research Staff, HFD-705

DOCUMENT REVIEWED: **Final Report of Yale Hemorrhagic Stroke Project, CHPA Phenylpropanolamine Working Group Comments**

EPIDEMIOLOGICAL REVIEWER:
Lois La Grenade, M.D., M.P.H., Epidemiologist
Parivash Nourjah, Ph.D., Epidemiologist
Division of Drug Risk Assessment 1, HFD-430

INTRODUCTION

This consult is in response to a request from the Division of Drug Risk Assessment I, Office of Postmarket Drug Risk Assessment to review CHPA Phenylpropanolamine Working Group comments and the final report submitted by Yale University, entitled Hemorrhagic Stroke Project Report, provided by CHPA. This review consists of three parts, protocol review, comments on the comments of CHPA Phenylpropanolamine Working Group and summary review of the Yale's report of CHPA sponsored Yale Hemorrhagic stroke study.

A. PROTOCOL REVIEW (BACKGROUND)

As early as 1984, the FDA was alerted to the potential safety concerns with risk of hemorrhagic stroke associated with the usage of Phenylpropanolamine (PPA). Most of the reports prior to 1984 were case reports. O'Neill and Van de Carr's case-control study using Medicaid data of Michigan and Minnesota was the first retrospective epidemiological study to address the issue [1]. In this unpublished 1984 study, prescription PPA was compared with prescription ephedrine, phenylephrine and pseudoephedrine on their association with hemorrhagic stroke. Based on a 60-day exposure window, they found association with PPA usage in both genders and both states. However, only a moderate association with PPA usage in a Michigan male patient population was statistically significant. The report addressed many factors that would bias the result towards a no association finding in a computerized database. Jick, Aselton and Hunter's 1984 incidence density analysis based on Group Health Cooperative of Puget Sound data provided the only published epidemiological study addressing this issue. The PPA user incidence rates of stroke were calculated by dividing the number of events that occurred in the 60-day exposure window by the sum of all 60-day exposure windows in the study. The incidence rate for non-users is the ratio of the number of

stroke events divided by the sum of all non-PPA exposure window times. Jick et al found no significant association between PPA exposure and hemorrhagic stroke among the prescription drug users. This study suffered similar problems to the ones pointed out in O'Neill and Van de Carr's report.

Jolson [3] studied reports of CVA (cerebravascular stroke) in the FDA spontaneous reporting system database. In her study, she compared the proportions of reports of CVA of PPA with all other drugs reported to SRS for women aged 10-59 years from 1977 through January 1991. She found that **CVA is the single most commonly reported event for PPA-diet products (35.3% overall, 40.8% in Direct reports, 0 in the manufacturer reports), and represented 5.8% (overall, 5.7% of direct reports, 5.1% of manufacturer reports)) of all PPA-cough/cold ADEs, in contrast to less than 1% of all ADEs reported among all drugs (See Tables 1 and 2). Most of the reports were associated with first use of the products.**

Table 1 PPA (phenylpropanolamine) and Number of CVA reports in women aged 10-59 (1977- Jan. 1991)*

Direct Reports			
Product	CVA	Non-CVA	Total
PPA-Diet	20 (40.8%)	29 (59.2%)	49
PPA-Cough/Cold	4 (5.7%)	66 (94.3%)	70
All Non-PPA	78 (0.5%)	14168 (99.5%)	14246
Total	102 (0.7%)	14263 (99.3%)	14365
Manufacturers Reports			
Product	CVA	Non-CVA	Total
PPA-Diet	0 (0.0%)	3 (100%)	3
PPA-Cough/Cold	4 (5.1%)	74 (94.9%)	78
All Non-PPA	643 (0.9%)	72799 (99.1%)	73442
Total	647 (0.9%)	72876 (99.1%)	73523

* 1991 FDA memorandum "Epidemiologic Review of PPA Safety Issues"

Table 2 Direct Domestic Spontaneous Reports of CVA in Women Aged 10-59 Years Received by the FDA (1977- Jan. 1991)

Product Category	Number of CVA Reports	% of Total Reports
PPA-Diet	19	26%
Oral Contraceptive	15	20%
Thrombolytic Agent	7	10%
Lactation Suppressive	6	8%
Chemotherapeutic	5	7%
Radiocontrast	4	5%
Anticoagulant	3	4%
PPA-Cough/Cold	3	4%
Miscellaneous	11	15%
Total	73	100%

With concerns raised in this 1991 report, the Nonprescription Drug Manufacturers Association, NDMA (now Consumer Healthcare Products Association, CHPA) initiated a contract with investigators of Yale University to carried out the current case-control study as a verification of the strong signals generated from the FDA SRS study.

The Protocol of the NDMA sponsored Yale Hemorrhagic Stroke project was thoroughly discussed in many NDMA-FDA meetings and communications. In general, FDA reviewers were concerned with

1) the feasibility of the study in terms of assumed background rate used in sample size and power calculation,
2) feasibility of the study in terms of sample size and power to detect the association between dietary suppressant and hemorrhagic stroke among the first PPA use,
3) the potentially large misclassification error of using surrogate interview for case patient who can't communicate,
4) interim analysis for study feasibility.

Through the multiple meetings and communications, the protocol was revised by NDMA and the Yale investigators. The FDA concern #1 was taken into consideration by NDMA and Yale investigators and the protocol was modified to an interim analysis design for the feasibility study. Yale investigators confirmed the FDA concern #3 and the case definition was modified accordingly. The FDA concern #2 was accommodated with the following four equally important primary objectives as given in the current protocol

1) To estimate the association between PPA and hemorrhagic stroke among men and women aged 18 – 49 years.
2) To estimate the association between PPA and hemorrhagic stroke by type of PPA exposure (diet suppressant and cough/cold product) among the same target population
3) Among women aged 18-49 years to estimate the association between first use of PPA and hemorrhagic stroke
4) Among the same target female population to estimate the association between PPA in appetite suppressants and hemorrhagic stroke.

Details of the comments and revisions in 1992-1993 were documented in NDMA letters, FDA letters and FDA memoranda [4-11].

The final protocol as given in Yale's report clearly demonstrated that all the concerns discussed in 1992-1993 were taken into consideration and all the necessarily steps were put in place to minimize the potential bias often found in case-control studies Details of the strengths and weaknesses of this protocol discussed between the statistical reviewer of the Quantitative Methods Research Staff and epidemiological reviewers of the Division of Drug Risk Assessment are documented in the FDA's statistical and epidemiological review reports [4,5].

B. REVIEWER'S RESPONSE TO THE STATEMENTS MADE IN THE CHPA'S REPORT OF CPHA PHENLPROPANOLAMINE WORKING GROUP'S COMMENTS ON YALE'S FINAL REPORT OF NDMA (now CHPA) SPONSORED HEMORRHAGIC STROKE STUDY

In this section, reviewer's response was typed in "times new roman" font in order to distinguish from CPHA Phenlypropanolamine Working Groupis comments typed in "courier new" font.

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

   The objective of the project was to assess and evaluate the association between hemorrhagic stroke and PPA use. The study was initiated because of the FDA's concerns about the unusually high proportion of stroke reports among the ADE reports (attributed to PPA use) received in the FDA spontaneous reporting system. The study was proposed by Yale University Investigators (and sponsored voluntarily by CHPA) with a careful design in order to either confirm or refute the safety concerns. The investigation of the association (due to causality, promoting factor or ineffective OTC labeling, etc) between PPA use and hemorrhragic stroke was the goal as planned and discussed at its planning stage for OTC marketing concern. Nevertheless, the investigators detected a strong association between use of PPA in diet suppressant products and hemorrhagic stroke. They also detected a dose-response relationship between PPA and stroke which strengthened the association.

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.

   The NDMA sponsored Yale HS project was voluntarily initiated by NDMA based on the safety concerns raised from the information in the FDA spontaneous reporting system database. Its protocol was carefully reviewed through many NDMA and FDA meetings (see attached ref. 3-10). Because of bias involved with the earlier studies, the findings of this carefully planned and conducted study should be given greater weight as confirmatory safety evidence than to be equally weighted as one of the studies in a meta analysis form.

   With over 700 stroke cases, careful design and conduct, thorough analysis, the Yale HS project is unique in its standing among all PPA studies.

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 of any relationship between exposure and stroke.

The fact that the sample size of the NDMA (now CHPA) sponsored study may be "too small" was probably due primarily to the minimum sample size requirement to detect a 5-fold odds ratio in all-PPA all users population due to the practical feasibility concern with low stroke incidence and low prevalence of PPA. However, FDA had more concerns with compromised power than with potential bias speculated by CHPA due to a "small sample". Because of the small size of the study, the consistency of the association shown in all four primary objectives and analyses that control for the confounders strengthen the findings over and beyond the sample size dependent p-values. The consistency is clearly shown across objectives and stratified analyses and subset analyses as shown in the following summary tables.

First, for objectives #2 and #4, although the numbers are small, the results are consistent and support the concern raised in the review of the FDA spontaneous reports of an association between the PPA dietary suppressant product and stroke. The association found in this study is large (OR =11.98 in all subjects (adjusted p=0.013), and in females only the odds ratio is 12.19 (adjusted p=0.01)(Table 3). When stratified by the status of sentinal symptom, the OR is both large and statistically significant (OR>7, adjusted p-value=0.029) among patients with no symptom. Though the number of patients with the symptom is small and the number of exposures is also small, the odds ratio is large (unadj OR=4.83, p=0.11). Among patients without a history of hypertension, there are 3 matched exposed case- unexposed control pairs but no unexposed case- exposed control pair. Of this cohort, the unmatched OR is 10.26 (unadjusted p=0.01)(Table 7). The association is both strong and statistically significant in subpopulations stratified by status of aphasia (unadj OR=12.09, p=0.007, adjusted OR=15.5, p=0.013 among patients without aphasia (rating 1-3)(Table 10). With a more restricted definition of the status of without aphasia (rating=1), the unmatched OR>16.00, p=0.013 (4 exposed cases and no exposed control) among patients without aphasia.

The associations between cough/cold PPA and hemorrhagic stroke is much weaker, which is consistent with the findings in the Jolson report.

Second, for objective #3, the results support the safety concern raised from Jolson's review of the FDA spontaneous reports of a strong association between PPA and stroke among first users exposed within 24 hours before the focal time. The association found in this study is large and statistically significant (unadj OR=3.20, adj OR=3.14, p-value =0.029) of all PPA products (Table 3). The same association was detected in patients without the sentinal symptom (unadj OR=3.0 , p=0.08, adj OR=3.34, p=0.04). An association of the same magnitude was detected in patients with the sentinal symptom present, even though the numbers are small (unadj OR =4.0, p=0.259, adj OR=2.7, p=0.215) (Table 4).

In response to the FDA reviewers' request, the Yale investigators performed analysis by controlling history of hypertension through stratification (Tables 6 and 7). We detected that the association is independent of hypertension history as shown in patients without a history of hypertension (unadjusted OR=4.13, p-value=0.02, adjusted OR=3.99, p-value=0.03). The same association was shown consistently in subgroups stratified by the presence of aphasia (unadj OR=4.0, p=0.019, adj OR=3.59, p=0.023 without aphasia present; unadj OR=5.33, p=0.009, adj OR=4.60, p=0.015 with aphasia present) (Table 10).

Third, for objective #1, the unadjusted odds ratios are between 1.5 and 2.6 in all analyses (the whole population and subgroups defined by status of sentinal symptom, history of hypertension, or status of aphasia). With adjustment for smoking, hypertension, race and education, the odds ratios are still greater than 1.30 though the p-values vary. This finding is consistent with the safety concern raised in Jolson's review of FDA spontaneous reports.

Table 3 Analyses of the four primary objectives

	Case (n=702) No. %	Controls (n=1376) No. %	Unadjusted Matched OR	Adjusted for smoking, hypertension, race and education OR LCL p-value
No use	664 94.6	1310 95.2		
Use in 3-day window				
Any PPA	27 3.8	33 2.4	**1.67**	**1.49** 0.95 0.084
Cough/cold	22 3.1	32 2.3	**1.38**	**1.23** 0.75 0.245
Appetite suppressant	6 0.9	1 0.1	**11.98**	**15.92** 2.04 0.013
Current Use within 24 hrs of Focal Time				
Current Use	21 3.0	21 1.5	**1.98**	**1.61** 0.93 0.078
First use	8 1.1	5 0.4	**3.20**	**3.14** 1.16 0.029
Non-first use	13 1.9	16 1.2	**1.62**	**1.20** 0.61 0.329
Prior use	6 0.9	12 0.9	**1.01**	**1.16** 0.47 0.393
By Gender Analysis				
Female	Case (n=383)	Controls (n=750)		
No use	355 92.7	713 95.1		
Any PPA	21 5.5	20 2.7	**2.15 (p=0.014)**	**1.98** 1.12 0.024
Cough/cold	16 4.2	19 2.5	**1.70 (p=0.089)**	**1.54** 0.85 0.116
Appetite	6 1.6	1 0.1	**12.19 (p=0.006)**	**16.58** 2.22 0.011
Male	Case (n=319)	Controls (n=626)		
No use	309 96.9	597 95.4		
Any PPA	6 1.9	13 2.1	0.90 (p=0.529)	0.62 - 0.203
Cough/cold	6 1.9	13 2.1	0.90 (p=0.529)	0.62 - 0.203
Appetite	0 0.0	0 0.0		

Table 4 subgroup analysis by Sentinal Symptom

No Sentinal Symptom	**(n=548)**		**(n=1075)**					
No use	519	94.7	1022	95.1				
Any PPA	20	3.6	26	2.4	**1.55 (p=0.104)**	**1.33**	0.77	0.194
Cough/cold	17	3.1	25	2.3	**1.35 (p=0.221)**	**1.12**	0.64	0.371
Appetite suppressant	4	0.7	1	0.1	**7.08 (p=0.046)**	**12.10**	1.39	0.029
Current use	17	3.1	18	1.7	**1.85 (p=0.054)**	**1.42**	0.78	0.169
First use	6	1.1	4	0.4	**3.00 (p=0.077)**	**3.34**	1.08	0.040
Not-first use	11	2.1	14	1.3	**1.55 (p=0.196)**	**1.02**	0.50	0.479
Prior use	3	0.6	8	0.7	0.76 (p=0.481)	0.98	--	0.489
Sentinal Symptom Present or Uncertain	**(n=154)**		**(n=301)**					
No use	145	94.2	288	95.7				
Any PPA	7	4.6	7	2.3	**2.13 (p=0.141)**	**2.19**	0.80	0.099
Cough/cold	5	3.2	7	2.3	**1.48 (p=0.365)**	**1.71**	0.58	0.206
Appetite	2	1.3	0	0.0	**4.83 (p=0.111)**	-	-	-
Current use	4	2.6	3	1.0	**2.67 (p=0.173)**	**2.95**	0.76	0.096
First use	2	1.3	1	0.3	**4.00 (p=0.259)**	**2.70**	0.34	0.215
Not-first use	2	1.3	2	0.7	**2.06 (p=0.395)**	**3.17**	0.53	0.145
Prior use	3	2.0	4	1.3	**1.53 (p=0.418)**	**1.51**	0.36	0.318

Furthermore, the Yale investigators observed that the odds ratio was 2.31 (LCL=1.10, p=0.031) among patients with current use of dose above 75mg (i.e. median daily dose of users of controls) comparing to an odds ratio of 1.01 (LCL=0.43, p=0.490) among patients using less than 75 mg (Table 5). These results suggest a possible dose response relationship.

Table 5 Dose Group Subgroup Analysis

Current dose	OR	LCL	p-value
> 75 mg (=median)	**2.31**	1.10	0.031
≤75 mg	**1.01**	0.43	0.490

4. Conclusions from the study should be based on overall PPA exposure, which is the study's first objective (i.e., "Do PPA uses 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 that reportedly took PPA to allow for effective controlling for confounding factors.

The strength of this epidemiological finding is not limited to a significant p-value. It is the consistency of the findings with the signals generated from FDA spontaneous reports. It is also in the consistency of the ORs in the study when adjusted for the potential confounders through modeling or stratified analysis. In addition, although the four objectives were specified as of equal importance as proposed by Yale investigator and endorsed by NDMA (now CHPA) (NDMA-to-FDA letter, October 14, 1993, ref. 11), the priority of the objectives #3 and #4

(first use, dietary suppressant PPA women only) were suggested by Jolson's findings in FDA spontaneous reports. .

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 the deviation from the study protocol.

- Some examples of confounders that were not adequately controlled for included 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.

  - 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 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 high-risk group for hemorrhagic stroke (hypertension, cocaine and alcohol abuse, caffeine consumption, family history of hemmorrhagic stroke, obesity) with controls drawn from the general population, with limited control of confounding.

The protocol of this NDMA (now CHPA) sponsored project was fully discussed between NDMA and Yale investigators before it was submitted for discussion with the FDA. The limitations of controlling for all confounding factors were carefully considered. In the analyses reported by the Yale investigators, the most serious and common confounding risks of hemorrhagic stroke, namely smoking, hypertension, race and education, were studied and included in the logistic regression adjustment of the association. This reviewer believes that the last bullet item is more speculation than real for this data. For example, in order to eliminate the impact of hypertension on the association, the Yale investigator estimated the odds ratio also using logistic regression with hypertension as a covariate. In addition, the FDA reanalyzed the data limited to the population with no history of hypertension and found that PPA is independently associated with hemorrhagic stroke from hypertension.

First, in the following table of patients with hypertension history, it is shown that there was actually a lower percentage of hypertension history among PPA users than non-users in cases.

Table 6 Subjects with hypertension history among PPA users

Hypertension History	All subjects		Cases		Controls	
	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
3-day exposure window						
Yes	536 (26%)	17 (28%)	263 (39%)	9 (33%)	273 (20%)	8 (24%)
No	1551 (74%)	43 (72%)	482 (61%)	18 (67%)	1069 (80%)	25 (76%)
Total	2087	60	375	27	1342	33
Cough/cold PPA Users						
Yes	537 (27%)	16 (30%)	264 (39%)	8 (36%)	273 (20%)	8 (25%)
No	1486 (73%)	38 (70%)	416 (61%)	14 (64%)	1070 (80%)	24 (75%)
Total	2023	54	680	22	1343	32
Appetite suppressant PPA Users						
Yes	551 (27%)	2 (29%)	270 (40%)	2 (33%)	281 (20%)	0 (0%)
No	1519 (73%)	5 (71%)	426 (60%)	4 (67%)	1093 (80%)	1 (100%)
Total	2070	7	716	6	1374	1
1st Users						
Yes	552 (27%)	1 (8%)	271 (39%)	1 (15%)	281 (21%)	0 (0%)
No	1512 (73%)	12 (92%)	423 (61%)	7 (85%)	1089 (79%)	5 (100%)
Total	2064	13	694	8	1370	5

On the other hand, when the data were reanalyzed for the subset of patients with no hypertension history, the association was consistent though not always statistically significant, with 3-day exposure window, cough/cold PPA exposure, current exposure, first exposure and even not first exposure patients.

Table 7 Analyses in patients without a hypertension history

	Case No.	%	Control		Matched OR	LCL /UCL	p-value	Adjusted OR	LCL /UCL	p-value
3-day Exposure Window										
Yes	18	3.0	25	2.3	**1.934**	1.08	0.03	**2.05**	1.10	0.03
No	482	97.0	1069	97.7		3.47			3.82	
Cough/Cold APP Users										
Yes	14	3.3	24	2.2	**1.461**	0.79	0.15	**1.643**	0.87	0.10
No	416	96.7	1070	97.8		2.69			3.10	
Appetite APP Users										
Yes	4	0.9	1	0.1	**10.26**[a]	1.75	0.01	--	--	--
No	426	99.1	1093	99.9		60.34			--	
Current Users										
Yes	14	3.3	15	1.4	**2.424**	1.22	0.02	**2.422**	1.17	0.023
No	416	96.7	1079	98.6		4.82			5.04	
1st Uses										
Yes	7	1.6	5	1.4	**4.130**	1.32	0.02	**3.997**	1.21	0.03
No	423	98.4	1089	98.6		12.95			13.25	
Non 1st Users										
Yes	7	1.6	10	0.9	1.749	0.72	0.15	**1.746**	0.67	0.17
No	423	98.4	1084	99.1		4.26			4.57	

a: Unmatched odds ratio. The only exposed control has an exposed case for match.

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 Yale investigators would be apparent if only four controls were misclassified as unexposed to PPA.

With double-blind (interviewer and patients blinded from knowing the drug of interest) setup and careful verification through picture identification, the chance of misclassification was minimized if not totally eliminated. The impact regarding to CHPA PPA Working Group's hypothetical concerns on the CHPA sponsored Yale project can be illustrated as follow. For example, the CHPA PPA working group pointed out with only 4 exposed controls misclassified as unexposed, the significant OR would nullified. This means that the CHPA PPA Working Group assumed a highly unlikely 80% (4/5) misclassification rate of exposed controls.

The odds ratio can be corrected if the misclassification rates were known. Let p_0 denote the misclassification rate of exposed-control and p_1 denote the misclassification rate of exposed-case. Let the true and observed case-control/exposure frequencies be represented by the following two tables.

Table 8 Notation Table of Misclassification

True Case-Control/Exposure Table

	Case	Control
Exposed	K_{11}	K_{01}
Unexposed	K_{10}	K_{00}

Observed Frequency Table of Case-Control/Exposure

	Case	Control
Exposed	N_{11} ($=K_{11}(1-p_1)$)	N_{01} ($=K_{01}(1-p_0)$
Unexposed	N_{10} ($=K_{10}+p_1K_{11}$)	N_{00} ($=K_{00}+p_0K_{01}$)

Hence $K_{10} = N_{10} - N_{11}\,(p_1/(1-p_1))$, $K_{11} = N_{11}/(1-p_1)$, $K_{00} = N_{00} - N_{01}\,(p_0/(1-p_0))$, $K_{01} = N_{01}/(1-p_0)$.

With p_0, p_0 given or estimated, the true odds ratio $OR= (K_{11}K_{00})/(K_{01}K_{10})$ can be estimated by the observed frequencies as follow,

$$OR = \{[N_{00} - N_{01}\,(p_0/(1-p_0))]\,N_{11}/(1-p_1)\}/\{[N_{10} - N_{11}\,(p_1/(1-p_1))]\,N_{01}/(1-p_0)\}$$

Under various assumption on misclassification rate ranges from 20% to 40%, the true odds ratio is estimated to be greater than 7.10 even under the most conservative situation (Table 9).

Table 9 Estimate of True Odds Ratio Under Various Exposure Misclassification Assumptions

p_1: prob(case-exposed being misclassified to case-unexposed)	p_0: Prob (control-exposed being misclassified to control-unexposed)	Corrected OR
0%	20%	9.47
10%	20%	10.53
20%	20%	11.86
0%	30%	8.28
10%	30%	9.21
20%	30%	10.38
30%	30%	11.88
0%	40%	7.10
10%	40%	7.90
20%	40%	8.89
30%	40%	10.18
40%	40%	11.90

- 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 (without PPA).
- Telephone interviewers 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 telephone, suggesting it was more 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.

Verification of each reported medication was done after the interview with the help of a Product Identification Book with photographs (see. page 11 of Yale study report).

- Forty percent of the interviewed cases had a degree of aphasia. The proportion of aphasia cases could have affected accurate identification of a case reported to have used PPA products.

The Yale Investigators' additional analysis stratified by aphasia status showed that except in patients with no prior use of PPA, the associations were consistent in all subsets.

Table 10 Association analysis in subset of patients with no aphasia present

	Case (n=702) No.	%	Controls (n=1376) No.	%	Unadjusted Matched OR	Adjusted for smoking, hypertension, race and education OR	LCL	p-value
No use	664	94.6	1310	95.2				
No Aphasia present rating = 1-3	**Case (n=603)**		**Controls (n=1184)**					
No use	567	94.0	1129	95.3				
Any PPA	26	4.3	27	2.3	1.98 (p=0.013)	1.65	1.00	0.050
Cough/cold	21	3.5	26	2.2	1.63 (p=0.072)	1.35	0.80	0.175
Appetite	6	1.0	1	0.1	12.09 (p=0.007)	15.50	2.04	0.013
Current use	20	3.3	18	1.5	2.23 (p=0.012)	1.70	0.95	0.066
First use	8	1.3	4	0.3	4.00 (p=0.019)	3.59	1.26	0.023
Not first use	12	2.0	14	1.2	1.73 (p=0.123)	1.20	0.59	0.334
Prior use	6	1.0	9	0.8	1.63 (p=0.368)	1.45	0.57	0.257
No Aphasia present (more restricted definition) (rating = 1 only)	**Case (n=388)**		**Controls (n=759)**					
No use	363	93.6	726	95.6				
Any PPA	17	4.4	13	1.7	2.60 (p=0.008)	2.07	1.10	0.029
Cough/cold	14	3.6	13	1.7	2.16 (p=0.035)	1.80	0.93	0.070
Appetite	4	1.0	0	0.0	>16.00* (p=0.013)	-		
Current use	16	4.1	10	1.3	3.17 (p=0.003)	2.66	1.34	0.009
First use	8	2.1	3	0.4	5.33 (p=0.009)	4.60	1.45	0.015
Not first use	8	2.1	7	0.9	2.33 (p=0.082)	1.93	0.80	0.110
Prior use	1	0.3	3	0.4	0.67 (p=0.593)	0.25	--	0.158

* Unmatched OR

- 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 interview (hospital versus home) could also 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.

One of the strength of this CHPA sponsored case-control study was the double blind feature. With it, neither the interviewers nor the patients knew the exposure drug of interest. Hence it is difficult to comprehend the potential bias speculated by CHPAWorking Group.

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 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 confounder of the association of interest. Exclusion of the most severe patients could have affect 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.

Since it has been pointed out in many epidemiologic reports that surrogate interviews of patients who were unable to communicate was the major source of bias, the FDA reviewers raised these concerns and proposed to exclude these patients from the study. This concern was verified by the Yale investigators with pilot information. Regarding the exposure difference between the excluded cases and study cases, there were no data found in either the literature or in this study for support.

8. The study report fails to acknowledge that the findings cannot be entirely generalized to the U.S. population, as the controlled 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 final stroke.

The ability to generalize the study findings into a more general population was never an issue when the protocol was proposed and sponsored by NDMA and it was not an issue when it was reviewed by FDA reviewers in 1992-1993. It was not an issue then and it is not an issue now. Conducting an epidemiological study with simple random sample of whole U.S. consumer population is not realistic. The strength of an epidemiological study is in controlling the potential confounding factors and in minimizing the bias in the conducting and data gathering phase. Hence results of regional epidemiological studies such as Framingham Study can be generalized to U.S. population.

This strength of this study was verified through internal validity. As one of the matching factors, potential bias due to social-economic status is minimized in the study design. If there is indeed a difference in stroke type distribution between this study and the general population, it is mainly due to the exclusion of cases with communication difficulties in order to minimize bias. It would be the same if the sampling frame were the U.S. general population instead.

9. The large differential in participation rates between cases and controls could affect the findings and is not adequately explained in the report. Likely, 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.

The difference in participation rates between cases and controls does not bias the study findings. It is the participation associated with exposure status or with the

confounders of exposure may bias the findings. The majority of the non-enrolled cases (82%) were not enrolled because case subjects were not contacted within the 30 days window. Hence non-enrollment of cases is clearly independent of exposure status. As for non-enrolled controls, no information was available regarding exposure status. However, since both the interviewer and patients were not informed of the drug of interest, there is no reason to believe that non-enrollment is exposure related.

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 confoundings.

- 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 do not satisfy the criterion. Therefore, analysis of exposure to appetite suppressant should use exact, rather than asymptotic, statistical methods.
- The attempt to control for confounding by including cofounders 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 cofounders as a very likely explanation for the observed association. Further, these cofounders cannot be considered controlled in the asymptotic analysis, since the assumption for this analysis is violated.

  As pointed out earlier, the strength of this CHPA sponsored case-control study is not in the significance level of the p-values. The level of significance is hampered by the sample size, which was determined as the minimum required sample size under a pre-assumed exposure rate in the control population and a large targeted odds ratio (OR=5) for the population of objective #1. The sample size requirement was not reasonably attained for other equally important objectives of the protocol. However, it is clear from the data that the association between hemorrhagic stroke and appetite suppressant use existed and the associations across all four objectives and all subset analyses are consistent internally and with Jolson's findings with FDA spontaneous reports in general. The issue on the criterion between asymptotic method and exact method is often over emphasized. In an early published simulation study, it was shown that the asymptotic method controls type I error rate even with minimum expected cell frequency as small as two. On the other hand, the exact method is still conservative at this level for it has type I error rate less than 5%. To be more specific, in this study, the minimum cell frequency is 2.5 for cases exposed to PPA-appetite suppressant.

- A reflection of the inappropriateness of the asymptotic statistical analysis is the fact that the strength of the

association between exposure and disease 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.

The statement given by CHPA Working Group is incorrect. It is often observed in clinical trials that the treatment effect may be greater and with more statistical significance when the confounder such as baseline measurement is adjusted. It is often also happen in epidemiological study that the odds ratios increase in the analysis with stratified table when the association is consistent across stratum.

- 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, these minor changes are within the range of usual increase 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.

The CHPA PPA Working Group's comment emphasizes on 1) blood pressure increases in clinical trials and 2) when used according to label recommended dose. However, it is well understood that clinical trial is not designed with the capability to detect rare adverse event such as hemorrhagic stroke. In addition, without advise by a physician, consumers of OTC drug products often do not use the product according to label recommendations as they would when they take it as prescription product. Hence, this CHPA sponsored case-control study plays a much more important role than any previous studies. This is a well-planed postmarketing study designed to confirm the safety concerns raised from the FDA Spontaneous Response System findings dated in 1993.

C. SUMMARY OF REVIEW

1. This is a well-designed and conducted case-control trial. Both NDMA (now CHPA) and FDA scientists carefully reviewed its protocol before the study was conducted. Its unique double-blind feature (i.e. both interviewers and interviewees were blinded from the target exposure drug) minimized the potential bias of an observational study. It is clear in this FDA reviewers' experience that it is one of the best planned, conducted and most thoroughly analyzed studies reviewed in the last ten years.

2. The study was designed with four equally important objectives:

    1) To estimate the association between PPA and hemorrhagic stroke among men and women aged 18 – 49 years.

2) To estimate the association between PPA and hemorrhagic stroke by type of PPA exposure among the same target population
3) Among women aged 18-49 years to estimate the association between first use of PPA and hemorrhagic stroke
4) Among women aged 18-49 years to estimate the association between PPA in appetite suppressants and hemorrhagic stroke.

The level of importance of objectives #3 and #4 should be emphasized because of the safety concerns raised in Jolson's review of the FDA spontaneous reports.

3. Positive associations between PPA use and hemorrhagic strike were shown in all study objectives. All except in the cohort of the first objective, the associations were statistically significant. In the cohort of the first objective, the association was near significant. The strength of the study is in the consistency of the associations. First, the ranking of the associations under the four objectives found in this study was consistent with the primary safety concerns in Jolson's review of the FDA spontaneous reports. Second, the strong consistency of the associations found through internal validation of the study data and multiple analyses with adjustment for confounders and within subgroups stratified by the confounders. The weak association found for objective #1 was due partially to the lack of association among male patients in this data.

4. The strength of the associations was strengthened by the strong association found in the subset of patients with no history of hypertension. The associations suggest that PPA use is a risk factor independent of hypertension history.

5. In an ad hoc analysis of a subset of patients with proper dosage information, the association was further strengthened by the statistically significant association within current PPA users of more than 75mg PPA (median dose). There was no significant association among patients currently using no more than 75 mg PPA.

ACKNOWLEDGEMENT

Contributions from Dr. Parivash Nourjah of Division of Drug Assessment 1 in addressing CHPA PPA Working Group's Comments on Yale report of hemorrhgic stroke study are to be acknowledged.

_____

Yi Tsong, Ph.D., Mathematical Statistician
Quantitative Methods Research Staff

Concur: _____
Stella G. Machado, Ph.D.
Director, Quantitative Methods Research Staff

copies: HFD-430 Beitz/Trontell/La Granade/Nourjah/Guinn
HFD-705 QMRS Chron/Machado/Tsong
Electronic copy/O:/QMR/chron00/pdra/ppa.yale.review.

References:

1. O'Neill RT, Van De Carr SW, A case-control study of adrenergic decongestants and hemorrhagic CVA using a Medicaid database. *FDA report*, CDER/FDA, Rockville, MD, 1984.
2. Jick H, Aselton P, Hunter JR, Phenylpropanolamine and cerebral hemorrhage. *Lancet*, 1984:1017.
3. Jolson HM, Epidemiological reviews of phenylpropanolamine safety issue, FDA Memorandum, CDER/FDA, Rockville, MD, April 1991.
4. Tsong Y, Statistical review of Yale proposal to study hemorrhagic stroke and PPA, *FDA Internal Memorandum*, Rockville, MD, 1993.
5. Graham DJ, Tsong Y, Phenylpropanolamine (PPA) and Yale hemorrhagic stroke project (OTC Trac No. 310-04), *FDA Internal Memorandum*, 1993.
6. *Memorandum of November 9, 1992 Meeting:* Between Nonprescription Drug Manufacturers Association and FDA, CDER/FDA, Rockville, Md.
7. *Memorandum of August 15, 1993 Meeting:* Between Nonprescription Drug Manufacturers Association and FDA, CDER/FDA, Rockville, Md.
8. Freiman J, Review of a revised protocol entitled "Hemorrhagic Stroke Project: Case-control study of PPA and hemorrhagic stroke", *FDA Internal Memorandum*, June 16, 1994.
9. Gilbertson WE, FDA Letter to R. William Soller, Senior Vice President of Nonprescription Drug Manufacturers Association, FDA Docket No. 81N-0022, Comment No. PR7, CDER/FDA, Rockville, MD, June 17, 1993.
10. Soller RW, NDMA Letter to William E. Gilbertson, Director of Monograph Review Staff, Office of OTC Drug Evaluation, CDER/FDA, August 11, 1993
11. Soller RW, NDMA Letter to William E. Gilbertson, Director of Monograph Review Staff, Office of OTC Drug Evaluation, CDER/FDA, FDA Docket No. 81N-0022, October 14, 1993.
12. Soller RW, Totman LC, Consumer Healthcare Product Association (CHPA), Letter to Docket management Branch (HFA-305), Office of OTC Drug Evaluation, CDER/FDA, May 24, 2000.