very small.

Not speaking now as the head of the panel but just as somebody who's here this morning, I just wanted to respond to Doctor Wolfe's comment that this seems to be another example of a case control study which has shown an association and which has found an important relationship that likely is causal. He made analogy to the association between aspirin and Reye's syndrome, DES and vaginal adenocarcinoma, estrogens and endometrial cancer. I'm familiar with the data on all those studies and, at least in my personal opinion, neither the quality of the evidence nor the quantity of the evidence in this instance is anything like those others and should be viewed quite very much on its own.

Now, as I said, the other panelists will speak in more detail about some of these issues, and the first will be Lew Kuller.

DOCTOR KULLER: Thank you very much. My name is Lew Kuller. I'm an epidemiologist at the University of Pittsburgh, and I'm going to review certain aspects of the study in relationship to its interpretation.

First, I want to say that when you see up here that this was a failed study, it has absolutely

nothing to do with the design, which was outstanding, nor the investigators, who were equally outstanding, but every one of us does failed studies and, if we didn't, then we would basically not understand that we have done failed studies, which would even be worse.

Why do we say that this is probably a failed study design or failed study problem? And there are two problems, as I see it. One of them is that only 41 percent of the potential cases are in the study, and you can't say anything about the other cases because you're not really sure what they are. But most important, there's a very substantial problem in selecting the controls, as you'll note. A hundred and fifty one telephone numbers had to be identified to find one potential control and then three eligibles when they did find the potential was basically into the study.

To just show you what this could mean in terms of selection bias -- the next one, please. If you look here, they tried to basically match on social class, which is important, or education because education drives a tremendous amount of human behavior, and you can see here that this is just a major, major problem and it's not adjusting for education in the analysis. It's the problem you

really don't know what the people are who didn't get into the study, the controls, the ones who didn't answer the telephone and, most important, the ones who did answer the telephones and told you they didn't want to participate and basically when you see this, you get very, very nervous. Twenty percent of your cases with less than high school and only nine percent controls and reverse for college education. And that probably accounts for some of the data which we'll see.

Now, very interesting thing to do is to presume that the prevalence of use was similar -- and I just put four percent -- was similar to the use in the cases, that is, 3.8 percent in three days, and then say of the 4,200 controls that they didn't get in the study, if their use was four percent, you'd get 168 users and it would turn out that the overall prevalence of use in the controls would be 3.6 percent. We have absolutely no idea what the use rate was in the 4,200 which basically didn't get in and certainly have no idea, even in the larger number, of those 101 telephone calls and there's no way of answering that question. It's just a major question mark, but when they see the small differences that occurred in this study and the small numbers, that is

a very worrisome observation that you have this huge number of people who didn't get into the study. Next slide, please.

Now, there's also a problem, a rather interesting one, and that is rather if you turn this around, look at the data, why is there greater use in the controls in two weeks to three days prior to the event? If you look at the data here, you get basically the overall use is 5.4 and 4.8, but it's 1.7 and 2.5. There's actually more use of controls from three days to two weeks and it's just a little bit of a problem in terms of defining the date of exposure because it doesn't make any sense why you should see something of this magnitude. It's almost as great as the other magnitude. You should note also that the first use, eight and five, is where most of the action is in this whole study. A total of eight and five cases. Next one.

Now, the argument was raised that men weren't exposed, but this is not true. Actually, the exposure rate in the controls in the men and women is not significantly different and, if you leave out the appetite suppressant group of women, it turns out basically -- and look just at the nasal decongestant controls, it turns out it's 2.5 percent and 2.1

percent. The only difference in this whole study is the 5.5 percent in the women cases, the men cases. The controls in the men and women are exactly the same, and there should be enough power to test the hypothesis in the men because the use in the controls in the men is the same. The interesting thing. There's no use in the men who are cases. Next.

Likewise, it's a rather peculiar phenomenon if we look at cough and cold suppressants that was noted, and this is not a power issue. It turns out that the risk is 1.5 in the women, but it's 0.62 in the men and, again, it's hard to believe that this is a protective in the men. It may be a biological basis related to subarachnoid hemorrhage. The only problem is then if you believe that, as it turns out, there are only four subarachnoid hemorrhage cases in the women who are not hypertensive or cigarette smokers. Every other one of them women with subarachnoid, while a large number of the women that are cases with intracerebral hemorrhage, a larger number, there are very few of them, were neither hypertensive nor cigarette smokers. So this is a subarachnoid hemorrhage phenomenon. Again, it's not internally valid.

I just point this out. It's small

numbers. I get a little nervous. Six and one is an odds ratio of 12 for appetite suppressant but prior use in men is one case in eight controls. It goes exactly the opposite way, and this would be a bonanza in men because it would prevent cerebral hemorrhage and, of course, that's totally unlikely.

Now, we talked a little bit. Somebody mentioned about the use, and I just want to point out that the nine cases basically in current users within the first three days, and this is in the group in the study that are reported in eight/five controls and just to point this out. One of the women -- this is everybody -- drank 10 cups of coffee a day, one eight and a half cups, one had 10 glasses of soda, one had eight glasses of soda a day, one had six glasses of soda a week and a prior history of stroke, one with one glass of soda and a history of stroke, and two of the cases had just prior headache and nothing and, of the five controls, six cups of coffee a day, six glasses of soda, two cups of coffee and one had just a cup of tea. But it's hard. If you look at this, you have eight or nine cases to deal with in your whole study and basically at least four of those people were basically red hot consumers of either coffee or soda in huge amounts per day and they're not

typical of the U.S. population by a long shot.

Well, thank you very much.

DOCTOR WALLACE: I always hate to follow you, Lew. Good morning. I'm Bob Wallace from the University of Iowa where I do epidemiology and preventive medicine. Noel and Lew and Phil and I have really had mostly a lot of unanimity with respect to our concerns about this study, which is certainly a good faith and logistically very daunting study to do, so I'm beginning to worry that many of my own feelings are going to be a little bit redundant, but I'm going to go through this fairly quickly.

Some of the concerns. Again, I think based on what the investigators have suggested and the panelists and other comments, I think almost everything has been suggested. I'm very concerned about sample size with respect to dose and every epidemiologist wants to see whether they could grade the exposure, that is, the amount of exposure, and see that there's a lesser effect than those with lesser exposure, and so it would really be nice, for example, if we could look at those separately who were exposed three days prior to the event versus those who are exposed in the 24 hours. And again, it's very, very difficult to do because of the difficulty of capturing

that kind of exposure.

I'm also concerned about other events that occur. I talked to my neurosurgical colleagues. Not a systematic survey, I will quickly add, on my part. The issue of cocaine came up. The issue of alcohol came up which I was somewhat aware of and I just want to say that a lot of the effects of alcohol, particularly the acute effects of alcohol, are on alcohol withdrawal and so yes, it is a risk factor to drink more than two glasses a day, two drinks a day of conventional alcoholic beverages. On the other hand, I would hope that the same care with which the study of PPA use in the period prior to the event, the same care and the same rigor is taken for looking at alcohol use and the cessation of alcohol use.

Everybody has made the case that more than half of the cases couldn't be studied. I don't have an easy solution for this myself, but it's not different than an animal study in which half the mice got away, and one is always worried about it.

Lew has covered control selection, and I think I'll go on. We all face the problems with control selection. As you know, everybody gets telephone solicitations to the point where they screen calls and do all sorts of other things, and it's very

hard for us epidemiologists to come along and try to find a population that's referent to the general community because everyone is out there doing it also.

I wanted to quickly say -- and it's a point that's probably been made half a dozen times today -- that these cases are different. I think this is really a collection of different kinds of diseases. Now, I'm not going to argue whether they're cousins or distant relatives, but they are at least a little bit different, and I thought Doctor Broderick gave a good explanation talking about mechanisms that may be a little bit different but I'm also worried about risk factors that might be different. My own search of the literature, for example, found very little in the way of risk factor studies of arteriovenous malformations which are part of the case load. Maybe somebody has information, and I would like to see that. But I believe this is a series of closely related diseases that may not be the same, either in their etiology and their mechanism and their genetics and family history and so forth, and it would be really nice if we could look at them separately.

Again, a lot of the risk factor questions have been addressed and, in fact, I saw a little bit of information that I wasn't aware of. I'm personally

concerned about alcohol use and withdrawal, particularly in that period before the event. I'm very much interested in caffeine use, in part because caffeine in my view does raise blood pressure and Lew pointed out that we're looking at a population, we may be tapping into a population that's a little bit different. I'm amazed. Maybe it's just being simple-minded, but 10 glasses of soda a day or eight and a half or six. That is just a lot and I'm wondering if we're looking at behavioral patterns that we don't in fact fully understand, and I'm also interested in undiagnosed hypertension and we carry around the dogma that half of people with hypertension don't know that they have it and, since hypertension is such a dominant factor in subarachnoid hemorrhage, I'm always worried that in fact there's this reservoir out there that we really don't know how to measure because once they're in the hospital with their events, blood pressure fluctuates a lot and it's very difficult to tell, and I am interested in the cocaine history, as has been mentioned several times. So these are the data that you've already seen that, in fact, Doctor Kernan presented and I hope it looks the same.

I'm very concurrent, as Lew was just before me, that there is really an important class

difference, social class difference between cases and controls. Some of that may be due to the nature of the disease, but I want to know how much of these differences that we're seeing in fact can be explained by what I think are dramatic differences in social class that are really not explained by ethnicity although, like the one panelist, I did see that Hispanics may have an increased risk, particularly in some counties in the southwest. But I am interested in why there are these differences. For example, a 17-fold difference in the history of cocaine use and issues with respect to caffeine and body mass and so forth.

So in summary, for me, this is a logistically extremely difficult and daunting activity and I think personally that there are enough issues left open that it's very hard to make a judgment.

DOCTOR GORELICK: Good morning and thank you. Next slide, please. I'm Phil Gorelick and I hail from the great city of Chicago where I serve as professor and Director of the Rush Center for Stroke Research and the section of cerebral vascular disease and neurologic critical care. I am a board certified neurologist and, over the years, I've developed a busy clinical in-patient and office consultative practice.

I do have familiarity with case control studies. I have been the PI of four such studies and, as Noel mentioned, I do have a master of public health degree in epidemiology, though my daughter used to refer to it as the miles per hour degree. Next slide, please.

I've had a long-standing interest in the role of drugs in stroke. I've previously published as a co-author a paper on the topic which included a review on PPA, and I've spent a good portion of my career studying alcohol and stroke in case control form. Next slide, please.

What I'd like to do in the next several minutes is give you an overview of a clinical neurologist's view of the risk factors for hemorrhagic stroke and key clinical points to consider when evaluating the Hemorrhagic Stroke Project. We will have an opportunity to look at some of the details of these specific cases as I walk you through the ones for appetite suppression. Next slide, please.

As you've heard, hemorrhagic stroke makes up about 15 to 20 percent of all strokes. As you've heard previously, there's two types: intracerebral which we abbreviate here as ICH and subarachnoid as SAH. Generally speaking, the intracerebral is more common and usually but not exclusively it's caused by

a rupture of a deep artery in the brain and the blood is within the brain tissue. The subarachnoid, as has been previously mentioned, is usually due to a blister on the blood vessel which ruptures and then blood forms around the base of the brain and over the coverings of the brain.

The other type of malformation is an AVM or arteriovenous malformation which is an abnormality or tangle of blood vessels that has an abnormal connection directly between the arteries and veins. This can also cause subarachnoid hemorrhage. So as you can see, there are different causes and these may produce different outcomes and we must consider the underlying health status in evaluating the contributors to risk. Next slide, please.

Well, here are the hemorrhagic stroke risk factors by sub-type. Intracranial hemorrhage on your left, subarachnoid on your right. And these are from the American Heart Association Risk Factor Panel, of which I was a member of the writing committee, and from other sources. The factors that are highlighted or bolded are the lead factors so, for intracranial hemorrhage, hypertension, heavy alcohol use, anti-coagulants. This problem increases with age so the older are a little higher at risk. There tends to be

more men. African Americans and drug abuse has also been implicated, specifically cocaine.

On the subarachnoid hemorrhage side for these important risk factors, the one that seems to stand out substantially is cigarette smoking though, again, hypertension, alcohol, heavy alcohol use also come in. This is a disease in which there tends to be a disproportionate amount of subarachnoid hemorrhage in younger person as compared to ischemic stroke and specifically women seem to be a higher target and then again, African Americans have a very high risk. So these are the major risk factors for these two types. You'll see there's some overlap. Next slide, please.

Let's look specifically at the Hemorrhagic Stroke Project with some of the neurologic considerations. As you've already heard, there's a higher frequency of independent risk factors for hemorrhagic stroke in the case group as compared to the controls and specifically such things as cigarette smoking, hypertension, alcohol use, cocaine use and so on. So this is an established factor in these cases. Interestingly, if you look at the individual cases which we'll do shortly, history of AVM or aneurism was in at least four of the six appetite suppressant cases. Next slide, please.

Let me walk you through this table of the appetite suppressant cases to show you some of my concerns. I'm not showing the cough/cold information, but they also had risk factors, but to simplify the presentation we'll look at this. In the far left hand column you notice that case three had an arteriovenous malformation as the cause. The other five cases had subarachnoid hemorrhage and, of those, an aneurism was identified in one, two, three cases. These UNC cases mean that there was a subarachnoid hemorrhage but no aneurism or other vascular malformation was found.

Of interest now, let's look in the cigarette smoking category, and you can see bolded in yellow that one of the cases was a current smoker, a pack per day. Another case was a current smoker, one and a half packs a day. Another case was a currently smoker, two packs per day. Another case was an ex-smoker. Let's look in the hypertension column. One of the cases that smoked also was hypertensive. Another case had hypertension as well.

Let's look in the alcohol use column. This patient was drinking three drinks per day. We have a patient who had a history of abuse of alcohol but denied use more recently. Here's one who was drinking eight per week and here's one who is drinking

13 per week. So what I'm pointing out here is that all of these cases, generally speaking, had risk or most of them had traditional risk factors for intracerebral hemorrhage or subarachnoid hemorrhage, as you can see here. Next slide, please.

Another issue for me has to do with the attributing PPA as a factor here. I've concluded, based on my analysis, that even if the association is real, the number of cases attributed to PPA has to be extremely low and then we're left without a biologically plausible mechanism. Next slide, please.

So here's my conclusion and, again, I've shown you all of these risk factors in these cases and simply the PPA exposed cases and the HSP had typical risk factors for hemorrhagic stroke. We've shown you hypertension, we've shown you smoking and alcohol consumption. Aneurysms in AVM appeared to be responsible for at least four of the six cases in the appetite suppressant group and, finally, insufficient control of these risk factors as confounders contributes to uncertainty surrounding the interpretation of the HSP results.

Thank you.

DOCTOR SOLLER: Thank you very much.

I'd like to now introduce Doctor Charles

Hennekens.

DOCTOR HENNEKENS: Thank you, Doctor Soller. My name is Charles Hennekens. Since last October, I've served as a consultant in epidemiology to the CHPA when I first learned of the Hemorrhagic Stroke Project. Ralph Horwitz and Larry Brass have been colleagues and friends for decades. Since honest scientists have honest differences of opinion, I trust they'll remain so after today.

Let me begin by congratulating the investigators and their staffs from Yale, Brown, Cincinnati and Texas. They've done yeoman's work in assembling over 2,100 participants. As an epidemiologist who's conducted case control studies, I applaud as well as sympathize and empathize with their outstanding efforts.

My issues relate less to the design but more to the analysis an interpretation of this study. The Independent Expert Panel has presented their cogent joint as well as individual perspectives about the real likelihood that chance, bias and/or uncontrolled confounding each could easily explain the observed findings in the HSP. I'd like to highlight several major issues that derive from the initial epidemiology and biostatistical reviews conducted by

myself and Bob Hirsch, who's here in the audience today and is professor of biostatistics and medical statistics at G.W. and also a consultant to CHPA.

With respect to chance, this is a large study of over 700 cases and 1,400 controls, but it's crucial to recognize that even the most robust and informative overall test of the hypothesis that PPA is associated with hemorrhagic stroke is based on just 27 exposed cases and 33 exposed controls. This overall finding does not achieve statistical significance, even using what I believe to be an inappropriate one-sided test that yields a p-value of 0.085 which is about one-half of the more appropriate two-sided p-value of 0.17.

The fact that a two-sided p-value is more appropriate is in part because of convention but also because this study was designed in the context of a totality of evidence that included, on the one hand, some concern from adverse event reports and, on the other hand, some reassurance from prior epidemiologic studies.

My own view is that regardless of whether the investigators, sponsors, and FDA agree to using one-sided p-values in the design, the most important point in the analysis is that several of these major

analyses go from statistical significance to non-significance when one goes from a one- to a two-sided p-value. Further, while the overall finding is based on a total of 60 participants, the sub-group of women taking PPA as an appetite suppressant is based on a total of only seven participants, six exposed cases, and one exposed control.

Interestingly, one of these six cases had also used PPA as a cough and cold remedy. In the analyses, she is counted twice, once as a user of PPA for cough and cold suppression, but also as a user of PPA for appetite suppression. Interestingly, her BMI was 19 which compares with the U.S. average of about 27. Had she been classified only as a user of PPA for cough and cold suppression, the two-sided p-value would no longer be statistically significant for the test of the sub-group hypothesis that PPA used by women as an appetite suppressant increases the risk of hemorrhagic stroke.

Indeed, if the primary aim were to study the association between PPA used as an appetite suppressant and hemorrhagic stroke, I would have studied 2,100 women, not 1,153. Perhaps most importantly, chance would remain a plausible alternative explanation, even if this were a

randomized double blind placebo-controlled clinical trial of PPA versus placebo. But, in fact, this is a retrospective case control study with additional limitations of bias and uncontrolled and indeed uncontrollable confounding.

With regard to bias, selection is an inherent limitation of all case control studies and is a major problem in the HSP because the response rates are low in differential. Parenthetically, I would accept the investigators' estimate of 75 percent for cases because I think the failure to enroll the fatalities limits the generalizability, not the validity, of their estimates. However, as has been pointed out, the participation rate and controls is about 35 percent.

Observation bias is also likely because cases were hospitalized with hemorrhagic stroke and 40 percent were aphasic at the time of the interview and the controls were selected from random digit dialing. Among patients with aphasia, I believe I would not just have more difficulty verifying exposure but an even greater problem with the timing of the use. So the likelihood for noncomparability between cases and controls due to selection and observation bias is substantial and also impossible to assess.

With respect to confounding, uncontrolled confounding is clearly present because cases reported a significantly higher prevalence of numerous major and independent risk factors for hemorrhagic stroke. These include race, family history of hemorrhagic stroke, history of hypertension, a major risk factor for intracerebral hemorrhage, cigarette smoking, a major risk factor for subarachnoid hemorrhage, alcohol use, illicit drug use including cocaine, and lower socioeconomic status.

Further, the interpretability of even the state-of-the-art methods of statistical adjustment for confounding used by the investigators are seriously limited by the fact that the crude analysis for the sub-group of women using PPA as an appetite suppressant is based on six exposed cases versus one exposed control. This problem of a very small sample size for the sub-group analysis is compounded further by the fact that all these major and independent risk factors are statistically significantly higher in the cases than in the controls. So the sophisticated multi-variant model does give an estimate of a so-called adjusted relative risk but one must question what it means when the crude analysis is based on six exposed cases and one exposed control.

Further evidence of problem with this sub-group analysis derived from the fact that controls for all these positive confounders in an analysis of a robust sample size would reduce the size of the adjusted relative risk but, in fact, this adjusted estimate was higher than the crude. This, to me, is an unfortunate but logical consequence of the analysis of case control study having one exposed control resulting in a misleading apparently adjusted estimate due to a simple inability to control for confounding in any analyses of data of this sort.

But my only concerns today are not about the HSP or even its over-interpretation but relate to making a recommendation for a policy statement based on as yet insufficient totality of evidence. Any judgment of where do we go from here should be evidence-based given where we are today. I would caution that any attributable risk estimates assume causality. The absence of causality gives attributable risk estimates of zero. So in my view, attributable risk estimates or population-attributable risk estimates are appealing but unwarranted at present.

I certainly understand the intuitive appeal of making a recommendation for a policy

statement for a drug use as an appetite suppressant or for cough and cold suppression for which there appears to be other alternatives. It also has some intuitive appeal that a premature recommendation may appear preferable to waiting for a sufficient totality of evidence. Nonetheless, I remain hopeful that sound scientific reasoning will prevail over emotion.

There are examples where a sufficient totality of evidence turned out to be completely contrary to possible early signals. These include breast implants where FDA's early regulatory action led to permanent and irreversible psychological damages to those with the implants and legal damages to defendants that remain largely unaffected by a current totality of evidence that is far more reassuring than alarming.

In conclusion, I urge more research, not any recommendation for a policy statement that is premature and unwarranted based on the current totality of evidence. Mark Twain once said, you can always tell when academics are in dispute because the emotions are so high and the stakes are so low. This may well be true for all of us as speakers here today, but it's certainly not true for you, the Advisory Committee.

Thank you very much for your attention.

DOCTOR SOLLER: Thank you. In conclusion, I'd like to comment on FDA's OTC policy in this area and provide industry's recommended next steps.

FDA's OTC policy is that product availability and labeling should be scientifically documented, clinically significant and important to the safe and effective use of the product by the consumer. The value of this three part policy can not be under-estimated. The first hurdle scientific documentation focused us to look very closely at the quality and strength of the underlying data before reaching clinical or end use conclusions.

Based on the expert epidemiologic review, the first hurdle of FDA's policy is not met by the HSP Study. Because of inherent limitations, its small numbers of exposed cases and controls, inherent bias, inadequate control for confounding, concerns about chosen statistical methods, the HSP Study does not provide the quality and the extent of scientific documentation necessary to support a change in OTC status of PPA.

However, prior to the HSP Study, industry was committed to further research on PPA and this commitment remains unchanged. While limited value in

terms of its questionable results, the HSP nevertheless shows us that the exposure to PPA among patients with hemorrhagic stroke is small, rare, and it provides insights on possible optimum design for future studies.

Hence, we recommend the next three steps to be. Further epidemiologic research. This might be undertaken either in conjunction with PHS or there may be other models to do this and certainly with greater peer input on the design, conduct issues, and analyses, all of which we've been talking about this morning. Second, we think it would be prudent for FDA to finalize the labeling requirements that it has proposed for PPA that include recommendations relating to maximum dosage use, contraindications with specific conditions that are listed, various end use precautions and drug/drug interaction information.

And third, we think it would also be prudent to step up surveillance through voluntary submission of serious AERs from companies to FDA and the companies would be interested in working with FDA to identify a procedure to do that.

I thank you for your attention, and I would now like to open this up for Q&A to the panel and the committee.

CHAIRMAN BRASS: Thank you very much. Perhaps I'll begin with a couple of clarifications. Would you agree that the HSP can not be used to exonerate PPA as associated with stroke?

DOCTOR SOLLER: Well, I think if we look at the questions to the panel with getting ahead, 3(c), we think that the association is uncertain. We don't think, 1) that it has been shown and we wouldn't say that it would be C2 in that particular question where you would walk away and say this has demonstrated a negative.

CHAIRMAN BRASS: If I could ask for clarification from Doctor Gorelick who used the phrase "extremely low to estimate the absolute risk." Could he clarify what "extremely low" means?

DOCTOR GORELICK: I would ask Doctor Hennekens to address this issue. He's made a couple of comments about this in our group. Charlie.

DOCTOR HENNEKENS: We're a little out of synch because I thought I said that absolute estimates are premature and unwarranted. However, I think working with Doctor Hirsch we looked at the HSP data and some outside data and came to some conclusion of a population attributable risk percent estimates of about -- it was between seven and nine percent or

something like that, I think it was. But I think these are very treacherous on the base of the available data.

CHAIRMAN BRASS: So we should ignore the extremely low conclusion?

DOCTOR HENNEKENS: No, I'm not saying you should ignore the extremely low conclusion. I'm saying that if you have an uninterpretable study with a really difficult study to interpret with regard to making assessment of whether there's a valid statistical association, to go further and say that on the basis of even the extremely elevated risks that are seen in some of these sub-groups that using those to assess the impact on the population would be premature and unwarranted.

CHAIRMAN BRASS: In terms of the confounding variables, I just want to clarify. Was there a hinting that there may be an interaction between PPA and other risk factors or that no conclusion can be drawn?

DOCTOR HENNEKENS: Well, I'll take a first stab at this and ask Doctor Weiss perhaps to comment. I think the issue is -- and I think one of the major contributions of this study will enhance our quantitative estimates of the risk factors for

hemorrhagic stroke, both intracerebral and subarachnoid here, and they are so significantly different. Seven of the major risk factors for hemorrhagic stroke are significantly higher in the cases than in the control, so it's difficult to assess that with noncomparability of this sort that one can begin to achieve control for the differences between the cases and controls when you have only one control to deal with in the analysis.

Noel, do you want to make a statement about that?

DOCTOR WEISS: Clearly, to address the question of interaction, the investigators are in a better position than the reviewers, but I think it's safe to say that the numbers are so small, it's hard enough to even find the main effects, much less whether there's a particularly stronger effect, depending on the presence or absence of other risk factors.

CHAIRMAN BRASS: Doctor Katz.

DOCTOR KATZ: I'll address this question to Doctor Soller or really anybody who wants to answer it. Is there any evidence that the magnitude of weight also that has been documented in adequately controlled trials has any consequences for the public

health concerns that we've heard about related to obesity?

DOCTOR SOLLER: We're not aware of any long term studies that have been done on weight control agents, OTC weight control agents that would look long term out over a period of 10 - 20 years is what you're suggesting? No. Not aware of that.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: I want to ask a couple of questions. One is in terms of the statistical -- or make a statement -- in terms of the statistical analyses. You don't necessarily keep going back to square one for your allocation of alpha. I mean I understood from the way this was presented is that there was a hypotheses being driven to set this study up and it was first focused on women, appetite suppressant, first use. There's these procedures called closed procedures. There's the sequential procedures where you do in fact run through a sequence of hypotheses tests at the five percent level and you keep hitting a five percent level until you stop, and that is until you don't get the five percent level to be significant.

The way this was set up, I'm not completely convinced that one couldn't have said go

through the sequence of hypotheses that are set up at the five percent level for women appetite suppressant, for first use, five percent level, and then to full males plus females and I don't necessarily want to raise a debate here, but I think that the discussion of taking the alpha and dividing it by the number of potential hypotheses is not really where one has to focus on the appropriate hypotheses allocation of alpha. I think that there are many, many other ways of addressing it which would have said that what was done was in fact correct.

I have another question after that.

DOCTOR SOLLER: I think Doctor Strom was addressing the point that you were addressing, and I don't know whether he has additional comment that he might want to make in that regard.

DOCTOR STROM: I think the key thing to realize here is this was not a sequential type of analysis of the kind you're describing. These were three co-equal aims that were related to each other, and that was the way it was originally planned from the beginning. So if in fact one of the aims was positive and the others were not positive, it was still interpreted as a positive study, and that's in fact what was done here. Of the three aims which are

really five aims, some are positive and some were not positive.

DOCTOR D'AGOSTINO: The point I'm making is that I gave as an example you could have done it sequentially, you could have approached it differently, and you're dealing with safety, not efficacy here, and you might want to say that I don't really necessarily want to have alpha divided by number of tests when I'm dealing with safety. There are real issues, I think, in the alpha allocation that are not being really brought out correctly.

DOCTOR SOLLER: Yes, I certainly agree with you that that could have been done. That's not what was done, however.

DOCTOR D'AGOSTINO: They said they were going to use alpha .05. Let me go to another question. There have been some comments about using hemorrhagic stroke and then the sub-types. Are the experts telling us that because the end point was hemorrhagic or the cases were defined as hemorrhagic stroke without the differentiation of sub-type and then later on the same sub-type becomes so fragmented that that was a major mistake, that you can't use hemorrhagic stroke as a case definition?

DOCTOR SOLLER: Brian.

DOCTOR D'AGOSTINO: I mean it took two years to generate the protocol. Nobody thought of hemorrhagic stroke --

DOCTOR SOLLER: I would like him to address this, Doctor D'Agostino, if I could, since he brought it up in his comments.

DOCTOR STROM: Again, I'm not a consultant to CPHA. I should also be clear I am not a neurologist. I'm a general internist as well as epidemiologist. There are a lot of people here, I think, who are better qualified to answer than I. But my understanding from my neurology colleagues is these are different diseases and should be treated differently. They may be cousins. They may be related. They may be separate, but when you combine two different diseases into a separate case group, it's problematic. Why that was originally decided and the fact that there were five years and they could change --

DOCTOR D'AGOSTINO: The statement has tremendous ramification on a lot of cardiology trials that are going on now.

DOCTOR STROM: True, but I think the important thing to realize is these diseases may or may not have different risk factors. PPA may be a

risk factor for one and it may be a risk factor for the other, it may be a risk factor for both. If they are different diseases, if it is a risk factor for both, if they really are different diseases, then that is further evidence that it's due to bias rather than biology because you would expect the risk factors for the two things to be potentially different.

DOCTOR GORELICK: I think what we found in the case review, as you witnessed, is that in the appetite suppressant group there were five subarachnoids and one AVM and we were dealing with the traditional intracerebral hemorrhage case that we normally would, and so there is some suspicion here that the two things may be different.

DOCTOR D'AGOSTINO: Thank you.

CHAIRMAN BRASS: Ms. Cohen.

MS. COHEN: As a consumer member with a cold, a cough and overweight, I feel very comfortable on these subjects, and I have some questions to ask, and please, Doctor Brass, don't send me to the gift shop or the National Library of Medicine.

If a consumer came to me and asked me why PPA is necessary for appetite depressant or for cough, what kind of answer can I give them? My next question is why and how does PPA affect behavior modification?

Does it affect the brain cells? Why is it necessary? And lastly, as the wife of a scientist who was at NIH for 41 years, I really need to understand so I can complain to consumers where there's such a strong defense by the scientists of the use of PPA since it's not in the category of an anti-biotic. I really need to understand these things so I can go to a consumer and say, this is what I learned at this meeting and this is what I understand.

DOCTOR SOLLER: Let me answer the second question first and then return to the first one. In terms of behavior modification, it's thought that PPA as an appetite suppressant takes the edge off the appetite. It by itself without additional steps that are taken in terms of diet as well as in terms of exercise is very difficult to pull out a statistical significant clinically meaningful effect in the clinic unless you add those in, and the package insert does talk about encompassing this into an overall program. So it makes it easier for a person to engage in that kind of weight loss. And as a nasal decongestant, it causes constriction. It's not behavioral modification because it's direct effect in the nares and clears the nasal congestion.

Now, in terms of necessary, my comment

that I made earlier in terms of the policy and the fact that we shouldn't under-estimate it speaks directly to that. There's a susceptibility to move into the second and third part of that policy, and the policy is that the availability of the product, the labeling should be scientifically documented, clinically significant and important to the safe and effective use of the product to the consumer, and you're jumping to the third portion of that. In fact, the importance of this policy in a deliberation like this is to come to an assessment as to whether the study rises to the level of scientific documentation that would lead you into the second and third phase.

So in terms of our focus today and the way we look at PPA and the way we consider where we have been on this particular project as we look back over the last number of years is that from the ambiguities and the concerns that have been raised with the Yale Study, in reality, we're back where we were prior to starting the study, and that's why the industry remains committed to additional research and the trying to come to grips to get the appropriate documentation.

MS. COHEN: Doctor Brass, may I? Would you permit me? I still don't understand. Indirectly

I do understand, but I don't understand how I can answer a consumer saying that PPA is necessary. I don't understand how it's classified, what its efficaciousness is, if you'll pardon the big word, but I don't understand that. And the other thing, in your studies, did you do a study with behavior modification exercise and a low calorie intake versus with the PPA and how long? And I think someone asked here, how long did you follow it after? A year, two years? I still don't think I can go intelligently -- maybe I'm missing something -- and telling consumers what I need to know to answer in an intelligent fashion.

DOCTOR SOLLER: Well, in a broader issue, that type of questioning could be applied to many self-care products.

MS. COHEN: Well, hair color products I don't need. We're talking about PPA in blind --

DOCTOR SOLLER: No, but I'm talking about an overall perspective in terms of how you look at the self-care category and you could say, why do you need many of these? You could just tough it out. The point here is that once you look at the information that is supporting or not supporting PPA, you look at the level of scientific documentation and determine whether it rises to the level to suggest a change in

availability or alterations in labeling because the benefits that are available in terms of nasal decongestion and appetite suppression are real, and we heard comments earlier today from Doctor Schteingart that related to the demonstration that PPA can reduce weight in both the clinical setting.

CHAIRMAN BRASS: I think we'll hold off on that further until this afternoon.

Doctor Gilman.

DOCTOR GILMAN: Sid Gilman. I'd like to go to the issue of whether this group was looking at an improper end point by looking at hemorrhagic stroke, so-called. What they were looking at were patients who had extravasation of blood into the spinal fluid or around the brain or into brain tissue. These result, in the case of subarachnoid hemorrhage, from what is called a berry aneurism, a small outpouching of a vessel that is thin and that ruptures. There are risk factors for it, including hypertension and high blood pressure.

They're also looking at stroke in the brain. Again, hypertension is a risk factor for it. Those hemorrhages occur from actually little small outpouchings at the branch points of vessels often, but they represent extravasation of blood in brain.

Arteriovenous malformations are hereditary disturbances probably in which if a patient has, quote, "stroke," hemorrhagic stroke, there's extravasation of blood in the brain around these malformations. So even though these are somewhat different neuropathological entities we're dealing with, they're all characterized by hemorrhage in the brain and it strikes me that these are appropriately grouped together if there's a question about a risk factor.

So I guess I'm a little-- perhaps Doctor Gorelick would clarify this. I don't see that there is an improper rationale in grouping these cases together personally.

DOCTOR GORELICK: I think the answer is we don't know and the reason why I'm saying that is because you see that there was a plethora of subarachnoids and AVM in the appetite suppressant and it was not intracerebral hemorrhage. The reason why I say we don't know is because you see there's cross-over of risk factors between the two groups. So I don't think we know the answer for sure about what this particular agent, if it does anything at all to heighten risk, is doing in terms of these different pathophysiologic sub-types. I don't think we know

that yet. So I think it's probably still debatable.

DOCTOR GILMAN: But if we don't know it, then is there a reason not to group them together?

DOCTOR GORELICK: Well, the downside would be if it affected one type and not the other because of confounding chance or bias and then you ended up with the wrong results in terms of making a recommendation.

DOCTOR GILMAN: It seems like that would bias you against finding an association.

DOCTOR GORELICK: Exactly.

DOCTOR GILMAN: Can I just go on for a moment? So for example, if we were looking at the risk of an anti-coagulant agent, for example, if we were looking at Cumadin, a drug that people take to, quote, "thin the blood" so that people who have stroke or heart disease because of poor flow through the brain and through the heart, the blood is less inclined to clot. If we're looking at people on Cumadin and we wanted to see how many of these people had hemorrhagic stroke, we would include subarachnoid hemorrhage and cerebral hemorrhage and arteriovenous malformations. So the grouping would be fine. We apparently do not know the biological basis of whatever PPA does, but still I think there's a clear

rationale for grouping these cases together myself.

DOCTOR HENNEKENS: If I may make a comment. I would agree completely with Doctor Gilliam based on the current totality of evidence, and I think one of the real contributions of this study will be to look at the similarities and differences in the risk factor data they have collected for intracerebral and subarachnoid hemorrhage because I think we want to focus back on where we are today. We're starting off with a study that has lumped the two, looking at the small numbers and trying to make heads or tails out of them.

But I think a real important contribution would be to look at the qualitative and quantitative differences in a study of this size. It's an important study with regard to that point, and I think that, in the absence of those data, I personally think it's certainly reasonable to have both in there.

CHAIRMAN BRASS: I think we need to go on. Doctor Kittner.

DOCTOR KITTNER: Since the topic of the end point has come up, I'd just like to make a comment. One of the points we'll get to later on in the meeting is that there were a number of a prior reasons why, based on the case report literature, why

the study was commissioned. I'm just going to mention one of them, and that is that the case report literature was very heavily weighted towards hemorrhagic stroke, and that kind of a priori evidence, this is in the face of the fact that ischemic stroke is more common than hemorrhagic stroke. So there was a specificity of response which led to the original study.

I think that as we're reviewing -- I hope we'll come back to this -- as we're reviewing the data, we can not view this study in isolation independent of the preliminary evidence upon which the study was based. The preliminary evidence suggested diet pill use in women. I'll stop there.

CHAIRMAN BRASS: Yes, I'd ask you to because that's going to be intensely discussed this afternoon.

Doctor Daling.

DOCTOR DALING: This is for Doctor Gorelick. In your table where you review the seven cases, six cases and one control, would you comment on the fact that only one of the six cases was what we consider over-weight or even in the upper 25 percentile of body weight and two were actually quite thin that would have fallen in the first 15

percentile. So why were they taking these drugs if they were very thin?

DOCTOR GORELICK: Okay. I've reviewed the case report forms and I didn't get a -- that type of information was not available to me.

CHAIRMAN BRASS: Isn't it BMI?

DOCTOR GORELICK: No, no. The reason why somebody who has a low BMI or relatively BMI, you've got two cases here, 19 and 19, why they would be on the agent, so I don't know. This study is a snapshot in time, if you will, and we don't know.

DOCTOR DALING: But doesn't that affect your interpretation of the results?

DOCTOR GORELICK: Oh, yes. I mean it certainly could.

DOCTOR DALING: Whereas the control BMI was 38 so that was clearly someone who was quite obese. That makes you wonder why they were taking these drugs.

DOCTOR GORELICK: The tendency, I think, in the literature -- and this has not been substantially proven -- is that people who are on the lean side might be at higher risk for hemorrhage.

CHAIRMAN BRASS: Doctor Elashoff.

DOCTOR ELASHOFF: Yes. In terms of slide

17 which showed how much caffeine use there was, as I recall from reading the stuff prior to initiation of this study, there was a decision to take caffeine out of the appetite suppressants because of its potential to do harm, but it looks like it may not have done any good to take it out if people are drinking that much caffeine during the day.

DOCTOR SOLLER: Caffeine was taken out of the products in 1983, in and around that time. There was an abuse issue that was related to things called "black beauties," street-like drugs, and that was all embroiled in that particular issue. It was taken out and now is marketed solely as PPA and I would ask you, Doctor Blackburn or Doctor Hoffman, whether they have any additional comments that they might want to make in regards to caffeine and this issue.

DOCTOR HOFFMAN: Brian Hoffman. It's hard for me to say very much. I think caffeine to someone who's never been exposed to caffeine or hasn't been exposed to it recently can have effects on blood pressure, probably in part by stimulating release of catacholamines from the adrenal medulla and possibly the sympathetic nervous system. John Oates and his colleagues at Vanderbilt a number of years ago did some elegant studies on people who take caffeine

daily, and my recollection of their work is that after seven to 14 days these effects of caffeine disappear, that we become tolerant to those effects of caffeine.

So if these people suddenly went from no coffee to 10 cups of coffee on the day of their event, that might have been significant, but if this was a long-term pattern, I'm not sure of any pharmacological data to indicate that would be of pharmacological significance.

CHAIRMAN BRASS: I think because of the time we're going to move on to the FDA presentation with a reminder that there'll be ample opportunity for further discussion this afternoon.

DOCTOR LA GRENADE: Good morning. I am Lois La Grenade from the Office of Postmarketing Drug Risk Assessment and I represent the team of epidemiologists and biostatisticians who reviewed not only the Yale Study concerning phenylpropanolamine and the risk of hemorrhagic stroke but the entire issue of the safety of this drug and the risk of hemorrhagic stroke.

First of all, I'll take you through the format that my presentation will take this morning. I'll give you a historical background of the safety events that led up to this Advisory Committee today.

I'll go through two case reviews of reports received by our spontaneous reporting system. I will not spend a lot of time reviewing the Yale hemorrhagic stroke study. Doctor Kernan has already done an excellent job of this. I will, however, highlight certain important aspects of the study. I will address some of CHPA's concerns. I will summarize the results of the Yale Study and attempt to assess the public health impact of these results. And finally, we'll give our overall conclusions.

Prior to 1984, the agency received several case reports of PPA associated with hemorrhagic stroke. In 1984, as a result of these reports, Doctor Bob O'Neill, who was with the agency then and is still with us today and I'm happy to say is present at this meeting and sitting at the table, O'Neill and Van de Carr did a case control study because of these reports to try and examine this issue. They used Medicaid data from Michigan and Minnesota.

In 1991, our office reviewed the postmarketing experience of the spontaneous reports received on hemorrhagic stroke associated with PPA use. Between 1991 and now, we continue to receive reports of hemorrhagic stroke associated with PPA use. I'll spend a little more time discussing O'Neill and

Van de Carr's 1984 study.

That study showed an association between PPA use and hemorrhagic stroke compared with other adrenergic decongestants. This study, however, had important limitations which I must point out are inherent in all studies which are retrospective and involve automated claims databases including some of the studies referred to earlier by CHPA. For example, the Jick Study.

The limitations were that in a retrospective study it is very difficult to validate the outcomes, to validate the diagnoses, to validate the exposures. They were limited to using prescription only PPA use since OTC use was not captured in the databases that they used. Because of the problems of ascertaining the exposure, they had to use a 60 day exposure window. These problems lead to important and substantial misclassification which tends to bias the results towards the finding of no association. It is, therefore, all the more important that they did find an association between PPA use and hemorrhagic stroke, although this association was not found to be statistically significant.

To show you the strength of the signal that we received in our spontaneous reports. The 1991

review showed that of all the adverse events reported for PPA use, 14 percent were concerning hemorrhagic stroke with the use of PPA compared to less than one percent of hemorrhagic strokes found as an adverse drug event for all other drugs in our database.

The 1991 series went back as far as 1969 which is the date on which our database begins and it reviewed all adverse events reported with PPA use up until the end of January 1991. We found that there were 29 domestic cases of stroke associated with PPA use, 22 of which were hemorrhagic stroke. And I must point out, since there has been considerable discussion on whether we should have used intracerebral or subarachnoid hemorrhage that, in fact, the cases represented both intracerebral hemorrhage and subarachnoid hemorrhage. Seventy three percent of the cases at that time were associated with appetite suppressant use and 27 percent with cough and cold preparation use. They were predominantly of young age with a median of 27 for appetite suppressants and 35 for cough and cold and predominantly females. Fifty five percent of the hemorrhagic strokes occurred with first use of PPA.

This led to the generation of the hypothesis that PPA-containing products, both appetite

suppressants and cough and cold preparations, particularly first use, are associated with an increased risk of hemorrhagic stroke in young women.

As part of our preparation for this Advisory Committee today, we updated the review of cases in our adverse event reporting system. We started on February 1, 1991, which was the date on which the last review ended, and we went up to mid-July of this year. We again found 22 cases of hemorrhagic stroke. There were four well-documented deaths, all of which were in females. Eighty six percent this time were with cough and cold preparations and 14 percent with appetite suppressants. Females still predominated and the median age remained 35.

The median time to onset after the last dose was four hours. The median duration of use was 24 hours. Eighty two percent of the strokes occurred within three days of PPA use. All cases occurred with preparations containing 75 milligrams of the sustained release of phenylpropanolamine. We note that in this series there is a shift in the demographics with far more cough and cold users than the previous review, the 1991 review, but the median age remains the same.

Just to show you a sort of typical case

report. We would have a young person, otherwise healthy, who develops a cough or cold. In some cases, a runny nose is what was listed on the form. That person takes a PPA-containing product and within a few days, with absolutely no warning, develops a catastrophic event, a hemorrhagic stroke, is hospitalized and either dies or is permanently disabled.

Twenty two cases in the first 20 years, 22 cases in the second nine year period, a total of 44, might look like an unsubstantial number but I must hasten to point out that there is substantial under-reporting, even for prescription drugs in spontaneous reporting databases such as ours. Perhaps as low as one percent. Further, there is no legal requirement for manufacturers to report non-monograph drug adverse events and many PPA-containing products are in fact non-monograph drugs.

In addition, there is less attribution of these cases because there is no physician, no learned intermediary, who is aware of the PPA exposure and, in general, under-reporting for over-the-counter products is far less than for prescription products. All these features contribute to the under-reporting and it must be borne in mind that the figure of 44 dis literally

the very tip of the iceberg.

Now we come to the Yale Hemorrhagic Stroke Project which was a case-control study designed to study phenylpropanolamine use and the risk of hemorrhagic stroke. It was sponsored by CHPA and designed and conducted by the HSP Yale group. Our record show, as Doctor Sherman outlined to you this morning, that the protocol was extensively reviewed on many occasions by Yale, CHPA and the agency. It was designed to test the specific hypotheses generated by our data, and this is very important for us to remember as we consider this. It was not data dredging. It was a purpose-designed study.

The objectives of the study, as you have heard before, were that among men and women age 18 to 49 to estimate the association between PPA use and hemorrhagic stroke generally and by type of PPA use, whether cough/cold or appetite suppressant.

The third hypothesis was among women age 18 to 49 years to estimate, A) the association between first use of PPA and hemorrhagic stroke and, B) PPA use and appetite suppressants and hemorrhagic stroke. I must again point out from the agency's point of view, this hypothesis #3, parts A and B, was the single most important from our viewpoint as it was

generated by our data.

The study design was a case control method which, as Doctor Kernan pointed out, is best suited to rare events such as hemorrhagic stroke in young people. It's best suited because it is most efficient in terms of the number of cases required. It can capture all the cases in a specified time period and in a specified population. It's very efficient in terms of timeliness of the results. The results are available much more quickly than with a cohort study and it is far less expensive generally.

The strengths of this design were that it was targeted to test specific hypotheses. It was a prospective study. That is to say cases were enrolled into the study as they occurred making it much easier to validate the diagnosis and to ascertain the exposure. Controls were identified and enrolled into the study as the cases occurred. All of this was prospective. In general, the study was carefully designed to minimize bias. It was conducted with great attention to detail and it was carefully analyzed. The internal consistency shown across the various strata that were analyzed attest to the carefulness of the analysis, and we must out that it is to date the largest hemorrhagic stroke study ever

to be completed.

The limitations were in the relatively small sample size and power. As you have heard this morning, it was powered to detect an odds ratio of five or greater. I must hasten to point out that this was not for scientific nor public health reasons but for practical considerations. As it was, the study took longer than six years to complete. rom the design stage to the actual handing in of the report was in fact almost eight years. Had it been powered to detect a lower odds ratio, say an odds ratio of two, it would have required a far larger sample size and might have taken 10 or 15 years to complete. We do not think that this was reasonable to wait so long for an answer.

Now to address some of CHPA's concerns. They were concerned about the relatively small sample size, that it would give low statistical power to the study, that it made the results subject to exposure misclassification, that the low sample size could introduce important biases and the results might not, therefore, be robust.

We counter that by saying that this was the largest study ever of hemorrhagic stroke. Low power normally reduces the probability of detecting a

difference if one really exists. In spite of the low power, this study was able to demonstrate a major difference. Bias is usually a product of poor study design and conduct. The Yale Study was well-designed with internal safeguards to protect quality assurance, and the internal consistency in the subset analyses underscores the robustness of the data.

CHPA was concerned about potential confounders: aphasia, smoking, hypertension, race, education. Each of these was adjusted for in the analysis. There are two ways of controlling for analysis, by matching or by adjustment during the analysis process. Generally speaking in epidemiologic studies, you match on three or four major confounding factors and you deal with the others in the analysis stage. It's not necessary to match for every single confounding factor. It would make a study impractical, impossible to complete. It's far too large and it's far too complex.

This slide will demonstrate two things. It shows the internal consistency of the data and the fact that aphasia and hypertension were not in fact significant confounding factors. In the first column, you see the odds ratios as they were presented for appetite suppressants and first use of cough/cold. In

the second column, you see the analysis performed on the subset of the subjects without hypertension. You see, in fact, that the odds ratios remain practically the same.

In the case of cough and cold, it increases a little bit. In the third column, you see the analysis conducted on subsets without aphasia, and I must point out that the majority of subjects did not have hypertension and were not aphasic. In the column of subjects without aphasia, the odds ratios again remain the same and, in fact, increases with cough and cold suggesting that subjects with aphasia were, in fact, under-reporting their PPA use rather than the converse.

They were concerned about misclassification, that it could skew the results and that the areas that they had most concern with were participant recall and product identification. We respond, as Doctor Kernan pointed out, that the subjects were blinded to the exposure of interest so they had no way of knowing what the investigators were after. The interviewers used a highly structured questionnaire and an exposure verification process which included the product identification booklet. Record bias was minimized by the short interval

between the event and the interview for both cases and controls, and this was conducted within 30 days.

There is no data to suggest that there was differential misclassification that would generate a spurious association and, in fact, misclassification typically biases the odds ratio towards the finding of no association.

On the issue of surrogate responders, CHPA has been concerned that exclusion of fatal and severely aphasic cases was inappropriate, that excluded cases could be different in their exposure to PPA and other risk factors, and that analysis based on survivals only may introduce survival bias.

We respond that this was modeled in the design stage of the study. Even modest use of surrogate responders would have introduced overwhelming misclassification error, and this was verified in the design stage by the modeling. And CHPA at the time agreed with this finding. The misclassification error introduced by surrogate responders would have been so large as to render the study impossible of detecting an association and, therefore, it would have made no point in doing the study at all.

As we pointed out when we showed the

earlier slide, aphasic subjects may in fact be under-reporting their PPA exposure. There is no data to suggest that PPA exposure is related to the severity of the stroke or to survival after a stroke, and perhaps the most important point of all is that several epidemiologic studies show that use of surrogate interviews is a major source of bias in epidemiology studies.

In addition, we conducted our own analyses on the raw data submitted by Yale University, and we confirmed the major findings. We were able to explore the dose response relationship and found that, in fact, there was dose ordering. That is to say that the risk of hemorrhagic stroke increased with higher doses of PPA. We were able to conduct sensitivity analyses to examine the sparse data bias due to small sample size, and we found that this was really not operative in the study. We have a slide available of this if anybody wants to see it afterwards. We will have our statistician speak to the issue, if necessary.

Now we come to the results. The Yale Study supported an increased risk of hemorrhagic stroke associated with PPA use. The findings were statistically significant among appetite suppressants

users and first-day users of PPA as a cough/cold remedy, and you will remember that this is what we were interested in from the agency point of view.

Now another job of epidemiologists is not just to assess the strength of the association and the relative risk but to assess the public health impact of such a risk, and that's called attributable risk, and that is defined as how much of a disease can be attributed to a certain exposure and, in turn, how much of the risk -- and risk is defined by the number of new cases per year, the incidence of disease -- how much of the risk can we hope to prevent if we were able to eliminate the exposure to the particular agent.

Now, before we do that, we thought we'd show you the extent of usage of PPA products in the United States. Take the year 1999, for example. Six billion dose units were sold. Seventy five percent of it was sold in OTC products. In a population of approximately 300 million, as the United States is, six billion doses sold annually translates into 20 dose units for every man, woman, and child in the population. That's extensive use by any standards. We know that this is doses sold, but there must be a correlation between doses sold and doses consumed.

Otherwise, they wouldn't keep selling it.

This slide shows the distribution of dose units sold annually by indication, and we see here that 98 percent, the lion's share of PPA use sold, is for cough and cold. It's in the preparation for cough and cold remedies, and only two percent for diet preparations. This is important, these figures, when we come to assess the public health impact. In order to assess the public health impact, we extrapolated from the study population to the general U.S. population.

In order to do that, we had to assume that the population was similar to the United States population generally, and we tested these assumptions by looking at the demographic data of the study population, comparing it to the general population of the United States, and we used Census Bureau data to help us do that. The minor differences were that whites were slightly over-represented in the study population and blacks and Hispanics slightly under-represented. Nevertheless, we thought that the differences were sufficiently small that we could use the population to generalize to the U.S. population.

The total number of hemorrhagic strokes in the study that occurred in the study period was 1,714.

Various people have pointed out this morning that only 41 percent were actually used as cases. Of the cases, eight cases had first use of PPA as a cough and cold remedy and six cases had PPA use as an appetite suppressant. We went again to the U.S. Census Bureau data to find the exact figure for the population in the 18 to 49 age group and, as of August this year, the estimate was 130 million people in this age group. We went to the published literature to find the background incidence of hemorrhagic stroke, and we got an estimate of eight per 100,000. We took our estimate from population-based incidence stroke studies. Had we used a higher incidence that was quoted this morning of 20 per 100,000, our estimate would have been even larger, but we used the more conservative estimate.

Combining our incidence estimate and the population estimate, we get 10,400 hemorrhagic strokes per year in the 18 to 49 age group in the U.S. If we'd used the larger figure, it would have been at least twice that number. And this shows our calculations. I must point out that always attributable risk calculations are imprecise. They give you a rough estimate, a ball park figure, and, by our calculations, we found that between 120 and 290

strokes could be attributable to PPA use for cough and cold as a first use and 90 to 220 for appetite suppressants. The figures vary depending on whether you correct for the number of cases that actually did occur, the number of cases of hemorrhagic stroke, or whether you just use the number of the cases that were used as cases in the study. This gives you a total number of cases possibly attributable to PPA use of 200 to 500 in the 18 to 49 age group.

We have data that shows that PPA use continues in the over 50 age population. We have every reason to believe that biological effects continue in the over 50 population. The incidence of strokes is increased in the over 50 population, and we believe that there must be some strokes also in the over 50 population. So if we look at the entire attributable risk for the entire population of the United States, it is going to be much greater than the 200 to 500 that we have estimated here, and this is annually.

Another function of epidemiologists when an association has been detected is to try to make a causality assessment. The criteria for causal associations include the following. Temporal relationship and, in all our cases reported to the

agency, PPA use has preceded the event. It has come before hemorrhagic stroke. So we have that. That's temporal relationship. Strength of the association is measured by the magnitude of the relative risk or, in this case, the odds ratio. And clearly, 16 for an odds ratio for appetite suppressant is a large magnitude.

3.1 for cough and cold is a lower magnitude but we think that this may result from the wide variety of doses that was experienced in the study. The doses of PPA exposure range from 6.5 to in excess of 150 milligrams, and we do believe that the risk of hemorrhagic stroke is related to the dose so that this odds ratio would represent people taking the low dose diluting the effect of people taking the higher dose.

In the Yale Study, dose response is another measure of causal association, another criterion. The Yale Study showed an increased risk of hemorrhagic stroke with doses of PPA above 75 milligrams per day. We conducted our own exploratory analyses which did show dose ordering. That is to say that there was an increased risk with doses of PPA greater than 75 milligrams per day. In our current case review, the 2000 case review, all 22 reports were

with 75 milligram preparations of PPA.

Now we come to biological plausibility. PPA is a sympathomimetic amine and common to all sympathomimetic amines is that they have a demonstrated pressor effect. That is to say they raise the blood pressure. They cause hypertension. There is clear cut tachyphylaxis. That is to say that the pressor effect is reduced with continued doses of the drug. The pressor effect is also greater for the sustained release preparations.

The studies alluded to earlier on this morning were studies that were done in small sample sizes, 12 and 25 patients, and the mean elevation in blood pressure was found to be four millimeters of mercury. In fact, this cartoon represents the distribution of blood pressure spikes in response to PPA challenge in a large population. The spike represents the mean, but there are many, many people who would have a much larger increase in their blood pressure in response to PPA challenge. That would not be reflected just in the mean. There are many, many outliers, and we suspect, we postulate, that perhaps people who develop hemorrhagic strokes with PPA are those who have a much higher increase in their blood pressure in response to PPA challenge.1

What we also don't know is whether people remain static in their response to PPA challenge, whether at one time they will have a larger increase and at another time a smaller increase. We do not have these data available to us. We can only go by what we know.

Consistency with other knowledge. Again, we believe this criterion is satisfied. We have had numerous case reports in the literature. Just to mention two. Kase in 1987. He reported 10 cases, two of which were his own.

The Lake Study has already been referred to this morning. Lake reported the largest series of adverse events associated with PPA use, and he reviewed all the cases that had been reported in the literature up to that time. In his series, he found 24 cases of intracranial hemorrhage, 15 of hypertensive encephalopathy or seizures, all with onset within 24 hours and most at the 75 milligram per day dose. Then we have O'Neill and Van de Carr's study which, with all its flaws, did show an association, and we have our own in-house case reviews.

The only criterion for causality that has not been met is replication of the study, and we have

pointed out before that it would take another 10 or 15 years to replicate the study. The question that we must ask ourselves is is it in the public health's interest to wait another 10 or 15 years so that this could be replicated or do we have so many other criteria fulfilled for causal association?

In summary then, we have a hypothesis of an increased risk of hemorrhagic stroke with early PPA use generated from our case reports. We have a well-designed prospective case control study that strongly supports our hypothesis, and the criteria for causality have largely been fulfilled. We estimate that, at a minimum, 200 to 500 strokes per year in young people are potentially preventable.

We conclude that the use of PPA as treatment for cough and cold symptoms and as an appetite suppressant confers an increased risk of hemorrhagic stroke in young people, that there is a substantial burden to this risk. In excess of 200 to 500 hemorrhagic strokes per year are attributable to PPA use, and there is evidence to suggest that the risk of hemorrhagic stroke may be higher with PPA doses at or above 75 milligrams per day.

Finally, I'd like to thank the members of the team who all contributed substantially to my

presentation this morning. Thank you.

CHAIRMAN BRASS: Thank you.

Doctor Ganley, did you want to make remarks now or did you want to -- Okay.

Yes, Doctor Daling.

DOCTOR DALING: I'd like to ask in your attributable risks calculations, why did you use only first day or first use for your cough and cold remedies whereas you used the three days for the appetite suppressant, and how did you get the data on first use?

DOCTOR LA GRENADE: This was provided in the study. We used, in fact, the odds ratios that were statistically significant.

DOCTOR DALING: Well, then it would be your odds ratio for first day use or three day use of 1.23 which is actually --

DOCTOR LA GRENADE: That was proposed use as a cough/cold remedy.

DOCTOR DALING: I guess I'm wondering why you use the -- why did you just use the significant ones because certainly, if you were looking at any three days use and it was not significant so it was actually consistent with a protective effect.

DOCTOR LA GRENADE: We used the data that

we were testing for in our hypothesis generated by the agency and which were also the ones that were found to be statistically significant in the study.

DOCTOR DALING: So the attributable risk for any three day use could be actually a protective effect.

DOCTOR LA GRENADE: No.

DOCTOR DALING: Well, the confidence interval goes below one.

DOCTOR LA GRENADE: The data do not support, as Doctor Kernan pointed out. We can't use that sort of thing. We have to use what was statistically significant and what were the hypotheses that were generated by our data.

CHAIRMAN BRASS: Doctor Cantilena.

DOCTOR CANTILENA: Yes. To follow up on the information in your slide 41 with response to the effect on blood pressure. Are you aware of any information with regard to gender differences in terms of the response from the drug?

DOCTOR LA GRENADE: I am not aware of gender response in response to this particular drug. I don't know whether anybody on my team has information to that effect. There is one possible contributory explanation in that women are generally

smaller than men and we have found in our agency spontaneous reports that more of the adverse events occur in women and it may be that the doses that are prescribed, that are recommended, are the same for men and women and women are a little smaller in body size. That's just one possible explanation.

CHAIRMAN BRASS: Doctor Lam.

DOCTOR LAM: In one of your public health impact slides on slide #34, the background incidence of hemorrhagic stroke was over 100,000. Was that due to drug alone or was there any other risk factor associated with it?

DOCTOR LA GRENADE: That is all risk factors.

DOCTOR LAM: So to estimate the 10,000 hemorrhagic stroke would be also either drug or PPA risk factor.

DOCTOR LA GRENADE: All causes of hemorrhagic stroke. Yes.

CHAIRMAN BRASS: Doctor Blewitt.

DOCTOR BLEWITT: Yes. In slide 17 and 20, you had indicated that it wasn't reasonable to carry the study out any longer, and I frankly wonder, since we're here today, there seems to be a lot of controversy about the results of the study, whether in

fact it wouldn't have been reasonable to carry this study over a long enough time so that you could get conclusive results.

DOCTOR LA GRENADE: It perhaps ought to have been designed to test a smaller odds ratio, but we have to live with the decisions that were made back in 1991-92.

DOCTOR BLEWITT: In slide 19, reduces probability of showing a difference -- major difference observed despite low power and, in spite of that low power, couldn't those differences be due to chance?

DOCTOR LA GRENADE: Not for the two statistically significant odds ratios. I mean the p-value was, in fact, the conventional .05. That's one thing. And while we're on the subject of p-values, I must point out that a p-value of .05 means that the results could have been obtained by chance alone five percent of the time, and that's the conventional statistical cut-off point when we're looking at efficacy. For safety, we don't need to be as certain. We could accept that we could be wrong 10 percent of the time and right 90 percent of the time when we're looking at safety issues or even lower. We could accept, for example, being wrong 20 percent of the

time on a safety issue.

DOCTOR BLEWITT: I've seen that. In the slide 11 on under-reporting of cases, I guess intuitively that goes against my view of the natural history of a serious side effect. You mention that there's substantial under-reporting for Rx drugs, possibly as low as one percent. Seems to me that a condition as serious, you know, if someone is concerned that there's a possible relationship with PPA and stroke and that there's a literature on this, usually the natural history is that this actually provokes a lot of activity, that people then begin to report these kinds of occurrences at greater frequency.

In other words, if you get a stomach upset from aspirin, you're not going to see much of that. But if there's a serious side effect such as a stroke involved, it would seem to me that reporting would be a much higher percentage. I just wondered about your comments on that.

DOCTOR LA GRENADE: Doctor Graham will answer those comments.

DOCTOR GRAHAM: I'm David Graham. I'm part of the study team.

With under-reporting, there are several

things to take into account. One, as surprising as it seems, serious and catastrophic events commonly are not reported. Even with resulin and liver failure, we probably only got 10 or 15 percent of the cases that occurred. And there everybody knew about the exposure. With PPA taken in an over-the-counter setting, it's like the only person who might know about the exposure is the patient themselves. No one else is out there necessarily thinking about it.

In response to the question does publicity about events stimulate reporting to come in, it's been show that you can get stimulation of reports very close to in time to a very major publicity event but that that stimulation wears off within a month and, with PPA, I haven't seen anything in the newspapers over the last seven or eight years that have been beating the drug that PPA causes stroke, so I don't think that one can point to a publicity effect as being responsible for reporting.

CHAIRMAN BRASS: Doctor Johnson.

DOCTOR JOHNSON: I have a question. It's really just a clarification. Back on slide six. Doctor Lam was just asking about this. So the 14 percent versus the .8 percent, can you explain that again? That means that 14 percent of all strokes that

were reported?

DOCTOR LA GRENADE: No, of all adverse events that were reported for PPA, 14 percent of them were strokes.

DOCTOR JOHNSON: Okay. Thanks.

CHAIRMAN BRASS: Doctor Elashoff.

DOCTOR ELASHOFF: Apropos of the under-reporting issue, of the cases that took PPA in the Yale Study, were any of them reported as adverse events to the FDA?

DOCTOR LA GRENADE: We don't know the answer to that question. We don't have the data on the cases that were reported. We don't have the identifying information.

DOCTOR GRAHAM: We do know that we don't have any cases reported from the state of Connecticut where most of the cases in the study occurred.

CHAIRMAN BRASS: Doctor Kittner.

DOCTOR KITTNER: It's with some chagrin that, as a neurologist who specializes in young strokes and have a very wide referral practice for stroke in young adults over the past 10 years, I've never personally reported any PPA exposure to the FDA. That is my responsibility.

CHAIRMAN BRASS: Thank you for that

confession.

Lois, could you say something a little more expanding on slide 21. Part of the critique of the cases in controls and the imbalance in the risk factors is described in your slide 20 and you discussed in particular the lack of difference with regard to hypertension or aphasia in terms of what the observed risk factors were. That goes a long way towards saying that there is an imbalance, it's not responsible for what we're likely to be seeing. What occurs for the other potential confounders that people are concerned about and where might there be some residual concern still left?

DOCTOR LA GRENADE: Perhaps one member of the team might want to answer that question. Doctor Yi Tsong.

DOCTOR YI TSONG: I didn't do the analysis besides a few of the most important risk factors, and I think probably Yale has that in their report. I wonder if any person from Yale can address this issue.

CHAIRMAN BRASS: I think they presented the hypertension one earlier today where the stratification again showed that the odds ratio was sustained in the stratification analysis for hypertension and for smoking, as well.

I just want to observe with respect to the spontaneous reports that there continues to be approximately two per year which, if you took the one percent reporting rate, would match pretty well the 200 cases that was projected from the HSP analysis.

Any other comments or questions?

DOCTOR BLEWITT: Just a comment. I just wonder, Mr. Chairman, whether it's appropriate at all at some point to find out whether CHPA has any question or their consultants as to whether their concerns have been addressed adequately here and whether they would have an opportunity to ask questions themselves or at least comment on the analysis.

CHAIRMAN BRASS: Yes. I don't think it would be appropriate for CHPA to question. I'm not Jim Lehrer and so I don't want to moderate that debate. So I think in the course of the afternoon discussion, I think there'll be an opportunity for CHPA to comment on various points that might arise.

Doctor Ganley.

One question while Doctor Ganley gets set up.

DOCTOR NEILL: This is for FDA staff. I thought I heard a comment that PPA is also used in

non-monograph OTC medications, and that's been my experience when I walk down the street, and I'm curious about the extent to which PPA exists in those medicines, what kinds of places I might find those in, and whether or not any of those kinds of uses are represented in the data in NHSP or in FDA adverse event reporting system. I'm talking about medicines that are not specifically marketed for cough/cold or for appetite suppressant but that sit on the shelf and, because there's no specific claim made except in very vague terms, aren't covered by monograph.

DOCTOR KATZ: Well actually, on the shelf there are both monograph and non-monograph products that do contain PPA. There are cough/cold products that are not monograph products that are there. So I don't know if that addresses your question because not all of the cough/cold products that are out on the shelf now are monograph. Some are NDA.

There are also PPA in some Rx products, so that the database that we get into the FDA of reports would include NDA products as well as monograph products, if any are reported under the monograph. So the monograph though is totally voluntary reporting. The NDA is required reporting if there are serious adverse events.

DOCTOR NEILL: I guess what I'm imagining is a health food store where products that contain PPA might be on the same shelf with products used to boost energy, stimulate awareness, keep college students awake at night. I don't have a good sense for the extent to which those products exist or not compared to other similar uses for caffeine-containing, pseudoephedrine-containing other similar class type medicines are there.

DOCTOR DELAP: I think there are clearly other products out there available to consumers that include PPA in them. I'm thinking of some of the supplements that contain ephedra alkaloid type constituents of which PPA can be grouped as one. Obviously, that's a whole different situation as far as how much we know about those products and how the adverse experiences come in to us.

CHAIRMAN BRASS: Do you want to just comment on that, Doctor Soller.

DOCTOR SOLLER: Bill Soller, CHPA. I'd just like to comment. The products that you may be thinking about are dietary supplements that contain ephedra and PPA can be a component of ephedra but it represents about 10 percent or so by weight of what the ephedra is in that particular product and, in most

products, even less than that. That was discussed at a meeting in August.

But in terms of the presence of PPA in a product that would represent itself for weight control and place on it under the active ingredients PPA, we're not aware of any and I'm not saying that that doesn't occur.

DOCTOR NEILL: No. I'm talking about products that might contain PPA that specifically do not make a claim for cough/cold or for appetite suppressant but exist on a shelf by virtue of the FDA's exclusion from considering those medicines.

DOCTOR SOLLER: It can't be. Wouldn't be a dietary supplement. It would be a drug, and it couldn't be labeled that way or it would be misbranded and action could be taken on that particular product. So there's a regularity --

DOCTOR NEILL: My understanding is that misbranding occurs when there's a specific claim of efficacy made, and I understand that those aren't products that we're considering today. I'm just wondering whether or not PPA exists in other preparations for which no specific claims are made and so aren't being considered here but still exist on the shelf.

DOCTOR SOLLER: Well, I can tell you that we're unaware of that, and we don't believe that that's happening. I won't say that it doesn't happen because somebody hasn't decided to do it in the extreme but, at least as we understand the market place, I don't believe that that is any kind of reflection of what's going on.

CHAIRMAN BRASS: Thank you.

Doctor Ganley.

DOCTOR GANLEY: I just wanted to first start off by thanking Sandy Titus, who's our Exec. Sec., who has done an enormous amount of work in preparing for this meeting and also for tomorrow's meeting.

We've developed a group of questions and we've tried to address them in the order that we think is a logical sequence. The first group of questions address the analysis and interpretation of data from the Hemorrhagic Stroke Project. We're particularly interested in looking at this data in totality but also as a function of the condition of use. As Bob Sherman had noted earlier, PPA is involved in two rulemakings here, one for decongestants and one for appetite suppressants.

The other is as a function of dose. As

Bob Sherman has also noted, there is some differences in the recommendations for dosing for each of those rulemakings, and obviously as a function of first dose which would apply to both rulemakings.

I think the second portion of questions takes into account the totality of data and then based on the information, that is the adverse events reports, the pharmacodynamic effect and the HSP Study, is there an association between PPA use and the risk for hemorrhagic stroke?

When we talk about generally recognized as safe, I think reality tells us that drug products do present some risk for consumers and that no product is absolutely safe. To be generally recognized as safe, an ingredient must have a well-characterized, acceptable safety profile under the conditions of use. In the OTC monograph world, when we talk about conditions of use, we're referring to the clinical indication, dosing and labeling. It's totality of the package. I think it's also important to note whether it's the prescription product or an OTC product. The burden of proof and the burden of submitting data falls on the industry to show us that it's safe. It is not the burden of the agency to prove that it's unsafe.

I think other considerations to take into account, that adverse events resulting in serious morbidity or mortality are especially concerning, especially for products in the OTC world. We've already heard from numerous individuals already that the OTC adverse event reporting is limited. Companies that market drugs under OTC monographs are not required by regulation to provide safety reports to us and, at a minimum, I think the consumers need to be adequately informed. If there are adverse events associated with the use of a product, they ought to know about them.

On the other hand, generally we make risk benefits assessments. There's been some discussion of the benefit of these products and I think we would all acknowledge that PPA treats relatively benign conditions and, although they're very effective, for example, in decongestants, we also have to keep in mind that there is a great public health benefit by providing easy access to medications for self-care.

Finally, I just want to point out. There had been some concern about the recommendations in the OPDRA review that that was the position of the agency, and I think that is the position of the reviewers. It's important to us to listen to the Advisory

Committee recommendations that will help us to bring closure to the PPA rulemaking. This is the best data that we're going to see pertaining to this issue, and I think we have to realize at that point in time that we do have to make some decisions.

The next step for the agency is to proceed with rulemaking and designate PPA as either Category I, Category II or Category III. Those conclude my comments.

CHAIRMAN BRASS: Are there any questions or clarifications for Doctor Ganley from the committee? If not, we'll break for lunch and reconvene promptly at 1:30. Thank you.

(Whereupon, off the record at 12:34 p.m. to reconvene at 1:30 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:34 p.m.)

CHAIRMAN BRASS: I'd like to begin the afternoon session with the discussion of the issues raised by the presenters this morning. The discussion will be focused obviously by members of the committee, but I would like to encourage the committee members during these deliberations to raise questions as appropriate to any of the presenters from this morning which will aid the committee in addressing some of these issues.

The discussion this afternoon will be focused around a series of questions, as always, but I want to emphasize prospectively that the questions are divided into two thematic areas. One is a group of initial questions which are specific to the HSP and try to reach some understanding of what the HSP is and how it can be used. The second set of questions recognize that in terms of the overall assessment of safety for phenylpropanolamine, the HSP can not be examined in isolation but is part of an accumulated experience and database and attempts to integrate the HSP into the other information to try to reach some overall conclusions and recommendations.

So I will read the first question and may

or may not modify it as I read it along, as always. Do the results from the HSP Study suggest that PPA is safe from risk of hemorrhagic stroke in subjects 18 to 49 years of age or do the results suggest that there is an association between PPA and hemorrhagic stroke in subjects 18 to 49 years of age -- and I'm going to add another clause -- or is it inconclusive with respect to that association?

And the sub-questions have to do with whether the conclusion can be drawn across the entire study population, that is, gender and product non-specifically, with respect to the first dose of PPA in subjects using PPA as an appetite suppressant and subjects using PPA as a decongestant, is there a dose relationship?

In addressing these questions, please discuss any strengths or limitations in the design and/or conduct of the HSP that may affect the interpretation of data. Is there consistency or lack of consistency in these results? What member of the committee would like to begin the discussion? Doctor Gilman.

DOCTOR GILMAN: Well, first, I think it might be helpful to address these questions by looking at men because, as I read the data, heard the data

presented, I heard nothing to implicate PPA in hemorrhagic stroke in men, probably because there was no exposure to PPA as appetite suppressant and very few people took PPA who were men for cough/cold remedies. So we might be able to first clear the decks, in a way, by just saying well, there's no evidence or evidence is inconclusive that it has any effect in men. Then we could go on to women. That would make the discussion maybe simpler.

CHAIRMAN BRASS: Well, in thinking about that, again just reacting to that proposal, I think one has to differentiate that there was no study hypothesis about men and that it was the overall population that included men and the prospective sub-group analysis was to look at women. To the degree a sub-set related to men would have been done, the numbers would have been small, and that also would have been predictable, as I understand it, because the study wasn't powered around use or vet rates in men, so it's not surprising inclusive sub-group analysis perhaps.

DOCTOR GILMAN: Right, and so we could simply start off by saying the data are inconclusive with respect to its effects in men period and then deal with women.

CHAIRMAN BRASS: I'm sorry. To my understanding -- well, in my mind, it's not the same to conclude. One might conclude that there is a significant effect in the general population, a significant effect in a sub-group of women, no significant effect in a sub-group of men. With those three observations, it would be inappropriate to say that there is no data in men because the general population is positive.

DOCTOR GILMAN: I didn't want to say there were no data. I just said that the data are inconclusive for men period.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: Not to suggest a different strategy and so forth, but in terms of thinking of this first question, I really think that we want to remember the hypotheses that drove the study, and it was very much women. I'm not saying we shouldn't look at the men first and so forth, but it was really driven very much for the females, very much for the appetite suppressant, very much for the first use, and all the questions about alpha and so forth I don't think -- really, I think it's quite really appropriate. I think it's really appropriate to analyze as they did. Now, how we sort of chip away at

that is up for discussion, but I think it's the meat of the discussion in terms of where we want to think about things as what's happened in those females.

DOCTOR GILMAN: Well, since you mentioned that, to me, the data are more than suggestive that there is significant risk in women, so I would say yes, the results suggest that PPA is not safe for women when used with other type of exposure. In other words, the data are quite convincing to me that there is a large risk with taking PPA for hemorrhagic stroke in women.

CHAIRMAN BRASS: To put you on the spot a little bit more then, would you like to summarize the features of HSP which were most persuasive to you and why the limitations identified did not dissuade you from that conclusion.

DOCTOR GILMAN: I was impressed with the quality of the case control study. I was impressed with the quality of the interrogations that went on, with the objectivity of the interrogations, the fact that the interrogators who obtained the histories were blinded to the main purpose of the study.

CHAIRMAN BRASS: No. The questioners did know the main purpose of the study.

DOCTOR GILMAN: Did not. Correct.

CHAIRMAN BRASS: No, they did. The people being questioned did not. The questioners were aware--

DOCTOR GILMAN: Excuse me. You're right. I mis-spoke. Yes, you're right. The subjects answering the questions did not know the purpose. And for a rare disorder such as this, I thought this was a well-done study, extremely well-done study.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: Yes. Just to reiterate what you said this morning in terms of the end point. There was a lot of discussion about the end point being inappropriate. I'm not sure I followed, and I thought your comments were right on target in terms of how I think of clinical trials and being put together. Just to say again what was just said now, I think the study was well-designed, well-executed. There were lots of potential biases. It took 10 years to put together, and no matter what we do. If we say at this point, if we finish saying let's run another study, this study can't be dismissed. I mean we would only be in the position where we may make confirmation of this or not but this study can't be dismissed and so I think chipping away -- and I'm not sure this is the sequence I'd want to

chip away at because I think the women who were alpha-type suppressant to first use and then you sort of build up and it isn't necessarily solely driven by alpha of .05/.05 but how do the hypotheses that led to the study lay out and how do the end points get suggested.

I think all of those things were quite appropriate, given the history of this drug and the concerns of it.

CHAIRMAN BRASS: Germane to that, I'd like to pose a question to any of the neurologists on the panel or actually anybody else. The question of biological plausibility came up many times earlier today, and I heard two different common sense appeals. One, why is this unique to women and why were there so many subarachnoid hemorrhages?

But to me, those are actually conversely strengthened, explained each other because it's my understanding that gender is in fact an independent risk factor for subarachnoid hemorrhage and so that if there was an interaction exclusively, that kind of enrichment might be what one might have anticipated in a true association. Would any of the neurologists comment on whether that is reasonable or not?

DOCTOR GILMAN: I think that's eminently

reasonable and, again, I think there's good rationale for grouping together subarachnoid hemorrhage with intracerebral hemorrhage with arteriovenous malformations with hemorrhage. Presumably there's some sort of hemorrhagic diathesis connected with use of PPA. So I think there's very good justification for the grouping. And, in addition, this was an hypothesis-driven trial based upon what could be called anecdotal evidence, at least frequent reports, actually quite compelling frequent reports.

CHAIRMAN BRASS: Yes, Doctor Daling.

DOCTOR DALING: I guess I'd have to say I'm not convinced at all from the study that there is a problem. I find it very large concern to me the response rates. We do RDD all the time. We certainly get response rates higher than 70 percent. They only got a response rate of 41 percent. And one thing we found from doing these studies is that people with high BMI are less likely to respond and participate in studies, so I think that's a potential bias.

But I think my biggest concern is the inability to control from confounding. It was clear from their data that these women who used this drug were likely to be smokers and drinkers, and I don't see how you can control when you only had one exposed

control for these confounding factors.

CHAIRMAN BRASS: Doctor Elashoff.

DOCTOR ELASHOFF: No. No evidence has been given as to what PPA users, how they differ from other people. Only evidence has been given as to how the cases differ from the controls and, in fact, it's not at all surprising that the cases have all these confounding effects because, if only a certain number of the strokes are due to PPA, most of the rest have to be due to the standard things that they're due to. So the fact that the two groups differ markedly in all those features is only to be expected.

DOCTOR DALING: If you look in this report, they clearly show the characteristics on smoking of the people who use PPA, and 50 percent of them were smokers whereas the control population, only 30 percent were smokers.

DOCTOR ELASHOFF: That's cases, not people who use PPA.

DOCTOR DALING: No. Controls.

DOCTOR ELASHOFF: Cases versus controls.

DOCTOR DALING: They have a table in here.

CHAIRMAN BRASS: Use the microphone.

DOCTOR DALING: There's only seven PPA users in the whole study -- I mean appetite

suppressant one.

DOCTOR ELASHOFF: They showed all the -- they didn't do it by appetite suppressant. They only had one, and that was a non-smoker. But if you look at page 37, they give the PPA exposure and how many are smokers and you can count how many are smokers. Two, four, six, eight, nine out of 20 and nine out of 20 is more than 30 percent.

CHAIRMAN BRASS: Then with respect to the confounders, you actually raise two separate points. First, your concern, and this was raised also about the response rate in the recruiting controls. Am I correct that in order to effectively recruit a control they had to agree to a personal interview? In other words, it was more than just will you talk to me on the phone. There had to be some physical contact between the program and the -- if you go to the microphone. They can't see you shaking your head.

DOCTOR KERNAN: Yes. That's correct. When we identified controls, we had to enroll and interview that control within 30 days of the case's strike event, so we were under terrible pressure to get people in and, once a control agreed to participate, they had to participate in an in-person interview.

CHAIRMAN BRASS: So Doctor Daling, so the rates for RDD control recruitment that you cited in terms of expectations, did they include a direct personal interview?

DOCTOR DALING: When you do -- I'm just quoting from what was presented this morning, but you have to take into consideration, first, not only how many that you get to that agree but the people who hang up on you and so forth. That makes it very different, and my understanding from what I've read was that it was 41 percent.

CHAIRMAN BRASS: But again, you cited an expectation of 70 percent. What I'm trying to understand is your --

DOCTOR DALING: We get 70 percent or better.

CHAIRMAN BRASS: -- to come to a personal interview?

DOCTOR DALING: That's right. In their home.

CHAIRMAN BRASS: Okay. And then in terms of the confounders, so you were unconvinced by the stratification analysis?

DOCTOR DALING: They only had one control to stratify it by. I mean you only had one exposed

control, yet if you looked at the exposed controls for weight control, you will see that people who use PPA in general -- I assume these are general population -- that they're more likely to be smokers than are the general population.

CHAIRMAN BRASS: I think Doctor --

DOCTOR DALING: Why is that wrong?

CHAIRMAN BRASS: Because these are in the cases.

DOCTOR DALING: Okay. I'm talking about the controls.

CHAIRMAN BRASS: Who are you comparing it to? What are you comparing the controls to?

DOCTOR DALING: Controls in general. Thirty percent were smoking.

CHAIRMAN BRASS: Yes.

DOCTOR DALING: Smokers. If you look on page 37, nine out of 20 of the controls who used the drug or close to 50 percent were smokers. That's different than the 30 percent overall, indicating that people who use this drug are more likely to be smokers. The data is right here.

CHAIRMAN BRASS: Okay.

DOCTOR D'AGOSTINO: The stratification analysis though talked about those who didn't smoke,

didn't it?

DOCTOR DALING: Well, there was nobody in that strata for weight control. I mean for the smokers, there was only one person in weight control who used it in the controls. That was --

DOCTOR D'AGOSTINO: You're talking about exposure but I'm talking the analysis is saying here are the non-smokers. Now what happens with the exposed and non-exposed and the non-smokers.

DOCTOR DALING: Well, the one control was a non-smoker.

CHAIRMAN BRASS: Okay. I think the point is that that's irrelevant in the stratification analysis because that included cases that were non-smokers only and compared the cases who were non-smokers and cases that were not hypertensive and had the same trend analyses.

DOCTOR DALING: The problem is you needed more controls in this study so that you could adjust for some of these confounders. One is not enough.

DOCTOR D'AGOSTINO: You're saying you need more exposed individuals.

DOCTOR DALING: Yes.

DOCTOR D'AGOSTINO: Not more controls.

DOCTOR DALING: And they knew at the

outset that -- he said that this is exactly what we'd expect, that we would only have one person who used this for weight control who was in the control group, one person. He said .5 of one percent were expected to be using this for weight control.

DOCTOR D'AGOSTINO: This is an event with very small probability attached to it.

DOCTOR DALING: Use of this drug.

DOCTOR D'AGOSTINO: No. It's the cases and controls, then how many of the controls are exposed to the drug is what you're --

DOCTOR DALING: Yes. How many of these controls would you have expected to have used this drug?

DOCTOR D'AGOSTINO: Very, very few.

DOCTOR DALING: Only one who used it for weight control.

DOCTOR D'AGOSTINO: And that's what they saw and they saw more exposed individuals in the cases, and that's what was driving the analysis.

DOCTOR DALING: That's true, but it's difficult to control for confounding in a study of this size with that many controls with only one exposed control.

CHAIRMAN BRASS: In terms of the one

control who was exposed, the issue of the sensitivity analysis I think is extremely important and to the degree to which having two or three instead of one would have affected the outcome. I understand the FDA did such an analysis. Could you just comment on that sensitivity analysis very briefly just with respect to if that one had been two or three.

DOCTOR YI TSONG: Is there any way we can use the slide I have on the machine from the FDA's presentation, slide #84? I think we need to use 74 to start with. Regarding the one exposed control, let's think about it this way. Suppose we have a study, have 100 cases and 100 controls, and we try to do a study and find out there is no exposed on the control but all are exposed in the case. Does that mean there's more association or more? Means there's no association. We are hung up on so much about one exposed control. If there's no exposed control, you get even more significant results. So we have to consider it that way rather than one control, there must be some mistake. If we can prove there is misclassification, then it's a problem. If there's no misclassification, that's not a problem.

Okay. Let's go to slide 74.

CHAIRMAN BRASS: While it's coming up,

Doctor D'Agostino, do you want to --

DOCTOR D'AGOSTINO: Yes. Again, I think the discussion is that if you made the study bigger and bigger and bigger, you would have started seeing some of the controls with the exposure and the argument or the discussion is that the study wasn't big enough in terms of number of controls, but I think that you do have the sensitivity analysis and I think the sensitivity analysis might bring some clarification on that.

DOCTOR YI TSONG: The original slide I prepared was to address the comments raised by CHPA regarding if we have four additional exposed in the control, the total result is totally different. I mean the four additional exposed sounds like a small number, but if we consider those exposed misclassifications, that essentially means that's 80 percent misclassification which is supposed to be exposed but classified non-exposed. This is extremely impossible to have 80 percent misclassification.

So instead, what I tried to do is use a mathematical formulation to correct assume the percentage of misclassification and to correct the odds ratio. So we can go to the next table. Next slide, please.

In this one, I give a different scenario. The first column is the probability of misclassification of case exposed and the second column is the probability of misclassification of control exposed and then we have a corrected odds ratio based on our -- data. As you see, if we go to all the misclassification up to 40 percent in the control arm but no misclassification in the case arm, then we still have about the 7.1 correct odds ratio. I think this is extreme misclassification assumption.

DOCTOR DALING: Can I say I'm not quarreling with the misclassification. I'm quarreling with the inability to control for confounding.

CHAIRMAN BRASS: I understand. Okay.

DOCTOR DALING: That's what I'm quarreling with.

CHAIRMAN BRASS: Please wait until you're recognized.

DOCTOR HENNEKENS: I wanted to make a comment about my concern about the over-reliance on statistical methods as a way to overcome an inadequate sample and to expand on Doctor Daling's point, you have a comparison of six exposed cases versus one exposed control. That exposed control does not smoke cigarettes and three of the six cases do not smoke

cigarettes. So a quote/unquote "stratification analysis" on cigarette smoking leads you that once you adjust for smoking in this analysis, you're comparing three versus one. Not significant.

If you're controlling for hypertension, the control did not have hypertension but two of the six cases had hypertension. So you're left in a stratification on hypertension for four versus one. And I think the most extreme example of these data is if you stratify by a BMI of greater than 35. You have none in the cases and one in the controls. This is what happens when you have such small numbers. There is no amount of statistical analysis that can overcome the inadequacy of the sample to control for confounding.

I accept the crude analysis. I do not accept any technique that tries to control for confounding. It simply can not be done, and I think to go ahead to make recommendations for policy, if that's the sub-group you're interested in, would be very premature and unwarranted.

MS. COHEN: I have a couple of concerns. The end product of this are consumers, and I don't know how one can make a total decision on the safety or efficacy without seeing what the insert is, and I

happened to pick something up and it talked about decongestants and they mention thyroid disease, diabetes, prostrate. What about interactions with other disease? I'd like to know about that, but I also want to know if this board, whatever they decide to vote, if they vote that this can continue on the market, I want to see what information is given to consumers. I want to make sure that consumers are safe and understand what they're taking because so far no one has really, to my satisfaction, described to me what PPA does.

CHAIRMAN BRASS: Okay. You can look on the screen. We'll have in a second a representative package label for a PPA-containing product and so that everybody will be able to see those things. I think there'll be a couple of interesting points. Everybody has commented about the percentage of users who were hypertensive in the group, and there already exists a warning with respect to hypertension on this label. Do you have some specific questions about this label?

MS. COHEN: I can't read it and, if I can't read it, consumers can't read it. I mean can other people read it? Do I need to change my glasses? I'm serious. Can you read it?

CHAIRMAN BRASS: Yes, I can.

MS. COHEN: Would you do it for me then?

CHAIRMAN BRASS: Would you like the whole label read in?

MS. COHEN: Well, I think we need to know if we're talking about safety, and I still want to know about --

CHAIRMAN BRASS: I think we'll go on to other questions and perhaps you can go up to the screen and read the label.

MS. COHEN: No. I think everybody in this room should know what that label says if we're talking about safety.

CHAIRMAN BRASS: What is your concern about the labeling with respect to safety?

MS. COHEN: I want to know what precautions are given to consumers if they take over 75 milligrams, for instance, if they have thyroid, if they have prostate, if they have heart disease. I want to know what else this label will tell consumers so they're going to know what they're taking and what they're taking it for. I don't know if anybody else agrees with me. I don't want to be the lone consumer in the world.

CHAIRMAN BRASS: I will read you the warnings. Do not use if you are now taking another