FOOD AND DRUG ADMINISTRATION

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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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Meeting on
Safety Issues of Phenylpropanolamine (PPA)
in Over-the-Counter Drug Products

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Thursday
October 19, 2000

The meeting was held at 8:00 a.m. at the Holiday Inn Gaithersburg, Two Montgomery Village Avenue, Gaithersburg, Maryland 20879, Dr. Eric P. Brass, Chairman, presiding.

PRESENT:

Eric P. Brass, M.D., Ph.D., Chairman
George A. Blewitt, M.D., Industry Liaison (non-voting)
Louis R. Cantilena, Jr., M.D., Ph.D., Member
Susan Cohen, Consumer Representative (voting)
Ralph D'Agostino, Ph.D., Consultant (voting)
Janet Daling, Consultant (voting)
Janet Elashoff, Consultant (voting)
Edwin E. Gilliam, Ph.D., Member
Sio Gilman, M.D., Consultant (voting)
Julie A. Johnson, Pharm.D., Member
Steven Kittner, M.D., MPH, Consultant (non-voting)
Y.W. Francis Lam, Pharm.D., Member
Richard A. Neill, M.D., Member
Hari Cheryl Sachs, M.D., Member
Donald L. Uden, Pharm.D., Member
Steven Warach, M.D., Ph.D., Consultant (non-voting)
Henry W. Williams, Jr., M.D., Member
Sandra Titus, Ph.D., Executive Secretary

Hemorrhagic Stroke Project Investigation

Walter N. Kernan, M.D.
Lawrence M. Brass, M.D.
Joseph P. Broderick, M.D.
Ralph I. Horwitz, M.D.
Lewis B. Morgenstern, M.D.
Catherine M. Viscoli, M.D.
Janet Lee Wilterdink, M.D.

Consumer Healthcare Products Association Panel

R. William Soller, Ph.D.
George L. Blackburn, M.D., Ph.D.
Philip B. Gorelick, M.D., M.P.H., FACP
Charles H. Hennekens, M.D., Dr.P.H.
Robert Hirsch, Ph.D.
Brian S. Hoffman, M.D.
Philip D. Walson, M.D.
Noel S. Weiss, M.D., Dr.P.H.

FDA Representatives

Robert DeLap, M.D., DDE
Charles J. Ganley, M.D., DOTCDP
David Graham, M.D., M.P.H., OPDRA
Linda Katz, M.D.
Russell Katz, M.D., Neuropharm Division
Lois La Grenade, M.D., M.P.H., OPDRA
Robert O'Neill, Ph.D.
Robert Sherman, M.D., DOTCDP
Yi Tsong, Ph.D., OPDRA

Public Speakers

David E. Schteingart, M.D., Chattem
Brian Strom, M.D., M.P.H., Whitehall Corporation
Sidney Wolfe, M.D., Public Citizens Health Research Group

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(8:03 a.m.)

CHAIRMAN BRASS: Good morning. I'm Eric Brass from Harbor - UCLA Medical Center, and I'd like to welcome you all to this meeting of the Nonprescription Drugs Advisory Committee to discuss safety issues of Phenylpropanolamine in Over-the-Counter Drug Products.

I'd like to begin by going around the table allowing people to introduce themselves. We have a number of consultants with us today. I'd like to remind members of the committee and our consultants to please always use the microphone when raising issues. Please be sure to press the on/off button prior to talking, and I strongly advise if you do not want your side comments recorded to turn off the microphone when you are done speaking. Perhaps we could begin with Doctor Warach.

DOCTOR WARACH: Steven Warach from NIH.

DOCTOR BLEWITT: George Blewitt, industry representative for NDAC.

DOCTOR KITTNER: Steven Kittner from University of Maryland. I'm a neurologist/epidemiologist.

DOCTOR GILMAN: Sid Gilman, University of Michigan. I'm a neurologist.

DOCTOR UDEN: Don Uden from the University of Minnesota, member of NDAC.

DOCTOR GILLIAM: Eddie Gilliam, family nurse practitioner from Tucson, Arizona. Member of the NDAC Committee.

DOCTOR ELASHOFF: Janet Elashoff, biostatistics, UCLA and Cedars-Sinai.

DOCTOR NEILL: Richard Neill. I'm a family physician from the University of Pennsylvania, member of NDAC.

DOCTOR DALING: Janet Daling, University of Washington and Fred Hutchinson Cancer Research Center, epidemiologist.

DOCTOR WILLIAMS: Henry Williams from Howard University, a member of NDAC.

DOCTOR SACHS: Hari Sachs, pediatrician, member of NDAC.

DOCTOR TITUS: Sandy Titus, the Executive Secretary for NDAC.

DOCTOR LAM: Francis Lam from University of Texas Health Science Center at San Antonio. I'm a member of NDAC.

MS. COHEN: Susan Cohen and I'm the consumer representative.

DOCTOR JOHNSON: Julie Johnson from University of Florida and a member of NDAC.

DOCTOR D'AGOSTINO: Ralph D'Agostino from Boston University and the Framingham Study, a biostatistician/epidemiologist.

DOCTOR CANTILENA: Yes. Hi. I'm Lou Cantilena from the Uniformed Services University, a clinical pharmacologist.

DOCTOR SHERMAN: Bob Sherman, FDA's Division of OTC Drug Products.

DOCTOR LA GRENADE: Lois La Grenade, epidemiologist, Office of Postmarketing Drug Risk Assessment, FDA.

DOCTOR KATZ: Russ Katz, FDA Neuropharm Division.

DOCTOR GANLEY: Charlie Ganley, Director of Over-the-Counter Drugs.

DOCTOR DELAP: Bob Delap, Office of Drug Evaluation, FDA.

CHAIRMAN BRASS: Thank you very much.

I'll now turn the floor over to Doctor Titus for the conflict of interest statements.

DOCTOR TITUS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the

meeting and all financial interests reported by the committee participants, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Since this issue to be discussed by the committee at this meeting will not have a unique impact on any particular firm or product but rather may have wide-spread implications with respect to an entire class of products, in accordance with 18 USC 208(b), each participant has been granted a waiver which permits them to participate in today's discussion. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

We would like to note for the record that Doctor George Blewitt is the non-voting industry representative and is on the committee to represent industry's interest. As such, he has not been screened for any conflict of interest.

With respect to FDA's invited guests, FDA would like to disclose that Doctors Samuel Suissa, J.P. Mohr, Janet Wilterdink, Catherine

Viscoli, Lewey Morgenstern, and Ms. Melinda Cox were part of the Yale investigators which includes two members of the Data Monitoring Board. Data from the results of the Epidemiological Study designed to assess the risks of hemorrhagic stroke associated with the use of phenylpropanolamine will be part of today's discussion. We believe this information should be made public to allow the participants to objectively evaluate their comments.

In addition, Doctors Wilterdink, Morgenstern, Suissa and Ms. Cox also reported that they have been involved in studies concerning phenylpropanolamine for a variety of pharmaceutical firms.

Finally, Doctor Steven Kittner would like to disclose for the record that he has been involved in studies of phenylpropanolamine in over-the-counter products through his prior review of case reports of intracerebral hemorrhage for the FDA. He has also conducted a study of ischemic stroke in young women that includes some questions on phenylpropanolamine use.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of

the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRMAN BRASS: Thank you very much.

We will move on to the open public hearing. I would ask that each presenter during the session come forward to the podium for their presentation, identify themselves, their affiliation and any sponsorship associated with their appearance today. Most importantly, if they could each be sure to stay to the 10 minute absolute time limit.

Our first presenter in the open public hearing will be Doctor Brian Strom.

DOCTOR STROM: I'm Brian Strom from the University of Pennsylvania School of Medicine. Suffice it to say, University of Pennsylvania likes titles, but I'm a general internist/clinical pharmacologist and epidemiologist. I'm head of epidemiology and biostatistics at the University of Pennsylvania, and what I do mostly for my life is study the effects of drugs.

I am also in this role a consultant to

Whitehall-Robbins Healthcare, who asked me to provide an independent critique, independent of everything else that you've heard today and independent of them, of my sense and reactions to the Yale Hemorrhagic Stroke Project.

The Yale Hemorrhagic Stroke Project was initiated primarily due to a series of case reports about hemorrhagic strokes. I think this was an extremely appropriate action, given the severe limitations and spontaneous reporting that we all know about in their ability to evaluate cause. Until the Yale Study was done, the available data were these spontaneous reports and other epidemiological studies that were negative studies already published but were not felt to be absolutely convincing.

This was a huge, ambitious study. It was thoughtfully designed. Unfortunately, however, as finally done, it generated some methodologic issues and problems which is presumably why we're here today discussing it. What I'll briefly do is discuss it in the conventional way epidemiologists approach such evaluations, talking about chance, talking about confounding and talking about bias.

First talking about chance. This study started out with power that was marginal statistical

power. It was designed to detect an OR of five with a one-tail statistical test. The result means that there are very small numbers of exposed cases and exposed controls and very fragile results, and I'll bring this out more specifically in a few minutes.

As stated very clearly by the authors, there were three co-equal aims or five, depending on how you count them, seeing this as two of the aims had sub-aims. One could argue, therefore, because of the multiple testing, that the true alpha shouldn't have been .05 but should be .0166 or .01 if you consider this five equal aims.

The inconsistent results that you see in the sub-groups by gender and by indication and the inconsistent results between PPA and other sympathomen medics suggest chance as an explanation as well. And finally, the quote/unquote "dose response relationship" was in fact never tested statistically. That is, whether or not the higher dose users were at increased risk over the lower dose users and, looking at the data, almost surely that comparison is not statistically significant.

Let me show you the five key findings very specifically. This is the first of three co-equal aims looking at all PPA. As you can see, the 27 exposed cases, 33 exposed controls, and no

statistical difference.

Moving on to the second co-equal aim. In fact, these are two different aims. Looking at the results by indication within the cough/cold preparation, again even by conventional uncorrected criteria, there was no statistically significant difference with 22 and 32 exposed individuals.

Moving on to appetite suppressants, however, it is now statistically significant, borderline significant if you use the criteria of .0166 or not significant if you use the criteria of .01, and it is totally based on six exposed cases and one exposed control. And this is what I meant by a fragile finding, that essentially the entire results of the study rest on these seven individuals.

The third co-equal aim which again was really two aims were results in women. Part of that was all PPA first use. This is a borderline statistically significant result using conventional criteria. It is not statistically significant if you correct for multiple testing and is based on seven exposed cases and four exposed controls.

And the last finding which was statistically significant was appetite suppressants in women and, again, it's based on six exposed cases

and one exposed control. So the numbers here are very small and very fragile which is important to the rest of what I'm going to be describing.

Second general category of what epidemiologists worry about are confounding variables, variables other than the presumed cause and the presumed effect, which can be related to the cause and effect and, therefore, can create false associations or mask real ones.

In this study, the confounding variables were controlled using conditional logistic aggression, but the sample set, which is certainly an appropriate approach to use in a match case control study, but the sample size here was dramatically small for that level of sophisticated mathematical modeling. A better approach would have been to use stratification and/or exclusion although even there it could be problematic with only one exposed control to try to do stratifications. Again, the numbers are just too small.

Moving on to biases. One of the key biases epidemiologists worry about is mis-classification bias that is confusing cases as controls or confusing controls as cases. I am not a neurologist, and this is better addressed to our neurologic colleagues. But my neurologic colleagues

questioned whether or not it was valid to combine subarachnoid hemorrhage and primary intracerebral hemorrhage given they are quite possibly two different diseases.

Another bias that epidemiologists worry a lot about is information bias. In this case, it's the biased information about drug exposures. Getting valid drug histories is always very difficult to collect retrospectively. It is particularly difficult to collect, if you think about it, from stroke patients. People who've had strokes are going to have a hard time recalling what drugs they took and telling you about it resulting in unequal recall in the two groups.

In this study, great effort has been taken, and the authors are really to be congratulated, to collect good exposure data, but their validation procedure assures specificity, not sensitivity. In other words, you know that because of the great care that they took, you know that the people who said they were exposed really were exposed, but you don't know how many exposures were missed because people didn't remember it and very few missed exposures in the control group would have totally massed this association, eliminated this association, given as it is they had only one

exposed control. Increasing that to two or three would have eliminated the results.

Moving on to selection bias. The selection bias is any quality in the way the two groups were selected into the study in a way that places them at unequal risk of exposure. The ideal case control study should be population-based. You define a population, draw all cases from that population, and draw controls as a random sample from the population.

In this case, the cases were not representative of an entire population, however, since they were from isolated hospitals, many of them tertiary care hospitals, not from a defined population but rather individual hospitals in a number of places in the country. This is unlike the control group which did attempt to get a random sample of the population.

The completeness of case ascertainment was never defined -- never identified. And finally and very importantly, only 41 percent of those cases that were identified were enrolled in the study, and though most of this is an inherent problem of studying stroke patients and is not a criticism at all of what the investigators did, it leads to an enormous room for bias in a study that is inherently

fragile in its initial findings to begin with.

Finally, the controls. No information is given on the process and success of the random digit dialing process.

So in concussions, this is an ambitious and well-described study. It has a major risk of information bias and selection bias, however. The study was under-powered from its initiation leading to fragile results, subject to change, therefore, with even small errors, and given the nature of the disease that is being studied and the situation, this is subject to, in fact, large errors. At best, the study suggests the possibility of an association between the use of this common drug and the very uncommon outcome. In fact, documenting how uncommon the outcome and exposure is by simply the very small number of exposed cases they could find over many years in a wide geographic area.

The study certainly doesn't prove this association so, to me, this association remains uncertain. Thank you.

CHAIRMAN BRASS: Thank you.

Our next presenter will be Doctor David Schteingart.

DOCTOR SCHTEINGART: Good morning, and I'd like to thank the committee for the opportunity

to address the committee on this important issue.

My name is David Schteingart. I'm a professor of internal medicine at the University of Michigan in the Division of Endocrinology and Metabolism. I'm board certified in internal medicine and endocrinology and am a fellow of the American College of Physicians. I'm the Director of the Obesity Rehabilitation Program at the University of Michigan. I'm also the Director of the University of Michigan Training Program and Clinical Research. I'm appearing here as a consultant for Chattem. I've been studying and treating obesity for at least 35 years.

The focus of my comments will deal mainly with the role of PPA in the treatment of obesity and evidence of efficacy based on studies that we have conducted sponsored by Thompson Medical. It is accepted by the medical community and confirmed by consensus development conferences that overweight and obesity are a major medical problem because of their co-morbidities and associated risk for increased mortality. These major co-morbidities include type 2 diabetes, dyslipidemia, hypertension, atherosclerotic cardiovascular disease and stroke. Excessive weight also causes osteoarthritis, obstructive sleep apnea,

and alveolar hypoventilation, which are common ailments in people with severe obesity. There are also significant psychosocial and economic consequences of being obese.

Periodic national health and examination surveys have shown a progressive increase in the prevalence of obesity in the United States over the past decade in spite of efforts of public education and the availability of foods with reduced fat content and clear nutrient composition labeling. Currently, 22.5 percent of the population is obese and up to 24 percent of American children are overweight.

Obesity afflicts in greater preponderance certain segments of the population such as African-American, Hispanic and Native American citizens. These individuals also lag in health care access and proper nutrition counseling. Obesity also has a major impact on the cost of health care in this country. It was estimated that in 1995 the cost of treatment of obesity amounted to approximately $100 billion per year. To make things worse, most people seeking treatment of obesity were not covered by their health insurance for this condition and had to pay for this treatment out-of-pocket.

Treatment of obesity results in major health improvement and reversal of its co-morbidities with discontinuation of treatment such as insulin therapy and anti-hypertensive drugs. This improvement may also lead to a decrease in mortality risk. Treatment of obesity involves medical or surgical approaches. The mainstay of medical treatment includes reduced calorie diets, exercise, behavior therapy, and medications that reduce appetite or decrease food absorption. Drug treatment of obesity by currently approved prescription drugs is expensive and, again, not covered by most health insurance. Phenylpropanolamine is the only permitted over-the-counter non-prescription appetite suppressant. Its cost is much lower than that of most prescription drugs. PPA has been recommended for short-term treatment of obesity based on studies on the efficacy and safety of the drug published periodically over the past two decades.

In 11 of 16 double blind placebo controlled studies employing 900 subjects, the weight loss achieved with PPA was significant greater than placebo. Two of the most recent studies published in the early 1990s by Greenway and by our own group confirm the efficacy of the drug

for short-term treatment of obesity and its relative safety. Our study involved 101 subjects, 15 to 45 overweight but otherwise healthy. These individuals were on a 1,200 calorie diet.

During the double blind placebo controlled phase, as indicated on this transparency, subjects took placebos for two weeks and then were randomized to placebo or PPA for six weeks. The subjects on PPA, the left hand side column, showed a statistically significant greater weight loss than the placebo group. Next transparency, please.

A subset of these subjects chose to continue on their medication, placebo or PPA, for a total of 20 weeks. The difference in weight also continued. The PPA group lost 5.1 kilograms and the placebo group 0.4 kilograms by the end of the study. No difference was observed in blood pressure, pulse rate or subjective complaints between the two groups and no serious adverse events were reported.

These studies concluded that PPA is an effective and safe adjunct in the treatment of obesity. These studies, because of their design, were considered by the FDA to be the most convincing evidence of the effectiveness of PPA in the treatment of people with mild or moderate obesity. The degree of weight loss achieved with PPA was

comparable to that obtained with currently approved prescription drugs.

In conclusion, obesity is a serious chronic medical disease without effective cure. Any assessment of potential risk must take into account the significant benefit conferred by drugs like PPA when used as an appetite suppressant. Weight reduction improves morbidity and mortality. The loss incidents of side effects with PPA relative to the benefits of weight reduction should help place this issue into proper perspective.

Thank you very much.

CHAIRMAN BRASS: Thank you.

The next presentation, the open public hearing, will be by Doctor Sidney Wolfe.

DOCTOR WOLFE: Good morning.

We do not accept any money from the pharmaceutical industry. We do not get money from anyone who has an interest in this other than the public who supports our organization.

In this testimony and in a petition we have filed about an hour ago with the Food and Drug Administration, we are asking for an immediate ban of all uses of PPA in over-the-counter products including appetite suppressants and as a decongestant in cough and cold preparations.

We agree with the determination of FDA's Office of Postmarketing Drug Risk Assessment, OPDRA, that quote "PPA should not be generally recognized as safe" unquote. Since the only categories for over-the-counter drug ingredients, which is the way over-the-counter drugs are evaluated, are Category I, generally recognized as safe and effective, or Category II, not generally recognized as safe and effective, this would place it in Category II. The other category is insufficient evidence. I think that we are way beyond that at this point.

We also agree with the recommendation from the same part of FDA, OPDRA, that quote "PPA containing appetite suppressants, and separately the same recommendation, cough/cold remedies should no longer be available as over-the-counter products.

The background for the recent well-designed Yale Epidemiological Study that found PPA increases the risk for hemorrhagic stroke includes a long history of published serious adverse events including hemorrhagic strokes attributable to PPA going back to 1979. These cases are attributed to the drug because they usually occur shortly after ingestion -- the design of this study was strokes within the first three days of PPA -- and because of the lack of other plausible explanations, especially

in otherwise healthy younger people.

Additionally, there's been evidence for the specific mechanism or for a specific mechanism by which these strokes are induced by PPA. Similar evidence has existed for probably 30 years for the stroke-producing properties of amphetamines, once the most common drugs used for obesity. Both PPA and amphetamines are known to cause cerebral vasculitis, severe inflammation of the blood vessels of the brain which, probably in combination with the blood pressure raising effects of the drugs, can result in cerebral or subarachnoid brain hemorrhage and strokes.

In addition to strokes, other serious adverse reactions attributed to PPA include acute psychosis, convulsions, acute renal failure, heart damage, and hypertension, and there's abundant evidence, including from randomized control studies for hypertension in the literature. The similarities between amphetamine, phenylpropanolamine and ephedrine I think are well known to most of you, and the reason for putting the structures on the chart is simply to say that these are not just chemical accidents. There are a lot of pharmacologic properties, adverse effects, that are shared by all of them.

Ten years ago in a review published from the Uniform Services University for Health Sciences, Doctor Larkes Lake looked at 85 publications in which there were 142 case reports of problems usually occurring shortly after the initiation or use of PPA. They included 24 intracranial, either cerebral or subarachnoid hemorrhages, eight seizures and eight deaths, mostly due to stroke. The most common ones were acute hypertension, headaches, and two-thirds of these reactions occurred in women and two-thirds of them were in patients under the age of 30.

Further information about PPA and strokes comes from FDA's own Spontaneous Adverse Reaction Reporting System. In an FDA memo dated August 6, 19991, FDA Medical Officer, Doctor Heidi Jolson, reported there had been a total of 44 cases of strokes, 35 hemorrhagic in PPA users reported to the FDA until then. Subsequent update of that raised the total to 51 cases of hemorrhagic strokes. Given the reporting artifact, which is generally thought for prescription drugs to be only one in 10 that actually occurred get reported, sometimes thought for others such as over-the-counter to be one in 20, some think one in 100. This means hundreds if not thousands of cases of PPA-induced

hemorrhagic stroke have occurred.

As far as the Yale study, which will make up the bulk of the discussion today, funded by CHPA, I believe the results are quite clear, particularly if it's put in the context of a large number of other case control studies, retrospective studies. The difference between a retrospective case control study and a randomized control trial are that by randomizing and going forward, there really can't be or isn't any difference between the groups that you're looking at. In a retrospective study, there is and all of the precautions, including enormous input from epidemiologists and from the FDA's epidemiologists, made the design of this study as good as it can be, better than most case control studies.

More importantly though, it's not clear to me why this study needed to have been done. I think that the literature back 10 or more years ago was clear enough. It's one thing to have long-term problems where the problem occurs long after the time that the drug was started and it may be difficult to place the cause and effect next to each other. But here, when it occurs so shortly afterwards, the literature of case reports I think made it very, very clear so that the context in

which this study needs to be looked at is the context of 20 plus years of case reports on hemorrhage and other problems caused by the drug.

The methodologic criticisms which you've started hearing and will hear more of are over-shadowed by the fact that the same consultants who are now raising these criticisms could presumably have been retained by CHPA before it signed off on the design and details of the study before it began. For every case control study, there are always those who find something wrong with it because it lacks the perfection of randomized control trials.

What is notable, however, is that when case control studies are found to implicate a drug or device in connection with the disease, there's an extraordinarily skewed representation of industry-funded critics there to say nay or maybe not. PPA is just another example in a long history of many serious public health hazards caused by drugs or medical devices which were allowed to continue endangering people much longer than they should after sufficient evidence for action was available because of industry-funded nit-picking with the methodology of the studies, often case control studies such as the one being discussed today.

Other examples which we've been involved

in where there was a delay includes aspirin and Reye's syndrome where the same organization, the predecessor of it, Non-prescription Drug Association, fought for years to the detriment of many children who died and had brain damage from Reye's syndrome to pretend that there was no relationship between aspirin and Reye's syndrome. It delayed for years the labelings on those. Hyper-absorbent tampons and toxic shock, DES and clear cell vaginal cancer and DES daughters menopausal estrogen and uterine cancer. Eventually, action to ban and restrict was taken in each of these instances but much later than it should have been.

Even without any case control or other epidemiological study, most of the time that FDA takes action to take a drug off the market, there haven't been any epidemiological studies and the reason is that the number and specificity and relationship between the drug or device and the event is clear enough from well-documented case reports. Spontaneous reports to the FDA are documented up to a point and as well as they possibly can be, but when you look at the published literature on a lot of these things, you see clear evidence whether some of the drugs that have just come off the market in the last while, Rezilin,

Durac, Propulsid, Pozocor, Repoifloxocin, Trobafloxacin, Burke Shiley heart valve, no epidemiologic studies before they came off the market on safety and yet the case report sufficed.

It's been more than 20 years since the first alarms were raised about the dangers of PPA and about the fact that there's no evidence in the long term that diet drugs such as PPA actually help to lose and retain weight. In 1981, a study using another weight reduction drug, Fenfluoramine, looked at people who just got the drug, got it combined with behavior therapy or got behavior therapy alone. The initial -- and you saw data like this. The early weight reduction was actually the same in all three groups. The interesting thing was that the group that had just behavioral therapy kept their weight down much better than the others, and the theory was that in any long-term basis and it's, of course, the long term in which weight reduction makes any sense. Short term doesn't really make much difference -- in the long term that the use of a drug actually retarded the beneficial effects of behavior therapy.

Long ago in 1979, The Medical Letter, an independent authoritative source of evaluation of drug therapy, wrote quote "There is no good evidence

that phenylpropanolamine or any other drug can help obese patients achieve long-term weight reduction." The 20 or so weeks that you saw on that chart is not long-term. The only satisfactory treatment for obesity is a life-long change in patterns of food intake and physical activity.

Many early researchers who investigated PPA commented that the drug should not be available over the counter. One group of researchers in 1987 stated quote "The over-the-counter availability of PPA-containing medications may be inappropriate and in need of revision since it does not appear to be in keeping with current standards of public safety." End quote. Since then, hundreds more American patients have suffered stroke, psychotic episodes, heart damage, and other known adverse effects of PPA for no documented benefit in the long term.

During the last couple of weeks, through colleagues around the world, we conducted a very informal survey of the availability of phenylpropanolamine over-the-counter in various countries. With the exception of South Africa, it is not available over-the-counter for weight reduction anywhere else. There are a few countries where it is available for cough and cold over the counter but in more countries it's available by

prescription. One of the more interesting comments that we got was from Greece where apparently recently phenylpropanolamine has been placed under the Controlled Substance Act in Greece.

In light of the voluminous medical literature documenting life-threatening adverse effects of PPA such as hemorrhagic strokes and the confirmatory evidence of this in the industry-funded epidemiological study, it is not possible for PPA to remain in the OTC category of safe and effective, Category I. Thus, since all this evidence mandates and FDA's own OPDRA Division has concluded that it should not be generally recognized as safe, the only choice is to remove the drug from all OTC products. We hope this will be accomplished as quickly as possible. The longer the delay, the larger the toll of preventible strokes and other serious damage to the public.

Just two other comments. If you were considering today the switching of phenylpropanolamine from prescription only to over-the-counter, I think the answer would clearly be no, and the reasons for it would be the same as why it should no longer be considered. Doctor Janet Wilcock, to whom we addressed our petition an hour ago to take these drugs off the market over-the-

counter, has repeatedly said, and I fully agree with her, that there are a number of out-moded drugs on the market. In many cases, they're dangerous and that as well as the FDA's more common function of reviewing the possibility of reviewing new drugs coming on the market, it has another important public health function to get out-moded drugs off the market. PPA is a classic example.

Thank you.

CHAIRMAN BRASS: Thank you. We'll now move to the regular program with Doctor Sherman providing us a regulatory history of OTC PPA.

DOCTOR SHERMAN: Good morning. I'm Bob Sherman with FDA's Division of OTC Drug Products and the Center for Drug Evaluation and Research. I'd like to briefly describe the OTC drug review and provide some background on the regulatory history of phenylpropanolamine hydrochloride or PPA. I'll describe the events leading up to this Advisory Committee meeting to discuss the results of the Yale Hemorrhagic Stroke Project and its implications.

The OTC drug review began in 1972 as a three-phased review of the safety and effectiveness of the active ingredients in 26 classes of OTC drugs. The first phase of the review involved Advisory Review Panels comprised of independent

experts. The panels developed a report in which the active ingredients were placed into one of three categories based on data submitted to FDA. The panel reports were then published in *The Federal Register* as an advance notice of proposed rulemaking. A public comment period followed allowing interested persons to submit comments and additional data.

Based on the panel's recommendations and any new information, the second phase of the review is FDA's proposed rule published in *The Federal Register* as a tentative final monograph. This is followed by a second public comment period that allows for comments on the agency's proposal and additional data. The stars indicate where we are in the review of PPA. FDA has not yet published a proposed rule for PPA.

In the third phase of the review, FDA considers any additional comments and new information and publishes a final rule or final monograph in *The Federal Register*. The panel has placed active ingredients into one of three categories: Category I, generally recognized as safe and effective; Category II, not generally recognized as safe and effective; or Category III, insufficient data to permit final classification.

Under the monograph system, ingredients placed in Categories I, II, or III may remain on the OTC market until the publication of the final monograph in *The Federal Register*. At the final monograph stage, ingredients in Category II and Category III become non-monograph and must be removed from the OTC market with only Category I ingredients being included in the final monograph and allowed to remain on the market. FDA has been awaiting the results of the five year Hemorrhagic Stroke Project before publishing a proposed rule or tentative final monograph regarding PPA.

As you know, PPA is marketed for two OTC indications: as a nasal decongestant and as an appetite suppressant. Because these are two separate rulemakings, PPA was reviewed for each indication by separate Advisory Review Panels, and FDA will publish separate final rules for each indication. PPA need not be placed in the same category for both conditions of use.

This table shows what the panels recommended and what FDA published in the ANPR for each rulemaking. In September 1976, FDA published the Cough/Cold Panel's recommendations for nasal decongestants. These included single PPA doses of 25 milligrams every four hours or 15 milligrams

every eight hours with a total daily limit of 150 milligrams as a Category I nasal decongestant. When the Weight Control Panel submitted its report to FDA, this panel also recommended single PPA doses of 25 to 50 milligrams and a timed-release dose of 150 milligrams with a total daily limit of 150 milligrams as Category I for weight control.

However, before the advance notice of proposed rulemaking for weight control products was published, FDA became aware of case reports of blood pressure elevation with higher doses of PPA than were marketed for weight control at that time. Because of this safety concern in the ANPR, FDA specifically requested information regarding PPA's effects on blood pressure and the dissolution rates of timed-release products. FDA also limited weight control doses to those that had been on the market since 1975, single doses of 25 to 37.5 milligrams and a timed-release dose of 75 milligrams with a total daily limit of 75 milligrams.

Because the safety issues regarding PPA were the same for both rulemakings, PPA was deferred from the 1985 proposed rule for nasal decongestant drug products. PPA was also deferred from the nasal decongestant final monograph published in 1994 but may still marketed under the provisions of the OTC

review.

A proposed rule concerning PPA as a nasal decongestant will be published along with the proposed rule for weight control products.

After reviewing the blood pressure study submitted in response to the agency's request, FDA concluded that PPA causes a biphasic blood pressure response. That is, initially blood pressure rises above baseline, a pressor effect, then falls below baseline, a depressor effect. The pressor/depressor effects are dose-related. The blood pressure effects diminish with repeated dosing, and tolerance to the pressor effects develops within a few hours. FDA further concluded that the data were inadequate to respond to the agency's safety concerns.

As FDA was completing its review of the weight control data, the House Small Business Subcommittee on Regulation, Business Opportunities and Energy held a hearing on September 24, 1990 to examine dieting, weight control products containing PPA, and federal research efforts on obesity. Testimony included claims of wide misuse and several scientific witnesses called for removal of PPA from the OTC market. Subsequently, FDA received two submissions in rebuttal to the testimony given at the hearing and objecting to the data used to

support claims of misuse of diet drugs. On May 9, 1991, FDA held a public meeting to discuss the safety and effectiveness of PPA for weight control use.

Although PPA's effects on blood pressure and safety concerns relating to hemorrhagic stroke were discussed, FDA had not yet determined that PPA was effective for weight control use, and much of the meeting focused on PPA's effectiveness as an appetite suppressant.

FDA later concluded in 1994 that 75 milligrams controlled-release PPA combined with a reduced calorie diet is effective for temporary OTC weight control use. FDA also concluded that existing data on single doses of PPA were inadequate to support its effectiveness for weight control.

Prior to the public meeting, FDA reviewed its spontaneous reporting system for case reports associated with PPA from 1977 to 1991. Twenty two reports of intracranial bleeding suggested that PPA may be associated with an increased risk of hemorrhagic stroke. This will be discussed in detail by FDA's Office of Postmarketing Drug Risk Assessment.

Most of these reports were associated with first day use of PPA and with weight control

products, although it was estimated that cough/cold products accounted for 80 percent of PPA products sold. FDA concluded that a case control study of hemorrhagic stroke would be the most feasible approach to test this hypothesis.

Some of the factors that made an assessment of PPA difficult were the small number of adverse events, the lack of complete information in the case reports, the apparent rapid tolerance to the hypertensive effects of PPA, the low rate of reports associated with widely used cough/cold products, and no accurate estimate of the degree of under-reporting. That is, no information on the actual number of adverse events that the case reports represented.

Because of these difficulties, FDA consulted three independent epidemiologists to comment on the agency's evaluation of the stroke data. The consultants were Doctor Janet Daily and Doctor Steven Kittner, who are with us today, and Doctor Jack Whisnant of the Mayo Clinic. The consultants agreed on a number of important points: that FDA's conclusions were reasonable, that interpretation of the data depended critically on the reporting rate of adverse events which was unknown, that although the available data did not

show a causal relationship and association between PPA and an increased risk of stroke could not be ruled out, and that a case control study of hemorrhagic stroke was recommended.

In 1992, based on the available data, FDA concluded that although an association between PPA and an increased risk of stroke could not be ruled out, it was not necessary to remove PPA from the OTC market while additional data were obtained.

At a meeting in November 1992, the Non-prescription Drug Manufacturers Association or NDMA, now the Consumer Health Care Products Association or CHPA, proposed the stroke study along with a voluntary labeling program that included stronger warnings for PPA weight control products. In March 1993, NDMA submitted a draft protocol from the Yale investigators. FDA expressed several concerns including the proposed sample size and the choice of exposure window.

Through follow-up meetings and correspondence between FDA, NDMA and Yale, a revised final protocol was agreed upon and submitted by NDMA in April 1994. The study began in September 1994 and took approximately five years to complete.

In 1996 FDA published a proposed rule that would require stronger warnings on all OTC PPA

products. The proposed warnings advised consumers not to combine a weight control or cough/cold product with any other sympathomimetic drug, that taking more than the recommended dose can be harmful and, in the case of appetite suppressants, stating clearly that taking more will not increase weight loss and can be harmful.

Because the Hemorrhagic Stroke Project was ongoing and the results of the Yale study could impact on this proposal, it has not yet been finalized.

That brings us today's meeting to discuss the implications of the Yale study and FDA's options regarding PPA as an OTC drug. We will hear from the Yale investigators discussing the results of the Hemorrhagic Stroke Project. We will also hear from representatives of the Consumer Health Care Products

Association voicing some concerns about the study. The OTC Division consulted FDA's Office of Postmarketing Drug Risk Assessment to evaluate the Yale study and present its recommendations to the committee, and they will provide a detailed discussion of that review.

The Division of OTC Drug Products is seeking the committee's perspective and recommendations concerning PPA in light of the new

information that the Yale study provides in order that FDA may reach a decision regarding this widely used over-the-counter drug.

Thank you.

CHAIRMAN BRASS: Thank you.

We will now hear a presentation of the final report of the Yale Hemorrhagic Stroke Project by Doctor Kernan.

DOCTOR KERNAN: Thank you.

Although the Hemorrhagic Stroke Project has sometimes been referred to as the Yale Project, it really wasn't just the Yale Project. Throughout this study, research took place at four universities around the country, and I'm pleased to tell you that investigators from all four involved research institutions are here today. From Brown University, Janet Lee Wilterdink, from the University of Cincinnati, Joseph Broderick, from the University of Texas at Houston, Lewis Morgenstern, and from Yale University, Lawrence Brass, Ralph Horwitz, myself, and Catherine Viscoli.

Throughout the research, we also assisted in this study by a Scientific Advisory Group which operated independently of both the sponsors of the project and the investigators. I'm also pleased to announce that all three members of

the Scientific Advisory Group are here today including Doctor Louis Lasagna from Tufts University who is chairman of that group, Doctor J.P. Mohr from Columbia University, and Doctor Sammy Suissa from Magill University.

Although the investigators and members of the Scientific Advisory Group would like to claim responsibility for the conduct of this research, we could not have done it without the research staff including the research coordinators and interviewers at each of the sites. Joining us here today as representatives of that group are Carrie Crumpf from Yale University, Laura Sauerback and Janice Carrazella from Ohio and the University of Cincinnati, Naomi Tomasian and Carol Cerilli from Brown University, and Melinda Cox from the University of Texas.

By way of background, some of which you've heard already, during 1999 to 1993 at least 18 published case reports described hemorrhagic stroke after phenylpropanolamine or PPA use. Most of these reports involved young women taking PPA for appetite suppression, often as a first dose. Some case reports, however, involved cough/cold remedies. In 1992, manufacturers and the Food and Drug Administration joined to recommend the conduct of a

study specifically designed to examine the association between PPA and risk for hemorrhagic stroke.

The Hemorrhagic Stroke Project had the following co-equal specific aims. Among women, to estimate the association between hemorrhagic stroke and PPA, both in appetite suppressants and as a first time use, either as a cough/cold remedy or an appetite suppressant. Among men and women together, to estimate the association between hemorrhagic stroke and PPA use. For any exposure, either as an appetite suppressant or cough/cold remedy, and by type exposure.

The case control design was selected for the Hemorrhagic Stroke Project for the following reasons; Hemorrhagic stroke is a rare event among young persons affecting less than 25 per 100,000 per year. To examine risk for hemorrhagic stroke among young PPA users, a prospective cohort study would be unfeasible because hemorrhagic stroke is rare and a clinical trial would be unsuitable because of logistic and ethical reasons. Therefore, a case control design is preferred in circumstances where the outcome event is rare.

Case recruitment is described on this slide. There were four research sites from which

patients were recruited including sites in Connecticut and Massachusetts comprising a network of 23 tertiary and non-tertiary care hospitals. These represented all of the major hospitals in Connecticut. Ohio and Connecticut and Kentucky with 17 hospitals. Again, this was a network which attempted to recruit all cases of hemorrhagic stroke in its area. Texas with one hospital and Rhode Island with two hospitals.

At each site, patents were recruited by active surveillance including monitoring of admission logs and discharge logs and also on-site surveillance personnel who attempted to notify us as early as a patient was admitted to that institution.

Case eligibility is described here. The inclusion criteria included men and women ages 18 to 49 years who had been admitted with a primary subarachnoid or intraprankmal hemorrhage that was not related to trauma. Exclusion criteria included the inability to participate in an interview within 30 days of the stroke event. I'd like to explain this for a moment. This meant that we did not enroll patients who died or became noncommunicative as a result of their stroke event. For these patients, in order to obtain exposure data regarding

PPA, it would have been necessary to interview proxy respondents. That is, spouses or friends. Other research in the pharmacological and methodologic literature suggest that proxy respondents do not provide reliable information about drug exposures. In designing the trial, we actually modeled the effect of using proxy respondents and concluded that the use of those respondents would have resulted in a very inaccurate estimate of the odds ratio.

Other exclusion criteria included a history of brain lesion or stroke and residence in the hospital for over three days when stroke symptoms began.

Control subject selection is shown here. Eligibility for controls included men and women, ages 18 to 49 years of age with no history of stroke. The method for identifying controls was random digit dialing and, during this process, control subjects were matched to case subjects for age, gender, telephone exchange and race.

The ascertainment of exposure data is shown on the next two slides. A critical concept for our research was that of focal time. Focal time was defined as the date and time of day before which PPA exposures are counted. For the specification of focal time, it proceeded as follows. For case

subjects, focal time was the date and time of day that marked the onset of symptoms plausibly related to hemorrhagic stroke that caused the case subject to seek medical attention.

For control subjects, the focal time was set within seven days of the control subject interview data, and it was matched to the case subject for day of week and time of week. Additionally, all control interviews had to take place within 30 days of the case subject's hemorrhagic event in order to control for season.

The interview methods consisted of a structured interview that was delivered and conducted by a trained interviewer who used a calendar as a memory aid. This calendar was marked with holidays and events of personal importance to each subject, again to aid their recollection for specific exposures. Subjects were unaware of the study hypothesis and subjects were asked to recall cold symptoms in the two weeks before the focal time and medications used to treat them. These questions were asked equally of case subjects and control subjects to be sure that they had equal stimulation to recall of specific exposures of importance to this research.

Subjects were also asked about other

medications used in the two weeks in an open-ended format. Only PPA exposures rated definite or probable by subjects were counted for this research.

The sample size calculation is as follows. It was based on the aim to determine if PPA as a first use increases risk of hemorrhagic stroke within 24 hours among women ages 18 to 49 years. It was based on the estimate that .502 percent of controls would be exposed to PPA within 24 hours of focal time, and it was based on a one-tailed test of significance at the 0.05 significance level and an 80 percent power to detect an odds ratio of 5.0. The result of our calculation was the need to identify 324 female case subjects and 648 control subjects which was rounded up to 350 and 700.

We were interested in studying men as well and, to study men, we added the same number of male case and control subjects to essentially double the study sample size.

In the statistical analysis, we compared case and control subjects on several demographic, clinical and pharmacologic features. We used logistic models to estimate both adjusted and unadjusted matched odds ratios and, finally, we

performed stratified analyses to look at PPA effects within groups defined by selected clinical features.

All logistic models included the following: black race, which we included because matching was not perfect between our cases and controls; history of hypertension and current cigarette smoking because these are major risk factors for hemorrhagic stroke; and other features that, when included in the basic model, changed the odds ratio by 10 percent. I will note that education was the only baseline feature we examined that met this criteria.

The next few slides present our results. Nine hundred thirty eligible case subjects were identified. Among these, 222 were not enrolled, 182 because the subject was not contacted within 30 days and 40 because the physician or the subject declined to participate in our research. Seven hundred eight patients were enrolled. However, six were excluded from subsequent analysis, three because no control was identified, two because the interview took place more than 30 days after the stroke event, and one because of an uncertain focal time. This left a final case group of 702 subjects that would form the basis of my subsequent presentation.

Control matching is shown here. For 674

case subjects, they were matched to two controls for a total of 1,348 control subjects. Twenty eight case subjects were matched to only one control for a total of 28 control subjects for them. The total case group again is 702 and the total control group is 1,376.

The quality of control matching is as follows: All controls were matched to cases based on gender, telephone exchange, age and race. That was our intention. Controls were successfully matched to cases on gender and telephone exchange. There was 100 percent matching success. Ninety nine percent of controls were matched to cases on age and 96 percent of controls were matched to cases on race. Because of imperfect matching with race, race was included as an adjustment variable in subsequent modeling.

Selected features of case and control subjects are shown on this slide. The first three features refer to matching variables. For female gender and age, the proportion of patients with these features in the case group and controls was very similar. Black subjects comprised a slightly larger proportion of the case group than the control group. The other features from here down were not matching variables. Compared to control subjects,

cases were less educated, they were more likely to be current cigarette smokers, they were more likely to be hypertensive, they were more likely to report a family history of hemorrhagic stroke, more likely to consume two or more alcoholic beverages per day, and more likely to report cocaine use. Compared to control subjects, however, case subjects were less likely to use nonsteroidal anti-inflammatory drugs, but they were more likely to report use of caffeine in drugs or nicotine in drugs.

This slide shows the association between PPA and risk for hemorrhagic stroke among women. This slide is similar to several others that follow, and so I'll show you its structure. In this column are listed the PPA use definitions. No use, any use within three days, cough/cold remedy use within three days, appetite suppressant use within three days, or first use. First use was defined as use of PPA within the prior 24 hours but no other use within a two week period. These next four columns show the data for cases and controls according to percent that reported exposure under the use definition and number.

Results here are shown in an unmatched format for clarity of demonstration. The odds ratio, however, is a matched odds ratio and the

matching variables I've shown the adjustment features were race, hypertension, cigarette smoking, and education. In this column is the one-sided P value for this research because we were only interested in the adverse effect of PPA, not for a benefit in reducing risk for stroke.

So what are the results? No use of PPA was reported by 92.7 percent of cases compared to 95.1 percent of controls for an odds ratio in this reference group of 1.0. For any use within three days, the percentages were 5.5 and 2.7 for an odds ratio of 1.98 and a p-value of .024. For cough/cold remedy use, the percentages were 5.2 and 2.5 for an odds ratio of 1.54 and a p-value of .116. For appetite suppressant use, the percentages were 1.6, 0.1, and the odds ratio was 16.58 with a p-value of .011.

For first use, the percentages were 1.8 and 0.5 for an odds ratio of 3.13 and a p-value of .052. All first use involved cough/cold remedies. The results for men are shown on this slide. No PPA use was reported by 96.9 percent of cases compared to 95.4 percent of controls for an odds ratio of one in this reference group. For any PPA use within three days, the percentages were 1.9 and 2.1 for an odds ratio of .062 and a p-value of .203.

For cough/cold remedy use among men, the percentages were 1.9 among cases, 2.1 among controls for an odds ratio again of .062 and p-value of .203. For appetite suppressant use, there were no exposures among either cases or controls and an odds ratio could not be calculated. For first use, the percentages were 0.3 and 0.2 for an odds ratio of 2.95 and a p-value of .241. Again, all first uses involved cough/cold remedies.

This slide shows the association between PPA and risk for hemorrhagic stroke among the entire cohort including men and women. No use was reported by 94.6 percent of cases, 95.2 percent of controls for an odds ratio in the reference group of one. For any PPA use within three days, the percentages were 3.8 and 2.4 for an odds ratio of 1.49 with a p-value of .084. For cough/cold remedy use, the percentages were 3.1 and 2.3 for an odds ratio of 1.23 and a p-value of .245. For appetite suppressant use, the percentages were 0.9, 0.1 for an odds ratio of 15.92 and a p-value of .013. For first use, the percentages are 1.1, 0.4 and the odds ratio is 3.14 with a p-value of .029.

In the next few slides, I'd like to consider key biases which we considered in the design and analysis of the Hemorrhagic Stroke

Project. These included confounding, selection and information bias and under information bias I'll specifically mention temporal precedence bias, ascertainment bias and recall bias.

For confounding bias, the definition of a confounder is an extraneous variable related to PPA use and risk for hemorrhagic stroke that wholly or partially accounts for the apparent effect of PPA on stroke risk. The confounder is related to both the exposure and the outcome. Safeguards against confounding in the Hemorrhagic Stroke Project included matching cases and controls on age, gender, race and telephone exchange, all of which were considered potential confounding variables.

Furthermore, we also conducted adjustment for other potential confounding variables by both modeling and stratification, and I want to show you the results of that. This slide shows the effect of adjustment on the matched odds ratio among women. In this column are the PPA use definitions you've seen before. In this column the unadjusted odds ratio and in this column the adjusted odds ratio. Again, it is adjusted for smoking, hypertension, race and education.

For any PPA use within three days, the unadjusted odds ratio is 2.14 and the adjusted odds

ratio is 1.98. For cough/cold remedy exposure, the numbers are 1.7 and 1.54. For appetite suppressant use, 12.19 and 16.58. For first use, 3.50 and 3.13. What these analyses show is that confounding may have an effect in the overall results of the Hemorrhagic Stroke Project. However, the magnitude of the odds ratios, both under the unadjusted and adjusted numbers are quite similar.

Another way of accounting for confounding is stratified analysis. In this slide, we show a stratified analysis for women without a history of hypertension or smoking. Again, this column shows PPA use definition. This column shows results for 121 cases and 438 controls. Again, the data here is presented in an unmatched format. We present the unmatched adjusted odds ratio in this column. Previously you had seen the result of the matched odds ratio. We chose to present the unmatched odds ratio here for two reasons. First, it allowed us to get a larger sample size. Secondly, in our own analysis in which we look at the matched odds ratios and the unmatched odds ratios, the results are remarkably similar. The odds ratios are almost identical.

For no PPA use, the percent of cases reporting exposure is 90.1 compared with 96.8 in the

control group for a reference odds ratio of one. For any PPA use within three days, the percentages are 7.4 and 1.4 for an unmatched adjusted odds ratio of 5.61 and a p-value of less than .001. For cough/cold remedy exposure the percentages are 5.8 and 1.1 for an odds ratio of 5.04 and a p-value of .008. For appetite suppressant use percentages are 1.6 and 0.2 for an unmatched odds ratio of 8.16 and a p-value of .102. For first use the percentages are 3.3 and 0.5 for an unmatched odds ratio of 6.3 and a p-value of 0.38.

This alternative stratified analysis, the results from this, are similar to the analysis from the overall cohort in that the odds ratio for appetite suppressant use and first use are still elevated. It is different from the analysis in the overall cohort, however, in showing that the odds ratio for any PPA use and cough/cold remedy use are elevated and now statistically significant. We also would like to point out that in this analysis the magnitude of the odds ratios are really quite similar. They all range between five and 8.16.

Other than confounding biases, there are other biases we'd like to discuss that I mentioned earlier. One is selection bias. The definition of selection bias is selective referral to or less from

the study of case or control subjects based on PPA exposure. Safeguards in the Hemorrhagic Stroke Project included active surveillance for case subjects and enrollment of all eligible case subjects at the participating institutions. We believe that these safeguards were likely to be quite effective.

Another bias that we'd like to discuss is temporal precedence bias. This is a systematic error in which an exposure to PPA is counted although it occurs after the onset of hemorrhagic stroke and possibly in response to sentinel disease symptoms. I'd like to describe sentinel symptoms in more detail. We were very concerned about this potential bias when we designed the study.

Sentinel symptoms, the definition is commonly as follows: a transient headache hours or days before the onset of symptoms that lead a patient to seek medical attention. Remember that the symptoms that led a patient to seek medical attention defined our focal time. That headache, rather than when attention is sought, may mark the onset of hemorrhage. The implications for the Hemorrhagic Stroke Project are as follows: A patient may be classified as exposed to PPA when the medication was actually taken after the first

occurrence of hemorrhage.

Safeguards that we employed in the Hemorrhagic Stroke Project were twofold. First, we planned analyses using an alternate focal time, that is, the onset of the sentinel symptoms, and most of our subjects, case subjects who reported sentinel symptoms, had an alternate interview date and secondly, we planned an analysis excluding patients with sentinel symptoms, and I'd like to show you that analysis.

This slide shows the odds ratios by sentinel symptom status of case subjects. In this column are the exposure categories you've seen before and here are the matched odds ratios for case subjects with no sentinel symptoms of which there were 548 and for case subjects who reported sentinel symptoms of which there were 154. The matched odds ratios under any PPA use definition was 1.33 for cases reporting no sentinel symptoms and 2.19 for cases reporting sentinel symptoms.

For cough/cold use, the odds ratios were 1.12 and 1.71. For appetite suppressant use, the odds ratio among cases reporting no sentinel symptoms was 12.10. We could not calculate the odds ratio for subjects without sentinel symptoms because there were no exposed controls. For first use, the

odds ratios were 3.34 and 2.70.

These results suggest that temporal precedence bias may have played a role in the Hemorrhagic Stroke Project, particularly for the definitions of PPA exposure, any PPA use, and cough/cold use. You see the odds ratios increase. For first use, we were surprised that the odds ratio actually declined. Temporal precedence bias may still play a role in that event, although not in the expected direction. Not forcing a change in the expected direction.

The other thing we'd like to point out is that in the group of case subjects without sentinel symptoms, the findings, the major findings from this study are unchanged. That is, the odds ratio is significantly increased for appetite suppressant use and for first use of PPA, even when you exclude these patients with sentinel symptoms who we thought might artificially actually increase the odds ratio.

The next bias I'd like to describe is ascertainment bias. The definition is as follows: Unequal ascertainment of exposures in cases in contrcl subjects. Safeguards in the Hemorrhagic Stroke Project included a highly structured and scripted interview from which interviewers were

instructed not to deviate, blinding of subjects to the study hypothesis and standard exposure verification procedures.

I'd like to describe the exposure verification procedures because we think that this is a critical component of our research. I do not believe that this slide will be easily seen from the back of the room, and I do apologize. There were 67 patients who reported cough/cold or appetite suppressant drug use that subsequently we had reason to believe constituted a possible PPA exposure. The container was available for 52 of these reported exposures. Of these 52, 39 were brand name exposures. Of these 39, 37 brand name exposures included brand names for which there had been no recent formulary change, and we knew that these brand name medications included PPA, so patients were then classified as being exposed to PPA.

Among the 39 who reported brand name exposure, they reported exposure to two brand names for which a formulary change had been reported in available industry information. We then verified these medications by referring to the lot number on the medication. Actually on the package. Among the 52 subjects who were able to show us the container from which they took their pills, 13 of those

exposures involved non-brand name products. We again verified all of those using a lot number. We took the lot number and went to the manufacturer and confirmed that all 15 exposures, the 13 non-brand name and the two brand name with formulary changes, all included PPA.

The container was not available for 15 subjects. Ten of these reported exposure to a brand name product. We then showed these subjects a book that we had prepared that had pictures of the products and patients were able to identify their project definitely in all cases, and we counted those individuals as exposed to PPA. Two of the 15 subjects who did not have a container reported prescription PPA use. We verified the content, the actual drug and its content, with the pharmacy, and all patients in this group were categorized as exposed to PPA.

For three subjects, however, they reported brand name medication use but did not have the container. Since we didn't have a lot number for those individuals and couldn't show them a definite picture of the product, we counted them as unexposed. We also, even if we had pictures or could find a container, we are aware that formulation changes take place commonly among non-

brand name over-the-counter cough/cold remedies, and we felt it was not appropriate to attempt to classify them as exposed.

Recall bias definition is commonly as follows: The tendency of case subjects compared with control subjects to have more or less accurate recall of exposures. Safeguards in the Hemorrhagic Stroke Project included a structured interview, and this included specific questions on use of appetite suppressants, URI symptoms, upper respiratory tract infection symptoms, and use of medications for those symptoms. These questions, again, as I mentioned earlier, were asked equally of case and control subjects to try and equally stimulate their recall of medications and exposures of interest in this study.

We also had a short interval between the focal time and the interview date. It was less than 30 days for case subjects. I believe the average was approximately 14 days, and an interval of less than seven days between the focal time and the date of the control subject interview. The average was about three and a half days. We had a shorter interval between the focal time and the interview date for controls to try and overcome the greater stimulation for recall that case subjects would have

because of their serious health event.

I'd like now just to comment briefly on potential explanations for the different findings for cough/cold remedies and appetite suppressant use. Potential explanations include biology. That is, it's possible that individuals who choose to use appetite suppressants are somehow more susceptible to adverse consequences of PPA. We know that individuals who took appetite suppressants were female. We don't know about other characteristics that may have placed them at risk for hemorrhagic stroke. Our study was not designed to address the biology of hemorrhagic stroke or means by which PPA might increase risk for hemorrhagic stroke. We can only speculate.

Bias and chance we have previously discussed. I've mentioned several biases that we considered in designing the study, and we've addressed them. I've also addressed the issue of chance by reporting p-values.

I'd like though to briefly mention dosage. We wanted to know if patients who used appetite suppressants were taking a larger dose of PPA. This slide shows exposure type, appetite suppressants, cough/cold remedies, and it shows PPA dose in 24 hours before the focal time. For

appetite suppressants, there were three subjects who took PPA, case subjects who took PPA in the 24 hours before focal time. The average dose consumed was 250 milligrams. For cough/cold remedies, there are 18 exposed case subjects. The average or the mean dose of PPA consumed was 161 milligrams with a range of 20 to 730. So this analysis suggests that yes, consumers of appetite suppressants may have been exposed to higher doses of PPA. But is higher dose associated with increased risk for hemorrhagic stroke? And that is addressed on this slide.

This shows the dose response for any PPA use and risk for hemorrhagic stroke. In this column is the dose of PPA in the 24 hours before focal time. Here's the adjusted matched odds ratio and the p-value. For individuals who consume more than 75 milligrams of PPA, the odds ratio is 2.167 with a p-value of 0.084. For individuals who consumed less than or equal to 75 milligrams, the odds ratio was 1.16 with a p-value of 0.397. By the magnitude of the odds ratios, it would suggest that risk for hemorrhagic stroke may be related to dose of PPA consumed.

To summarize our main findings, among women, use of PPA and appetite suppressants within three days was associated with increased risk for

hemorrhagic stroke. First use of PPA was associated with increased risk for hemorrhagic stroke, as well. Since all first use involved cough/cold remedies, increased risk was found for both formulations of PPA, cough/cold remedies and as an appetite suppressant. Among men, there were no exposures to PPA in appetite suppressants and there were too few exposures to PPA in cough/cold remedies and for first use to conclude that risk for hemorrhagic stroke is different from women.

In conclusion, the results of the Hemorrhagic Stroke Project suggest that PPA is an independent risk factor for hemorrhagic stroke. The data provide valid information for use in completing a contemporary assessment of the safety of PPA.

Thank you.

CHAIRMAN BRASS: Thank you.

We have time for the panel to raise questions for the Yale presenters. I want to remind the panel that we will have lots of time for questions throughout the morning as well as the afternoon so, to the degree possible, if we could focus our questions now on issues with respect to the design and clarification of the interpretation.

DOCTOR GILMAN: We heard this morning from Doctor Strom that it is questionably valid to

combine subarachnoid hemorrhage and primary cerebral hemorrhage in your study. Can you comment on that?

DOCTOR KERNAN: I'll preface my comments by saying that I'm joined in answering your questions by the group of investigators who I introduced earlier, and I'd like to address this question, if I could, to Doctor Joseph Broderick from the University of Cincinnati.

DOCTOR BRODERICK: Thank you.

I do think this is a very important question. It's actually something we've considered as investigators. Just a little preface. Our group in Cincinnati has been working on intracerebral and subarachnoid hemorrhage since the mid-1980s. It's one of the reasons why we were very interested in participating in the study. And we've done population-based incidence studies as well as case control studies where we're looking at genetic environmental risk factors.

And it should be very clear that bleeding in the brain or around the brain has a lot of different mechanisms and intracerebral hemorrhage and subarachnoid hemorrhage have very different mechanisms and we think that we are looking at that as a type of stroke because it is a very severe type of stroke with a mortality of about 40 to 50 percent

for both sub-types. However, I do think there may be some clues about mechanism in that many of the cases that were exposed were subarachnoid hemorrhage.

Now, what you may not understand is that the main cause or mechanism for subarachnoid hemorrhage is an aneurism or blister on the blood vessel, and it may be that that's a necessary type of defect in a blood vessel that predisposes towards a rupture in the setting of elevated hypertension. So I do think it's very important that you separate the two diseases. We are doing that, but I can say that it also may give some clues as to mechanism.

For instance, women have a higher risk of subarachnoid hemorrhage than men and higher risk of aneurysms, and so this may be a way in which you could explain the biological effect of transient increases in blood pressure, particularly when associated in two-thirds of exposures with previous hypertension and smoking and then add an additional factor. So that's, I guess, my response to that issue.

DOCTOR GILMAN: I have one more question. Doctor Strom also commented that valid, I quote, "Valid drug histories would be much harder to collect from stroke patients resulting in unequal

recall." I wonder if the investigators would address that question.

DOCTOR KERNAN: We did address that question. First of all, we attempted to interview case subjects as early as possible after the onset of their event, and the same was true for control subjects, as I mentioned. We were primarily concerned that patients who demonstrated language impairment would have difficulty accurately reporting their exposure to PPA. We completed an analysis in which we looked at odds ratios and exposure histories among individuals with a history with mild aphasia in our cohort and individuals who did not have mild aphasia, and the principal findings of the study were unchanged. There was a tendency for individuals with aphasia to report slightly less PPA use, but when we eliminated those individuals from the analysis, the results of the study were unchanged.

So we don't feel that there is evidence in our study to suggest that the enrolled case subjects were any less likely to accurately recall PPA exposure than the control subjects. Recall that we did not enroll deceased subjects obviously but we did not enroll patients who had serious impairment in communication.

We also would like to point out, I think, that other case control research would suggest that individuals who have a significant health event are quite keyed in to recalling events immediately prior to that.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: I'd like to ask two questions. On your fourth slide, you give a list of specific aims and there was a comment made earlier about multiple testing which I think we'll have to grapple with later on. Your aims start off with women, appetite suppressant, first use, then go to the combined population. Could you just go over the history. Is this what was really motivating the study or was it general use and then breakdowns?

DOCTOR KERNAN: At the time this study was designed, the FDA in particular was particularly interested in women and women who used PPA as an appetite suppressant and for first use. The study was actually sized to look at women who used PPA as a first use, and so that was always really the major focus of this study. That's historically how this evolved. We considered these co-equal aims. I would like to point out that these co-equal aims are not independent but they all share the same exposure of PPA.

Does that answer your question adequately?

DOCTOR D'AGOSTINO: Yes, it does. Thank you. And the other question. You may have said it along the way and I'm sorry if I missed it, but you gave the chart of the verification of PPA exposures and, if I heard you correctly, there were three exposures non-brand that you removed later from consideration as exposures.

DOCTOR KERNAN: That's correct.

DOCTOR D'AGOSTINO: Where did they fall? Were they cases of the controls?

DOCTOR KERNAN: Can I ask my colleagues to comment on this? I don't recall whether those three were cases or controls. This is Catherine Viscoli from Yale University.

DOCTOR VISCOLI: One was a female case used as a first dose. She couldn't recall if she'd used Contac, Sine-aid or Sine-Off, and that may or may not contain PPA. The other two were controls. Actually, there was an error on the slide. One was Alka-Seltzer Cold which does contain PPA. But he didn't have the container and he didn't have access to the product ID chart. But we did rerun it with him as exposed. Didn't change the analysis.

DOCTOR D'AGOSTINO: That was going to be

my next question. Did you do a sensitivity analysis to say what if they were included, and you're saying you did it and it didn't change the results.

DOCTOR VISCOLI: Didn't change it.

DOCTOR D'AGOSTINO: Thank you.

DOCTOR NEILL: Richard Neill. My limited understanding of subarachnoid hemorrhage is that given its relationship to occur in patients perhaps with a pre-existing blister on a blood vessel, that many of these patients are going to die before they ever make it to the hospital, and I'm curious about the recruitment efforts that were made or surveillance efforts that were made to identify cases that may have escaped hospital admission discharge criteria and whether efforts were made to identify cases that occurred as deaths and therefore excluded by virtue of monitoring death certificates, that type of thing.

DOCTOR KERNAN: Doctor Broderick has a comment and then I have a comment on that.

DOCTOR BRODERICK: From our previous epidemiologic studies, about 10 percent of cases of subarachnoid hemorrhage will die in the community and you only get them because of coronary reports, and that's pretty consistent actually with studies from Rochester, Minnesota as well. We did not in

the course of this during the entire years look for all the autopsy reports of those patients, so at most, we would miss 10 percent of cases.

One thing about subarachnoid hemorrhage cases though is once they get to the hospital, they're actually more likely to survive and to be able to talk to people whereas the hemorrhage, the intracerebral hemorrhage cases, are more likely to have hemorrhage in the brain which affects their ability to speak and so that's why in the study you see actually more subarachnoid hemorrhage cases than intracerebral hemorrhage cases which is actually the opposite of what you would expect because intracerebral hemorrhage is about twice as common as subarachnoid hemorrhage. But unfortunately, if you have your brain affected and you can't give a history, those patients will be excluded. So that's why we see a difference here in this case group.

CHAIRMAN BRASS: Doctor Cantilena.

DOCTOR CANTILENA: Yes. If I can ask a question, actually back to the exposure slide you had. Under brand name you have excluded, if I understood you correctly, formulation changes. Is that true?

DOCTOR KERNAN: I'm going to ask Catherine Viscoli to comment on that, who oversaw

the verification procedure.

DOCTOR VISCOLI: We checked anything with possible formulary change by lot number. Basically, that was for the dose analysis because a well-known brand changed the dose of PPA in it during the period. But we didn't exclude them. We checked them with lot number.

DOCTOR CANTILENA: Okay. So you're not excluding them. It's just that --

DOCTOR VISCOLI: No. We just verified the dosage.

DOCTOR CANTILENA: For the dose. Okay. Thank you.

CHAIRMAN BRASS: I have a couple of questions. Did you do any differentiation between immediate release preparations and delayed release preparations, particularly in the first-use case cohort?

DOCTOR KERNAN: We've not completed that analysis yet, but we intend to.

CHAIRMAN BRASS: Second, in terms of the concern about confounders and imbalance of those confounders, to the degree you can within the model that was generated from this population, can one compare the impact of confounders like hypertension and smoking to other large databases and attempt to

provide model validity to the current cohort with respect to the magnitude of these effects?

DOCTOR KERNAN: We've spent a great deal of time among ourselves and with consultants talking about the dependability of our models, and I would like to ask my colleagues from New Haven to comment more fully on this, and I wonder if Doctor Horwitz or Doctor Viscoli would like to address this issue.

DOCTOR HORWITZ: We have considered these issues extensively, as Doctor Kernan has indicated. I think there are opportunities for us as we currently see them to use external data sets for validation of the way in which we've adjusted for these confounding factors. We do, however, believe that the methods that we employed provide internal consistency and coherence in the analysis. Both the methods of modeling that we employed as well as the methods of stratified analysis provide a consistent and coherent presentation of the risk between phenylpropanolamine and hemorrhagic stroke, and it's the coherence and consistency of those analyses using different methods that allow us to conclude that we had adequately adjusted for confounding factors.

CHAIRMAN BRASS: And finally, I'd be interested if on the back of envelopes you have done

some absolute risk calculations, and I'd be particularly interested in numbers like the number of -- assuming your point estimates are correct on relative risk -- what the number of PPA-associated events in the United States per year would be or the risk assumed in buying one package of PPA-containing products, etcetera.

DOCTOR KERNAN: We have completed this analysis, and I want to preface this by saying that we think that this analysis is really an estimate, and we're reluctant to give it too much credence, although we think it's an important analysis. The average incidence of hemorrhagic stroke for individuals between about 20 and 50 years of age is somewhere around 20 per 100,000. Certainly for individuals between about 25 and 50, 20 per 100,000 per year is a reasonable rate for the incidence of both hemorrhagic stroke and subarachnoid hemorrhage combined.

That comes out to a daily risk of about .6 patients per million per day. We use this to calculate what's considered a number needed to harm. That is, the number of women who would need to take an appetite suppressant in order to experience a hemorrhagic event. And we come up with estimates that vary between about 110,000 and 1,400,000. That

is, under these assumptions, and these are assumptions which may be taken, I think, thoughtfully, the risk would appear to be of about that magnitude and that would be the daily risk.

CHAIRMAN BRASS: Yes, sir.

DOCTOR KITTNER: As a follow-up to that question which may already have been asked, assuming that this is a causal relationship, did you perform any back-of-the-envelope calculations on the number of strokes in the country which would be attributable to this exposure every year?

DOCTOR KERNAN: We have not completed that analysis and estimation.

CHAIRMAN BRASS: Doctor Daling.

DOCTOR DALING: You asked a number of drugs that these women took. Did you find any other associations with other drugs in this population?

DOCTOR KERNAN: We're in the process of completing that analysis. I did show you results for cocaine, nonsteroidal anti-inflammatory drug use, nicotine in drugs and caffeine in drugs, and we've not completed a thorough analysis for those medications, but there was an association or there may be an association with caffeine, nicotine and cocaine. Cocaine has been well-reported. The association with nicotine in drugs probably is

because smokers take nicotine supplements and smoking is a risk factor for hemorrhagic stroke. The relationship with caffeine taken as a drug needs to be further explored, and we can only regard that as a very, very tentative exploratory finding.

Does that answer your question?

DOCTOR DALING: I was interested. Didn't you ask other medications?

DOCTOR KERNAN: I'm sorry. Say that again.

DOCTOR DALING: Other medications. What some would consider a medication.

DOCTOR KERNAN: Well, these were caffeine and nicotine taken as drugs. We have not yet looked at other medications thoroughly.

CHAIRMAN BRASS: Doctor Katz.

DOCTOR KATZ: I had a couple of questions. We know that you excluded patients who had very bad outcomes, either death or couldn't communicate, because proxy information was considered to be unreliable. Could you tell us how many patients fell into that category that you excluded and can we say anything about what would have happened if you could have gotten valid exposure information from them? In other words, what biases might have been introduced by excluding

them? Did you do any sort of -- I don't know -- sensitivity analyses including the worse case scenarios, that kind of thing?

DOCTOR KERNAN: Again, I believe it was about 182 eligible case subjects who were excluded because they died or were noncommunicative. Do you want to provide a more precise estimate?

CHAIRMAN BRASS: I think you actually had that on a slide.

DOCTOR VISCOLI: We identified about 1,700 hemorrhages. Of those, about 600 -- 400 died and 180 were not communicating within 30 days.

DOCTOR KERNAN: In terms of the effect of excluding those patients, I think we have no way of knowing what is the effect. We did do extensive modeling during the planning phase of this study which demonstrated that we simply could not obtain an accurate estimate of the odds ratio by using proxy data. This is Doctor Larry Brass, Lawrence Brass, from Yale University.

DOCTOR LAWRENCE BRASS: Just to follow up on that. In considering this though and how it might affect the results, we also looked at other known risk factors for hemorrhagic stroke, and there's really no evidence to suggest that they would result in better outcomes. In fact, known

risk factors, if anything, were to increase worse outcomes and worse severities so, if anything, by including them we would expect to have higher rates of risk factors, higher rates of medications that might be associated with hemorrhagic stroke and so on. So, if anything, it would move us away from the null hypothesis.

CHAIRMAN BRASS: Doctor Kittner.

DOCTOR KITTNER: One of the questions that was raised about the validity of the study was the possibility of recall bias, and just to follow up on one of the previous questions. Certainly drugs like aspirin are well known to the public to be associated with an increased risk of bleeding. That's a well known complication. Did you look to see whether the risk in the study was specific to PPA or whether there was also an increased risk associated with aspirin use?

DOCTOR KERNAN: This relates to the question that was asked earlier, too, about other drugs we've looked at and I recall that we have looked at aspirin and dextromethorfan as well. There was essentially no difference between cases and controls in the proportion that reported use of aspirin. We found this striking since aspirin is well known or much more well known, I think, that

PPA to be related to risk for bleeding and hemorrhagic stroke. But there was no difference between cases and controls for this exposure. This led us to have greater confidence that recall bias may not play an important role in this study.

CHAIRMAN BRASS: Doctor Johnson.

DOCTOR JOHNSON: I'm just a little confused about the questions about other drug use. Table III of the documents we received, it looks like it has a fairly long list of drugs that you looked at, aspirin, dextromethorfan, sympathomimetics. So these have been looked at.

DOCTOR KERNAN: They have been. Yes. I'm sorry. I had forgotten that when I answered the question earlier. We've looked at those that are in that table. They're actually, I think, reported in the May 10 report to the FDA.

CHAIRMAN BRASS: Doctor Warach.

DOCTOR WARACH: There's a suggestion in the literature that Hispanics may have a higher risk of hemorrhage. How did your case and control groups compare as far as composition for Hispanics?

DOCTOR KERNAN: We have not completed that analysis yet, although one of our investigators, Doctor Lewis Morgenstern, is very interested in that question. We do have only a

small portion of Hispanics who are enrolled in the study. I believe they comprised about five percent or less of the overall cohort. So we will have very limited power to make any comment about that group of patients.

CHAIRMAN BRASS: Yes

MS. COHEN: Do you have any idea how many of those people in trial took more than what was prescribed in their medication? It's the over-use of medication that I'm interested in. If some is good, more is better. So how much did you find out about how they actually used the drug?

DOCTOR KERNAN: The median dose consumed with 24 hours was, I believe, 75 milligrams which means that essentially half of the subjects in this study, case or control, were consuming greater than 75 milligrams.

MS. COHEN: So that more than the label indication?

DOCTOR KERNAN: More than 75 milligrams. Yes.

MS. COHEN: Yes, and then what does that tell you in terms of the patient population that's using this medication?

DOCTOR KERNAN: It only tells me that the median dose was 75 milligrams. We can't comment

on how our population differs from subjects who did not get into the study because we don't have information on patients who don't get into the study.

MS. COHEN: Then were your results stratified as to those who took the exact dose versus those who took much more?

DOCTOR KERNAN: Yes. In the last couple of slides I presented the dose response analysis showing that the odds ratio associated with higher doses of PPA was higher than the odds ratio associated with lower doses. So we are concerned about a potential dose relationship.

MS. COHEN: One of the things I'd like to see are the labels. If I missed it in the literature, I'm sorry, but I'd like to see the labels of the company, the medications.

CHAIRMAN BRASS: The gift shop will be open during the break. I just want to clarify, and this will probably come up later, but I think for many of the decongestant products, the label will permit more than 75 milligrams per day so that I think correlation to label has to be done cautiously and by--

MS. COHEN: Well, is there a disclosure to the results of something like that on the label?

CHAIRMAN BRASS: I think that will come up later.

Doctor D'Agostino.

DOCTOR D'AGOSTINO: I think you've said it, but I have a long history looking at PPA that should be known. I was on the miscellaneous internal committee and so forth looking at the efficacy and over the years I keep getting asked to look at some of the data and my recollection is 10 - 13 years ago before the stroke study that when you looked at the reported cases, you also found that they were using a lot of other drugs. Not medications, but they were cocaine users and things of that nature. How intense was the effort to find out what other drugs were being used? I'm really talking about illegal drugs.

DOCTOR KERNAN: You're talking about illegal drugs.

DOCTOR D'AGOSTINO: Right.

DOCTOR KERNAN: Yes. In our ascertainment of the exposure information, we ascertained every exposure to every prescription and nonprescription drug that a patient consumed, so we have very detailed information on this. Equal efforts were made to ascertain PPA-containing and non-PPA-containing drugs. Among our group of case

subjects, there were many individuals who were consuming other medications. I presented you with preliminary results for the use of cocaine in the control and case group showing that case subjects were more commonly exposed to cocaine than control subjects. When we adjust for cocaine exposure, however, it does not change the main findings of our study.

DOCTOR D'AGOSTINO: You have seven exposures in the appetite suppressant. What was the result for those seven in terms of cocaine?

DOCTOR KERNAN: Catherine, can I turn to you to ask if you're aware of that. Among the seven individuals who were exposed to appetite suppressants, were any also using cocaine?

DOCTOR VISCOLI: They were all women and none of the cases who were using appetite suppressants were also using cocaine.

CHAIRMAN BRASS: Doctor Katz.

DOCTOR KATZ: Yes. I'm interested to know how you'd address Doctor Strom's concern specifically with regard to the problems raised by small numbers, particularly in the one cell in which you had a very large odds ratio, both with regard to the fragility of the results, as he called it. In other words, one or two exposures in the controls

would have made it disappear. And also with regard to the appropriateness of the conditional logistic regression that you used and whether it was valid with these numbers.

DOCTOR KERNAN: We spent, again, a great deal of time among ourselves and with our consultants discussing the most appropriate method for completing an analysis which accounts for confounders and I'm going to ask Doctor Ralph Horwitz, who's really spear-headed our efforts in this, to address specifically your comments. Doctor Horwitz was with Doctor Lawrence Brass, principal investigator for the study.

DOCTOR HORWITZ: We, too, were concerned, as Doctor Strom indicated, in the numbers of exposed subjects in the appetite suppressant group. I should state first that the exposure prevalence in the control group that we achieved in the study was almost identical to that which had been developed or postulated in the design of the study. We had available to us in 1993 when we were designing the study information on marketing and sales of PPA by age group and by region of the country that allowed us to estimate what the exposure prevalence would be among controls to appetite suppressants and the estimated rate that we

used in sample size estimation turned out to be almost identical to the observed rate that was found in the study.

So we went in recognizing, all of us went in recognizing that the exposure prevalence for appetite suppressants in young women as a first dose or as a first dose was a very relatively small number, would require a large sample, and we set an odds ratio in calculating and estimating the sample size at a value of five in recognition of those concerns. So we think that the study was designed with that expectation and we met those anticipated exposure levels.

The other protections are really protections in the design and conduct of the study and we did everything that we believe is available to do in current state-of-the-art methods for case control research to identify and verify exposures to PPA in this case to ensure that they haven't been mis-classified and I think we have considerable confidence in the quality of those procedures and in the quality of the work that was done in the field to ensure that there is adherence to the methods and protocol of the study.

We have conducted, as has the FDA in their own internal analysis, sensitivity analyses,

to look to see what would happen if, as a result of the sparse exposure data, you were to change the classification of one or more subjects per category and, in general, as indicated in the report that you saw earlier, the data are quite robust and resistant to small changes in classification. So we started out with an exposure prevalence that we were able to estimate from marketing data and met that exposure prevalence. We used the best methods that we could to ensure verification and identification of subject exposure and I believe that the results are resistant to small changes and misclassification.

CHAIRMAN BRASS: Yes.

DOCTOR BLEWITT: Two questions. One goes back to the dose issue and the slide about the over 75, under 75, and I wonder whether you've analyzed the dose with over 150 versus less than 150 milligrams. We haven't calculated odds ratios for that dose range at this point.

DOCTOR BLEWITT: Secondly, on the slide of PPA and risk for hemorrhagic stroke in men, there's an adjusted odds ratio of .62 and my question is does this, in a sense, suggest a potential protective effect with this low odds ratio in men?

DOCTOR KERNAN: There are very few

exposures among men in the cohort, in the overall cohort, to any PPA and no exposures, as you know, to appetite suppressant use. We believe that we really can't conclude that PPA is either a risk for hemorrhagic stroke or protective against hemorrhagic stroke in men with the data that we have. The confidence interval around our estimates are just too wide. I can't think of a reason why PPA would be protective. I would not interpret that odds ratio of .062 as suggesting that it is protective.

DOCTOR BLEWITT: Does it argue, nonetheless, for performing a two-tailed test?

DOCTOR KERNAN: Again, I don't think so. There are very few exposed males. That estimate for the odds ratio has a very wide confidence interval around it, and I wouldn't place a great deal of meaning on its absolute value at .062. And furthermore, the decision to use a one-tailed test was based on reasoning that we were not looking for a beneficial effect of phenylpropanolamine.

Doctor Horwitz, you want to comment.

DOCTOR HORWITZ: I'd just like to add that in retrospect we were really quite under-powered to make any inferences at all about odds ratios in the sub-group of the patients who were men. If we had it to do over again and we were

designing the study, we would probably have sampled a much larger proportion of men because the exposure prevalence in men was so much lower than it was in women.

CHAIRMAN BRASS: Yes.

DOCTOR DELAP: I have a question about the interviews, structured interviews that were collected. The people who did those interviews, how much did they know about the study hypotheses?

DOCTOR KERNAN: They knew about the study hypothesis. They knew that the study really had two broad objectives. One was specifically to look at the association between PPA and risk for hemorrhagic stroke but that all the investigators who had designed the study had had an equal interest in looking at other risk factors for hemorrhagic stroke.

Protections. The question has been raised as to whether the fact that interviews were unblinded had an influence on the acquisition of study data. These interviewers were highly trained, went through in the use of the instrument and adhering to a very tight script for the use of the instrument.

CHAIRMAN BRASS: Yes.

DOCTOR GANLEY: Yes. I just want to get

some clarification on your exposure of three days and trying to think about that. Does that mean that someone who had taken a PPA three days prior and then had a stroke would be included plus it would also include people who were continuously -- they were on the third day of therapy?

DOCTOR KERNAN: That's correct.

DOCTOR GANLEY: So do you have a breakdown of what the exposure was in that regard based on if this is something that's related to increasing blood pressure and they've been taking it for three days?

DOCTOR KERNAN: Two answers to that. One, I can tell you within the group of individuals who took appetite suppressants, three of them were exposed within 24 hours, three were exposed in a broader time interval. We have done a preliminary analysis looking at recency of last exposure to PPA, so defining use as last exposure within 24 hours, last exposure two days before focal time, last exposure three days before focal time. We're reluctant to draw too many conclusions from this analysis because it's based on small numbers, but it does appear that the risk of hemorrhagic stroke is concentrated among individuals who've used phenylpropanolamine on the index day or the day

before. But again, that's a very tentative conclusion.

CHAIRMAN BRASS: All that data is actually in Table VI that allows that differentiation to be made because of the timing of the last dose.

Also related to those themes. When you did the dose analysis, was that based solely on the last dose or did you also try a cumulative three day dose relationship?

DOCTOR KERNAN: We've done several analyses. I'd like to ask Catherine Viscoli if she would comment on the constancy between the findings from the dose response analyses using different definitions of exposure. We looked at a magnitude of last dose, total amount taken in 24 hours, and total amount taken within three days.

DOCTOR VISCOLI: You saw the 24 hour dose which showed a doubling of the rate although, based on small numbers, you can't draw a firm conclusion from that. When we looked at the three day dose above the median of 150 milligrams and at or below that, we didn't see any dose response.

CHAIRMAN BRASS: Are there any other questions from the panel? Yes.

DOCTOR GILLIAM: Would you comment on

the statement made earlier that you should use .01 as your level of significance instead of .05 due to repeat testing.

DOCTOR KERNAN: This issue was considered during the design of the study and there's a member of the investigative team who I think is well-equipped to comment on this. Doctor Horwitz, if you'd like to comment.

DOCTOR HORWITZ: We did address this issue up front. I think as was indicated earlier, the hypotheses were pre-specified. They were highly inter-dependent. We set the alpha level as we did in recognition of the fact that these were not analyses that were conducted post hoc but really were pre-specified and inter-related.

CHAIRMAN BRASS: If there are no additional questions, we will adjourn for our morning break. We'll come back at 10:20. 10:20 please.

(Off the record at 10:07 a.m for an 18 minute break.)

CHAIRMAN BRASS: The next set of presentations will be comments on the Yale Study by the Consumer Healthcare Products Association. Doctor Soller's clock is about to start. The next set of presentations will be led by Doctor William

Soller, Senior Vice President, Director of Science Technology at the CHPA. Doctor Soller.

DOCTOR SOLLER: Thank you, Doctor Brass, members of the committee. Good morning. I'm Doctor Bill Soller, Senior Vice President and Director of Science and Technology for the Consumer Healthcare Products Association, a 119 year old trade organization representing the manufacturers and distributors of nonprescription medicines and dietary supplements.

Our presentation is in three parts. I have background comments and will be followed by Doctor Noel Weiss and the Independent Expert Panel which reviewed the Hemorrhagic Stroke Project Study, and I will close with proposed next steps. I'd like to start by answering the question, what did we know about PPA when the HSP Study was started?

First, we knew and know now that PPA is considered by FDA as an effective nasal decongestant for colds, flu, allergy as reviewed in the OTC monograph and in two NDAs for 75 milligram sustained release product. We also know that PPA is considered by FDA as an effective appetite suppressant producing a three to four pound greater mean weight loss over baseline versus placebo in both six and 12 week studies along, of course, with

diet and exercise.

I remind you of the significant morbidity and mortality associated with obesity in the United States and with NIH's recommendation that even over-weight people lose weight to help reduce or reduce the risk of blood pressure, elevated total cholesterol and elevated blood sugar. Note that the differences in the total daily dose for these two indications, 150 milligrams per kilogram per day for cough/cold and 75 milligram per kilogram per day for weight control.

We knew that PPA was reasonably safe for continued marketing based on the adverse experience reporting profile from spontaneous reports to FDA and industry. Typically, there is a low number of reports per year with no clear signal or trend, and this is the current picture as well with an average of about two spontaneous reports per year over the last 10 years.

Based on many clinical studies on normotensive, controlled hypertensive, obese and non-obese individuals in single, multiple and ascending dose models, PPA causes no clinically meaningful elevations in blood pressure, other vital signs, CNS stimulation or subjective effects at recommended dose. The largest of these studies is

by Blackburn et. al., and Doctor Blackburn is available today for Q&A.

In addition, two retrospective epidemiologic studies were available, one derived from the database of the Boston Collaborative Drug Surveillance Program and the other from the National Hospital Discharge Survey Database, and there was no indication of a signal in either epidemiologic study. In somewhat more detail in the first of these studies by Aselton and Jick reviewing the Boston Collaborative Drug Surveillance Program database, they reported over the '77 to '82 period many fewer hospitalizations for PPA versus non-users for a thrombotic or nonthrombotic cerebral vascular event shown here one for PPA covering seven million person days versus 275 for non-users covering 520 million person days.

In addition, we reviewed the National Hospital Discharge Survey database calculating morbidity ratios for observed to expected hemorrhagic strokes in the context of diet aid use by women 15 to 44 years of age and, with the background of hemorrhagic stroke rate calculated at about or estimated at 16 per 100,000 in women 15 to 44 years of age, we estimated morbidity ratios of .02 for first dose paradigm and .36 for exposure

under multiple dosing paradigm. So at that time, these epidemiologic studies supported a favorable safety profile for PPA.

At the start of the HSP Study, a hypothesis had been generated despite clinical epidemiologic support for PPA safety as well as demonstrated clinical benefit. The consensus was, therefore, OTC continued marketing with additional study to optimize our understanding of PPA safety profile based on PPA's known efficacy, favorable AER profile, and favorable clinical findings on blood pressure.

Our involvement with the HSP Study was very limited. We had input on design and funding, of course, but virtually no involvement on the conduct and analysis, and we understood that we may face clearly positive or clearly negative or ambiguous findings needing an advisory committee deliberation such as today. When we received the initial report, we were struck by an apparent over-interpretation of the study results and contacted leading epidemiologic and statistical experts, many of whom are here today. These experts are shown here. Doctors Blackburn, Hennekens, Hirsch, Hoffman and Walson will be present and/or be available for you for your Q&A during discussion.

And we also contacted an independent expert panel for a second view about the HSP Study and, at this time, I'll turn the podium over to Doctor Noel Weiss who chaired this panel of leading members of the U.S. epidemiologic community. Doctor Weiss.

DOCTOR WEISS: I'm Noel Weiss. I'm an epidemiologist at the University of Washington. A lot of my research is focused on clinical epidemiology, and I was quite interested in taking on this challenge when I learned of it. Next slide. The challenge specifically was to head an independent expert panel. We met in April of this year at the request of the CHPA to review the study. We were told that we should be independent and free to express our opinions, which we would have done anyway had we not been so instructed, and with the panelists -- and you'll see their identities in a moment -- collectively we had expertise in the design, conduct and analysis of case control studies as well as some expertise in neurology.

If I can have the identity of the panelists. There's Doctor Gorelick, a neurologist from Chicago, and then three epidemiologists, Doctor Kuller, Doctor Wallace, and myself. It's unusual for epidemiologists to associate with neurologists,

but Doctor Gorelick did have an MPH and we thought it was okay. Next slide.

We were given some materials to review, the protocol of the HSP study, the interview manual, some case summaries. The most important thing to us was the draft of the HSP study report, and we also had available an industry statistical assessment at that time. Next.

We did what epidemiologists do. We evaluated the study and tried to determine for ourselves how likely the association that was demonstrated was genuine or was it possible that either some sort of bias, confounding or chance might have contributed. Next slide.

Conclusions. When you get three epidemiologists, with or without a neurologist, it's difficult to come up with a consensus and especially if two of those epidemiologists are Lewis Koller and Noel Weiss. Nonetheless, we were abler to identify a small range of conclusions that we could actually agree on. There were a larger number of independent opinions that there wasn't any consensus on. But what I'm going to present to you are the opinions that we did share.

The first was that we were impressed with the magnitude of the undertaking and the scope

of it. Trying to study a rare disease, a rare exposure and an exposure for which it's almost essential to obtain interview information about it. The combination of all those things means that you have to do really a very large, ambitious study, and this was such a study. We felt, however, that there were numerous methodologic issues that confronted it and that ultimately limited the amount that could be interpreted and we were concerned specifically with chance, bias and confounding as plausible alternative explanations.

A key feature. Some of us gave different emphasis to this. For me, this is a particularly important one. The low level participation of potential study subjects, especially among the controls. How important this is can not be determined, but it could have potentially large degree of importance, not emphasized so far this morning and I don't think it's going to be emphasized in the FDA assessment of the study, was really the very substantial under-ascertainment of potential controls. Even among those identified as potential controls, some 35 percent were actually recruited into the study and if you were able to take into account those households where it was not possible to enumerate

potential controls, that percentage would even by lower. That, to me, really makes it difficult to place a lot of confidence in whatever data were obtained from those people who did agree to take part.

The last two points on the slide. There are differences between cases and controls in terms of various confounding variables. There was a lot of attention paid in the analysis and in this morning also to how that was dealt with and, to the extent that these variables could be measured, I think the efforts were good ones to try to control those. However, first, some variables could not be measured well and, second, the small number of subjects limits one's ability to control for confounding. Next, please.

We felt in the interpretation that there was selective emphasis of sub-groups which could be misleading and that fits in with the next which is no clear biological rationale to support a causal association. Not so much an underlying biological rationale like elevated blood pressure which conceivably could play a role, even though the elevations are temporary and modest, but there wasn't a clear biological rationale to support the difference across sub-groups. Why an association in