Gilbertson

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG - 6 1991

FROM: Medical Officer, HFD-733

THROUGH: Acting Division Director, HFD-730 8.5.91

TO: Office Director, ODE I, HFD-100

SUBJECT: Additional Analysis of Phenylpropanolamine (PPA) and Cerebral Hemorrhage

This memo responds to your request for further analyses of spontaneous stroke reports associated with PPA-diet pills and is a supplement to my memo entitled *Epidemiologic review of phenylpropanolamine safety issues*, which was dated April 30, 1991. As requested during the meetings on July 19 and 23, I have included the following information in this memo:

I Summary of all stroke reports associated with PPA-diet pills that have been received by the Spontaneous Reporting System, or by the Thompson Medical Company, or that have been published in the North American Medical Literature.

II A synopsis of the Drug Abuse Warning Network (DAWN) and Poison Control Center (PCC) databases, and an assessment of the "dosing episode" method for adjustment of drug mentions in each database.

III A comparison of the observed number of cerebral hemorrhage reports vs. expected number of cerebral hemorrhages in PPA-diet pill users by chance, when the underlying assumptions of reporting rate and period of risk are changed.

I Table 1 lists the relevant characteristics of the 44 reports of stroke that have been associated with PPA-diet pills. Included in this table are: (a) domestic spontaneous reports from health professionals in the SRS from 1969 through January 1991 (19 reports), (b) reports from health professionals that were received by Thompson Medical Company and sent to the FDA upon request in a submission dated April 25, 1991 (15 reports), and (c) published reports from the North American medical literature from 1966 - July 1991, which had not been previously submitted to the SRS (10 reports).

For your reference, Table 2 summarizes the salient characteristics of the reports of hemorrhagic stroke associated with PPA-diet pills.

II The spontaneous reporting experience of the DAWN and PCC databases was discussed during the May 9, 1991 meeting. There are two fundamentals issues regarding using DAWN and PCC data to resolve safety questions with PPA-diet pills: (1) the relevance of the databases, and (2) the adjustment methodology to control for differences in product availability for comparative analyses across drug classes.

The National Institute on Drug Abuse (NIDA) collects information on drug abuse related emergency room episodes and medical examiner cases through the Drug Abuse Warning Network (DAWN). The objectives of DAWN are to identify substances associated with drug abuse episodes, monitor drug abuse patterns and trends, detect new abuse entities and combinations, assess health hazards associated with drug abuse, and provide data for national, state, and local drug abuse policy and program planning. In DAWN, drug abuse is defined as the "nonmedical use of a substance for psychic effect, dependence, or suicide attempt/gesture". During 1989, a total of 770 hospital emergency rooms (ER) located in 21 metropolitan areas and 87 medical examiners located in 27 areas participated in DAWN.[1] A total of 153,650 drug abuse episodes involving 249,349 drug mentions were reported to DAWN ERs. The most frequently mentioned drugs in DAWN ER episodes were cocaine (61,655 mentions), alcohol-in-combination (46,735 mentions), heroin/morphine (20,566 mentions), and marijuana/hashish (9,867 mentions), acetaminophen (6,456 mentions), aspirin (5,048 mentions), PCP/PCP combinations (4,899 mentions), and diazepam (4,874 mentions). For the category OTC-diet aids (a break-down of specific products has been requested from NIDA) 390 mentions were reported. These 390 mentions occurred largely as a suicide attempt (67.2%) or for the psychic effect (14.9%). These episodes occurred predominately in persons under the age of 30 (79.6%), with 32.3% occurring in persons under the age of 18. While aspirin and acetaminophen each have a greater number of mentions, their motive for drug use and age distribution of drug use is similar to the OTC-diet aid pattern. For acetaminophen and aspirin, suicide attempt was the predominant motive of use (82.7% and 83.4% respectively), with similar proportions of use by age (33.8 and 33.7 respectively under the age of 18 and 79.4% and 77.3% respectively under the age of 30).

The American Association of Poison Control Center National Data Collection System (PCC) collects reported accidental poisonings from 70 participating centers. Approximately 1.6 million cases of poisoning were reported in 1989 and 61.1% of cases occurred in children under the age of 6[2]. During 1989, less than 1% of exposure cases of all ages were classified as "adverse reactions" to drugs. There were 2,063 exposure cases with PPA-diet pills (71.7% occurred in children under the age of 18), and 376 with PPA-diet pills and caffeine (60.9% occurred in children under the age of 18). These exposure cases were classified as adverse reactions in 1.7% and 1.6% of all PPA-diet pill poisoning cases respectively. Therefore, mentions in the PCC database reflect more on the availability of products in the home than on the adverse experience of drugs used for their therapeutic intent.

Differences in patterns of drug use further complicate comparative analyses in the DAWN and PCC databases. Dr. Raford introduced the concept of "dosing episodes" to try to adjust the number of drug mentions for differences in number of therapeutic courses[3]. Unfortunately, Dr. Raford sites anonymous and unpublished references for the derivation of these dosing episodes. Additionally, "dosing episodes" refer to therapeutic use of a drug and are not particularly relevant to the abuse experience of DAWN mentions, or the accidental poisoning episodes of the

PCC cases. There is no satisfactory method of adjustment to account for differences in product availability in the home at this time other than controlling for the amount of the dispensed product.

In summary, DAWN and PCC databases are designed to monitor trends in substance abuse and accidental poisoning, and do not provide information about adverse events that occur when drugs are used for their therapeutic intent. Additionally, DAWN and PCC are voluntary reporting systems, and can not provide population-based estimates of PPA-diet pill use or misuse. A national probability sample is needed to study patterns of PPA-diet pill use in the population.

III Scenario Analysis

In my previous memo, the background rate of hemorrhagic CVA in PPA-diet pill users was calculated in order to determine if the reported number of cases was in excess of the expected number of cases of hemorrhagic stroke by chance alone. As we discussed in our meeting with NDMA on July 23, I have expanded on this analysis by varying the underlying assumptions of period of risk and reporting rate.

The number of observed cases that are included in each of the following four scenarios varies depending on the assumption of length of risk for a hemorrhagic stroke after PPA-diet use. The length of risk for a hemorrhagic stroke following PPA-diet pill use might vary from a first day only risk to a risk that extends throughout the entire course of PPA-diet pill use. The expected rates for cerebral hemorrhage reports were calculated for both possible extremes of the risk period.

There were three different levels of reporting estimates that were considered at the 7/23 meeting (10%, 5%, and 1%). The ratios of the observed to the expected number of cerebral hemorrhage reports (O/E) were calculated separately for each of the three estimates of reporting, for each scenario of risk period. (see previous memo for discussion of reporting rates of ADEs).

The results of the ratio of the observed to the expected reports of cerebral hemorrhage are summarized in Table 3. As defined by NDMA, when the O/E ratio was >1, the observed number of cases exceeded the expected number of cases, and a causal relationship is suggested.

The assumptions that were common to all four scenarios are as follows:

- PPA-diet pill consumers/year - 9,000,000 (6,000,000 women aged $\leq$ 44 years, 2,100,000 women aged 45-64 years, and 900,000 men of any age)[4]
- PPA-diet pill courses/year/user on average - 2
- Median length of PPA-diet pill course - 16 days[5]
- Incidence of hemorrhagic stroke - 10 events/100,000 person-years[6]
- Total CVA reports (SRS, manufacturer, and literature) - 44
- Subset of CVA reports that are definitely hemorrhagic - 35
- Reporting rate estimates: 10%, 5%, and 1%
- Reporting to the literature and to the FDA from manufacturers of products without an NDA occurs at approximately the same rate or at a lower rate than does direct reporting to the SRS [there is no available data on this assumption].

The assumptions which varied with each scenario are itemized below.

Scenario A: First day risk, reports included of men and women of all ages, 1977-1990

Additional assumptions for scenario A:

- Period of risk for CVA - first 24 hours
- Hemorrhagic cases on first day or NOS - 22 reports
- Years included: 1977-1990 (14 years)
- Age/Sex of reported cases: male and female, 15-60 years

Consumers X Incidence X Proportion of year at risk X Number of courses/year = Expected cases/year

9,000,000 consumers X 0.0001 events/person-year X 0.0027 years/course X 2 courses/year = 4.9 cases/year

Expected cases/year X years of study = total expected cases if 100% reporting

4.9 cases X 14 years = 68.0 cases

Scenario B: Risk for all days of PPA-diet pill use, reports included of men and women of all ages, 1977-1990

Additional assumptions for scenario B:

- Period of risk for CVA - any day of a 16 day course
- Equal reporting of events occurring 1-16 days after starting PPA-diet pills
- All reported hemorrhagic CVAs, regardless of duration of PPA-diet use - 35 cases
- Years included: 1977-1990 (14 years)
- Age/Sex of reported cases: male and female, 15-60 years

Consumers X Incidence X Proportion of year at risk X Number of courses/year = Expected cases/year

9,000,000 consumers X 0.0001 events/person-year X 0.044 years/course X 2 courses/year = 77.8 cases/year

Expected cases/year X years of study = total expected cases if 100% reporting

77.8 cases X 14 years = 1088.6 cases

Scenario C: First day risk, reports included of women < 44 years, 1980-1990

Additional assumptions for scenario C:

- Period of risk for CVA - first 24 hours
- Hemorrhagic cases on first day or NOS - 14 reports
- Years included: 1980-1990 (11 years)
- Age/Sex of reported cases: female, 15-44 years

Consumers X Incidence X Proportion of year at risk X Number of courses/year = Expected cases/year

6,000,000 consumers X 0.0001 events/person-year X 0.0027 years/course X 2 courses/year = 3.2 cases/year

Expected cases/year X years of study = total expected cases if 100% reporting

3.2 cases X 11 years = 35.6 cases

Scenario D: Risk for all days of PPA-diet pill use, reports included of women < 44 years, 1980-1990

Additional assumptions for scenario D:

- Period of risk for CVA - any day of a 16 day course
- Equal reporting of events occurring 1-16 days after starting PPA-diet pills
- All reported hemorrhagic CVAs, regardless of duration of PPA-diet use - 22 cases

- Years included: 1980-1990 (11 years)
- Age/Sex of reported cases: female, 15-44 years

Consumers X Incidence X Proportion of year at risk X Number of courses/year = Expected cases/year

6,000,000 consumers X 0.0001 events/person-year X 0.044 years/course X 2 courses/year = 51.8 cases/year

Expected cases/year X years of study = total expected cases if 100% reporting

51.8 cases X 11 years = 570.2 cases

Comment: As is evident in Table 3, the ratio of observed to expected (O/E) reports is dependent on the assumptions of reporting rate and risk period. The ratio of O/E exceeded 1 for each estimate of reporting when the period of risk was assumed to be the first day of PPA-diet pill use. This finding was not dependent of the selection criteria for the age, the sex, and the year of the included reports. In contrast to this observation, when the assumption for the period of risk was extended for the entire course of PPA-diet pills, the ratio only exceeded 1 when the reporting rate estimate was 1%.

There are several assumptions in this analysis which merit further comment. The population at risk is estimated from NDMA marketing data for the age and sex distribution of PPA-diet pill use. The FDA does not have independent confirmation of their marketing data because of the difficulty with exposure ascertainment to OTC products, as described in my previous memo. Secondly, reports of cerebral hemorrhage were not excluded from analysis on the basis of possible alternative explanations. The inclusion of all possible cases for this analysis is appropriate since the population at risk and the incidence of cerebral hemorrhage can not be adjusted to exclude persons with such concomitant risk factors as hypertension, congenital vascular defects, or other illnesses.

In Scenarios B and D, attribution and reporting are assumed to be equal for each of 16 days of PPA-diet pill use. Whether adverse events are more likely to be reported in individuals who have recently started a drug is not known, however one can hypothesize that this may be the case. If this hypothesis is true and the reporting rate diminishes with each day of use, then the expected number of reported cases would be greatly reduced, and the O/E ratios increased in Scenarios B and D.

Please contact me if any issues require further clarification.

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Concur:
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CC:
HFD-100/Botstein
HFD-110/Lipicky/Dern
HFD-120/Leber
HFD-150/Burke
HFD-210/Gilbertson
HFD-700/Anello/Johnson
HFD-710/O'Neill
HFD-733/Stadel/Jolson/File chron, dru 1.7 phenylpropanolamine
HFD-735/Barash
HFD-737/Gelberg/Armstrong

Table 1. Demographic and clinical characteristics of patients with cerebrovascular accidents associated with PPA-diet products[1], reported to the Food and Drug Administration[2] or published in the North American medical literature[3], 1969 - January 1991

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
1	27,F,1977 Direct 93721 77081000202401	Permathene-12® 1 One dose	NOS	*	Nardil®	No	Slight return of function
2	19,F,1978 Direct 389497 86011000101451	Dexatrim® 8 (50mg) *	Yes	"otherwise healthy"	*	No	Death
3	27,F,1978 Manufacturer 002	Appedrine® (25 mg) 9 4 days	Yes	1 mo post-partum	*	NOS	*
4	60,F,1980 Manufacturer 011	Dexatrim ES® (75mg) 1 3 months	Yes	Migraine	Antihistamines	Yes ("ruptured congenital A-V aneurysm" - sic)	*

[1]Milligram content of product is indicated only when it was specified by reporter.

[2]SRS cases reflect domestic spontaneous reports from health professionals. Manufacturer cases refer to submission dated April 25, 1991 from Thompson Medical Company, Inc.

[3]Year refers to year of event for SRS reports, or year of publication for literature reports.

* indicated incomplete information on the '1639' reporting form; NOS indicates information not otherwise specified.

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
5	26,F,1981 Direct 123070 81101000206101	Dexatrim® 2 One dose	Yes	*	None	No	Alive
6	27,F,1981 Direct 162057 83061000114501	Ayds® 3 (75mg) one week at a dose of 1/day	Yes	No history of hypertension; previously healthy	None	No	Death
7	39,F,1981 Direct 130820 82031000217201	Dexatrim® "gradually increased dose" 2 weeks	Yes	*	None	NOS	Death
8	27,F,1981 Manufacturer 007	Dexatrim ES® (75mg) 1 1 day	Yes	Migraine, 3 1/2 wks post-partum	*	NOS	*
9	16,F,1981 Manufacturer 008	Prolamine® 10 4 days	No	Alcohol, substance abuse	*	NOS	*
10	31,F,1981 Manufacturer 012	Prolamine® 2 1 day	Yes	*	*	Yes (micro-AVM)	*
11	26,F,1982 Direct 131657 82041000102101	Dietac® 2 One dose	Yes	None	None	No	Residual hemiplegia

Table 1 (cont.) Characteristics of CVA cases reported with PPA-diet pills

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
12	31,F,1982 Direct 156885 83030100020171	Thinz® (25mg) 2 tabs taken 2hr apart 2 days	Yes	None	None	No	spastic hemiparesis
13	32,F,1982 Direct 137437 82071000104301	Dexatrim® 2 *	Yes	None	None	NOS	Alive
14	45,F,1982 Direct 389496 8601000101341	Dexatrim® 2 (75mg) 1 dose	Yes	"Healthy"	Nardil®, prn Valium®	No	Death
15	47,F,1982 Direct 137436 82071000104201	Dexatrim® 1 4 days	Yes	Hypertension off antihypertensives	None	NOS	Alive
16	32,F,1982 Direct 309329 8405100001491	Dexatrim® "as directed" 4 days	NOS	15 pack-years smoking; toxemia with first pregnancy	*	NOS	Recovery
17	15,F,1982 Manufacturer 009	Dexatrim ES® (75mg) * Intermittent during month and prior summer	No	substance abuse, migraine	Sine-Aid®, Tigan®	NOS	*

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
18	56,F,1983 Direct 160593 83050103600101 (published - ref [10])	Thera-Trim® (75mg) 2 first dose	Yes	None	None	NOS	Recovery
19	24,M, 1983 Literature [7]	Dexatrim® (50 mg) 8-10 3 months	No	"previously fit"	*	No	Recovered
20	55,M,1983 Manufacturer 006	Dexatrim ES® (75 mg) * 3 1/2 months	NOS	Hypertension, smoker, alcohol consumption	*	NOS	*
21	35,F,1983 Manufacturer 010	Dexatrim ES® (75mg) 2 2 days	Yes	Alcohol	*	Yes (aneurysm)	*
22	39,F,1983 Manufacturer 015	Dexatrim ES® (75 mg) 1 1 year	Yes	Smoker	*	NOS	*
23	40,M,1984 Direct 180501 84099000200181	Dexatrim® 1 1 year	No	5-6 cigars/d, otherwise "no other cardiovascular risk factors"	None	No	Residual lt arm weakness and lt central 7th
24	59,F,1984 Direct 394111 86041000101521	Dexatrim® (75 mg) 1 "chronic"	Yes	Hydrocephalus-1970 (stable)	None	No	Alive with disability

Table 1 (cont.) Characteristics of CVA cases reported with PPA-diet pills

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
25	25,M,1984 Literature [8]	NOS liquid PPA-diet preparation "5X recommended dose" *	Yes	"previously healthy"	*	No	*
26	35,F,1984 Manufacturer 014	Dexatrim® 1 5 days	No	smoker	*	NOS ("plaque in lt carotid)	*
27	20,F,1985 Literature [9]	Dexatrim® (50 mg) 2 6 months	Yes	None	None	No	Recovered
28	45,F,1985 Literature [10]	Dexatrim® (50 mg) 1 None in months	Yes	None	None	No	Recovered
29	16,F,1986 Direct 445923 87021000100091	Dexatrim®, Acutrim II® (mixture) 12 6 weeks	Yes	None	None	NOS	Alive with sequelae
30	20,F,1986 Direct 448898 87021000200451	Dexatrim® 6 1 dose	Yes	*	None	No	Alive with disability
31	22,F,1986 Direct 419887 86091000100781	Dexatrim® 2 1 dose	Yes	Cocaine used 3 weeks prior	alcohol, marijuana	No	Alive

Table 1 (cont.) Characteristics of CVA cases reported with PPA-diet pills

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
32	40,F,1986 Manufacturer 013	Dexatrim ES® (75mg) 2 1 day	Yes	Smoker, Alcohol	*	NOS	*
33	23,F,1987 Direct 417825 87081000100011	Dexatrim ES plus vit C® (75mg) 4 1 dose	Yes	None	None	No	Alive with sequelae
34	25,F,1987 Direct 507788 87111000201262	Dexatrim® 2 1 dose	Yes	2 weeks post-partum	*	No	Alive
35	20,F,1987 Literature [11]	NOS PPA-diet (75 mg) 1 None in 6 months	No	Preeclampsia 3 yrs. and 6 yrs. prior	None	No	Near-complete recovery
36	35,F,1987 Literature [12]	Dexatrim ES® (75mg) 1 None in months	Yes	3 wks post-partum, otherwise negative	pm Librium®	No	Recovered
37	39,F,1987 Literature [13]	Dexatrim® (75 mg) 1 first dose	Yes	well controlled hypertension; obesity	nadolol	No	Decerebrate
38	32,M,1987 Literature [13]	Dexatrim ES® (75mg) 2 first dose	Yes	alcoholism	disulfiram	No	Incomplete recovery

Table 1 (cont.) Characteristics of CVA cases reported with PPA-diet pills

#	Age, Sex, Year Source, Control #, Accession #, or reference	Suspect drug Dose(capsules) Duration	Hemorrhagic CVA (Yes/No/NOS)	Past medical history	Concomitant medication	Aneurysm or AVM (Yes/No/NOS)	Outcome
39	30,F,1987 Literature [14]	Dexatrim ES® 1 None in 10 months	Yes	3 wks post-partum, otherwise negative	No	No	residual deficits
40	48,F,1987 Manufacturer 003	Dexatrim ES® (75 mg) * 1 day	Yes	migraine, obesity, "Cushing's syndrome symptoms"	*	*	*
41	32,M,1988 Manufacturer 001	"Dexatrim"® * 6 days	Yes	Alcohol, smoking	prescription diet pill	*	*
42	*,M,1988 Manufacturer 004	Dexatrim® * *	Yes	*	*	*	*
43	38,F,1988 Manufacturer 005	Dexatrim ES® (75mg) 1 2 days	Yes	smoker	*	Possible ruptured aneurysm	*
44	17,F,1989 Literature [15]	Diet-Aid® (75 mg) 5 intermittently for 1 mo	Yes	excellent health	NOS	No	residual hemianopsia

Table 2. Patient demographics and PPA-diet pill usage patterns for cerebral hemorrhage reports associated with PPA-diet pills.

Characteristic	n	%[1]
Total Cerebral Hemorrhage reports	35	(100)
Age (years)		
15-24	7	(20.6)
25-34	13	(38.2)
35-44	7	(20.6)
45-54	4	(11.8)
55-60	3	(8.9)
NOS[2]	1	
Sex		
Male	4	(11.4)
Female	31	(88.6)
Duration of use		
One day	18	(58.0)
2-7 days	6	(19.4)
8 - 16 days	1	(3.2)
> 16 days	6	(19.4)
NOS	4	
Dose preceding CVA (capsules)		
1	10	(32.3)
2	13	(41.9)
3-6	5	(16.1)
8-12	3	(9.7)
NOS	4	

[1] Percentages indicate percent of total reports when the characteristic was known.

[2]NOS denotes not otherwise specified.

Table 3. Ratio of observed to expected reports of hemorrhagic CVAs for four scenarios of risk period and population at risk, according to reporting rate assumption

Scenario	Observed cases	Reporting Rate Estimates					
		10%		5%		1%	
		Expected cases	Ratio O/E	Expected cases	Ratio O/E	Expected cases	Ratio O/E
A	22	6.8	3.2	3.4	6.5	0.7	32.3
B	35	108.9	0.3	54.4	0.6	10.9	3.2
C	14	3.6	3.9	1.8	7.9	0.4	39.3
D	22	57.0	0.4	28.5	0.8	5.7	3.9

Summary of scenarios:

A: reports of men and women of all ages included; 1977-1990; first day of PPA-diet pill use

B: reports of men and women of all ages included; 1977-1990; any day of PPA-diet pill use

C: reports of women $\leq$ 44 years; 1980-1990; first day of PPA-diet pill use

D: reports of women $\leq$ 44 years; 1980-1990; any day of PPA-diet pill use

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4.Derived from testimony by William Stoller, Ph.D. at the FDA public meeting on the safety, effectiveness, and misuse of phenylpropanolamine hydrochloride for over-the-counter weight control use, May 9, 1991.

5.Critique by Charles winick, PhD on the Second Testimony by Paul Raford, M.D. Submission from Thompson Medical Company, Inc. to the FDA, January 1991.

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