product containing phenylpropanolamine, a prescription monoamine oxidase inhibitor, certain drugs for depression, psychiatric or emotional conditions or Parkinson disease for two weeks after stopping the MAOI drug. If you do not know if your prescription contains an MAOI, ask a doctor or pharmacist before taking the product. Ask a doctor before use if you have high blood pressure, thyroid disease, heart disease, diabetes, glaucoma, or breathing problems such as emphysema or chronic bronchitis, difficulty urinating due to enlargement of the prostate gland or have been reading too fast.

(Laughter)

MS. COHEN: Okay. And this is an OTC drug. Okay. So --

DOCTOR SOLLER: Could I make a brief comment, Mr. Chairman?

CHAIRMAN BRASS: Please.

DOCTOR SOLLER: I will mention that FDA has proposed labeling and that the products that we've reviewed have essential elements of that labeling and, ma'am, we take this labeling very seriously. It's important that it be driven by the information that we have. I think it's relevant that there is a statement that tells consumers not to take more than the

recommended dose and it's accompanied by a statement that says taking more can be harmful.

For PPA weight control products, there's a statement that it shouldn't be used by people under 18 years of age. There are statements about appropriate drug/drug interactions that should be looked out for and potential contraindications. And that's not unlike other labeling in other categories of OTC medicines. It's entirely consistent in its construct and the kinds of concepts that are being conveyed to consumers.

CHAIRMAN BRASS: Remember, our discussion now is on questions related to the HSP and I don't think, while the labeling issues are important, I don't think they're germane to the questions on the table. Doctor Cantilena.

DOCTOR CANTILENA: Yes. Just a question about the package insert that you just showed us.

CHAIRMAN BRASS: I'm trying to get us back on to the HSP.

MS. COHEN: This is what it's about.

DOCTOR CANTILENA: It is related to that. Is that the current one or is that what was available as the study was actually going on?

CHAIRMAN BRASS: Doctor Soller.

DOCTOR SOLLER: Well, Lou, I would have to look side-by-side, but I can say to you that I think it's probably the same one that was going on when the study was initiated. You're asking me to look at what's here and comparing up there. What it looked to me was the one that was on the major PPA-containing products, national brands as well as the house brands. I mean if you want me to take a look more closely and report back to you during this meeting, I can do that.

DOCTOR CANTILENA: Yes. Specifically in terms of the contraindications and those kinds of things.

DOCTOR SOLLER: Basically they were there. Yes.

DOCTOR CANTILENA: So those were in effect a label that was extremely similar to this, if not identical, was in platy for the subjects who actually ended up in the study. Is that true?

DOCTOR SOLLER: I would say reasonably similar for the major brands and at least one of those had something that was in drug facts-type of format. The house brands and at least one other national brand was not in that kind of format, so there were differences in the labeling and it was not across the board entirely consistent with what was proposed by

FDA, the reason that we suggested that there be a push to standardize that particular labeling. When that happens, it would also be standardized into the format that I know you're familiar with, the panel ANDAC has reviewed, that's the new OTC label format.

DOCTOR CANTILENA: Okay. Thank you.

CHAIRMAN BRASS: Doctor Elashoff.

DOCTOR ELASHOFF: With respect to confounders, I don't think any epidemiological study no matter how big or how well done, can prove without a shadow of a doubt that it's the drug in question that is the cause rather than some confounder. The issue though is does the study suggest that one ought to be worried about the drug in question.

CHAIRMAN BRASS: Doctor Gilman, since you did such a fine job of getting us into the two sub-populations, what is your feeling about the general population, the all-exposed population without a gender breakdown?

DOCTOR GILMAN: Well, based upon the data as we have seen them, I would say that the results in the HSP Study show that PPA is not safe from the risk of hemorrhage in the population as a whole.

CHAIRMAN BRASS: Does that elicit any comment? I just want to follow up I think on

something that Doctor D'Agostino was suggesting and actually was prompted by the comment from the CHPA group, and that is I endorse the concept that one has to be very careful about getting into sub-group analyses and to the degree they can be helpful, that's fine but when the sub-group analyses get even smaller, people are concerned about the small numbers in the primary end points which were prospectively defined adequately powered to address those issues and then confuse how sub-group analyses aren't clear. I think that's not surprising and, while it is okay to talk about them, I think that one has to focus the primary conclusions on the primary hypotheses that were posed by the study which, in fact, included women prospectively as a sub-group and the general population and the degree to which confounders were not balanced, one has to rely on overall general principles to assess whether or not they mitigate the response.

DOCTOR D'AGOSTINO: Again, I think the issue is that if this were a clinical trial in other settings or epidemiologic case control, you say you look at the global and then you look for consistency across the sub-groups. You don't look for statistical significance across the sub-groups. I think the

concern that's being raised is that some of these sub-groups and some of these variables, these confounders, may be what's driving the analysis. When you look at the sub-groups, none of them are inconsistent but we don't have the ability to perform a test that, as Janet just said, it's going to be everyone's satisfaction. But I think it is a good point to bring this back to what the study was designed to actually do and see what happens at that level.

DOCTOR DALING: Doctor Delap, did you have a comment earlier?

DOCTOR DELAP: I think my comments have been addressed in the discussion here. Thank you.

DOCTOR KULLER: Can I make a comment?

CHAIRMAN BRASS: Please.

DOCTOR KULLER: I think there's two questions here which still need to be resolved. First, this man/woman situation. The use of PPA in the control group in the men and the women is exactly the same. It is not statistically different. It is not low use of PPA in the men, and the number of cases in the study is very similar for men and women so that yes, subarachnoid hemorrhage may be more common, as we know, in women but in this study, the number of cases in men and women is not terribly different and the use

of PPA, especially if you exclude the use in obesity drug, is 2.5 percent versus 2.1 percent in the controls.

The interesting observation is that there is no exposure in the male cases, but that has absolutely nothing to do with PPA use in the population. It only suggests that there might be a difference in the characteristics of the cases.

The second problem, which hasn't been resolved and was pointed out by Doctor Daling a few moments ago, is that internally the study is superb but I just don't understand how one can resolve the issue that the controls are almost the same as basically going on a street corner and asking people whether they took PPA or not. I mean when you have that small a control group, when you have to make 100 and some phone calls to find one potential control and then only one out of three who you actually find ever get into your study, I don't understand how you can possibly interpret the control group in terms of the use of PPA when the whole study is based on eight cases that use PPA versus five controls. This is not a twelve-fold risk across the population. It's eight versus five, and when you have that much of a problem with selection of controls, even though the rest of

the study is superb and it is and everything they talked about and the FDA presentation, we all agree. But the problem is you still have the controls are just like doing a survey by asking people on the street who you're going to vote for or what do you think of something. That's not the way we do studies and, when you have that problem, it's almost impossible to interpret the results.

CHAIRMAN BRASS: If I could just ask you to clarify something you just said. I thought in the control, the use of PPA was higher in the women than the men.

DOCTOR KULLER: It's 2.5 percent versus 2.1 percent if you exclude the women who were taking the appetite suppressant and, if you don't, then it's 2.7 versus 2.1 and that is not even close to statistically significantly different. It is strikingly different among the cases. 5.1 in the women and 1.9 percent in the men, but that has nothing to do with PPA in the community. It has to do with the use of the drug in male cases versus female cases and the number of cases is 319 men and 383 women in the study. So it's not a function of there aren't any men in the study. This is not a power issue in men. It's a very interesting observation that men are

essentially protected and women basically have what's reported to be a risk in the study. But you can't attribute this to low use of PPA in men or basically to not enough stroke cases in the men to interpret the data.

DOCTOR HORWITZ: I just wanted to make a comment on Doctor Kuller's observations. We agree with Doctor Kuller about the total number of cases among men and women which are very similar in that the overall exposure prevalence for PPA between men and women is not greatly dissimilar. I think where we may disagree is that if you look among the controls for males, there were no appetite suppressant users among males and there was only one male user for first use of cough/cold.

So the reason we raised that concern and why we felt that there was an issue of this study being under-powered for that purpose was that there were no male appetite suppressant users and only one male first use of PPA in cough/cold products. It was that part of the analysis which was a pre-specified part of the hypothesis of this study for which we felt that we had insufficient exposure among the controls and left it difficult for us to answer specifically.

DOCTOR KULLER: But Ralph, you have to

admit you only have four women who are first exposures in the controls, also, so you have one man and four women in the entire study and that would be a little shaky in terms of interpretation. There's only four women in the control group that are first users and there's one man, so that's your entire presumption.

I think the more likely hypothesis is that there's something different, either the distribution of cases between intracerebral and subarachnoid between men and women or likely that the drug behavior, whatever it is or whatever else is going on here, is strikingly different between men and women. It's a rather interesting observation, but I don't think it can be washed out by power.

DOCTOR HORWITZ: I've learned over the years not to try and get into a dispute with Doctor Kuller. The emotion would be high and the stakes would be low, I'm sure. I did, however, want to point out that when we said with regard to first use in women the .5 percent, Doctor Daling, that we had referred to earlier had to do with the expected exposure prevalence for first use among women of .5 percent. You may feel, Doctor Kuller, and I understand that, that the four exposed women in that category represents a small number. It was the

anticipated number that led to the sample size estimation that .5 percent was what we anticipated from the market data, that .5 percent was what we found in actually conducting the study. Those four exposed controls-- you and I may wish there were more -- nevertheless were the basis for the sample size estimations that we used in the planning of the study.

CHAIRMAN BRASS: Doctor Gilman.

DOCTOR GILMAN: I don't think that the data show us any evidence that men are protected. What we saw was that there were very few effects in them, but that shows no -- to me, there's no evidence of protection in men.

CHAIRMAN BRASS: Doctor Blewitt.

DOCTOR BLEWITT: I propose that we go back to your question, question A, and I'd like to step back from all the details of this issue and just make a few comments if I may. First, it's my belief that the study results are not conclusive. Now, that's not to say, however, that there isn't useful information that can be potentially gathered from a study of this size. I personally don't think that we're going to-- for the committee's sake, I don't think we're going to resolve the epidemiological and statistical debate that's been going on here. It's just not possible,

particularly where the data are described as fragile, some of the results appear to be inconsistent.

My own reading, general reading of it, not being an expert, is that I really felt that the populations differed significantly as to make them non-comparable. I felt that comparing hospitalized versus non-hospitalized was not wholly appropriate. I felt that the cases differing significantly on seven different factors was important. I felt that there was a substantial difference in the patterns of use of the drug in cases in controls and so forth.

So my approach was to basically pretend that 27 cases were brought to me to take a look at, 27 charts, and say what do you think about these? There's a concern that maybe phenylpropanolamine is the culprit in all of this, and give us your feeling. And my approach to that would be to take each of the cases and to look at the dose that was given, the timing of the dose, what concomitant medications might be taken, what concomitant disease states might be present and the general demographics.

And so I went to page 37, Table 6 here, and without getting into too much detail because I'm not looking at hospital charts. This is the study report manuscript. But just in what I could perhaps

gather from looking at this chart compared to what I might be able to get if I were able to look at the cases in some depth and I found that if I looked at the case group, there were, in addition to what's been said about smoking and hypertension and so on, a lot of cases where the dose in three days was exceeded. I see a 600, I see an 890, a 480, 640, 600. I see the last dose in some cases being 150, 150, 150. I also see one which is low as 20.

So it leads me to question what's going on here and it leads me to say, well, is there a value in taking a look at these cases individually on that basis and could that lead you to a population that would perhaps be at risk for taking the drug? If a substantial percentage of these people have taken it beyond the labeling indications, I think that's a factor. If there are coexistent illnesses or medications, we're not entirely clear on medications, then those are factors, too, which would govern your judgment on that. So I would suggest that perhaps taking a look at these cases in depth, given that I really feel that it's going to be very hard to resolve the issues with regard to statistics and epidemiology. So that would be my comment.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: I think what was just stated is actually very important, but I also want to remind us of where we sit here. I mean 10 years ago, we had cases being reported and what you said would be very compelling. What do they consist of? Do they overdose? Are they taking other drugs and so forth? Because there was data that was indicating that in females with appetite suppressants, first users, there was this very long-term epi study and what you are suggesting now is that let's forget that this is a well-designed study, that there were cases, there were controls, and run to looking at the individual cases. I would think that because it was a study that was well-designed and so forth, we should look at what the analysis of the study says and, if we come up with something, if we said the study is completely inconclusive, we say that we don't think there's any relationship, then it ends but, if you say there's a relationship, then you ask the question, well, what's driving the relationship? Is it over-use and so forth?

And so what I'm suggesting is that let's remember that this was a case control study that was prospectively put together and I think we need to look and we should look at how the hypotheses played out

and then certainly for interpretation, if we think there's a relationship, to do exactly what you said. I think we have to be compelled to do what you said.

DOCTOR BLEWITT: If I may respond. I don't think that I've heard anyone here today say that this study wasn't properly designed. In fact, I think even those who have perhaps critiqued the study have all agreed that this is a well-designed study. I think that a lot then goes to the execution and really basically what comes out of the study. You can have the best of intentions, the best protocol design, as you know, but that doesn't necessarily mean that what you're going to get at the end is what you had desired to accomplish in the first place. So I agree with you. I don't see that as an issue.

I think the issues have been raised in terms of how the data were collected and whether they were validly collected and so forth. I mean that's what it comes down to. What is it that you have at the end, not what you have at the beginning.

CHAIRMAN BRASS: I'm sorry. You had a comment earlier.

DOCTOR LA GRENADE: I was going to point out that in the random digit dialing selection they were trying to match the controls to the cases. So

when they phoned the first person, you have to match the case on certain criteria. So it wasn't just as though you didn't respond, and I think this is a factor that we probably have lost sight of in the discussion. I just wanted to bring it back to the attention of the committee.

CHAIRMAN BRASS: Thank you.

Doctor Cantilena.

DOCTOR CANTILENA: Yes. Just in follow-up to George's comment. I mean if you look at that Table 6, George, I guess what I'm hearing you say is that it may not be less of a problem or as much of a problem because in five of the females and one of the males they exceeded the recommended dose in three days. But I sort of look at it in another way in that this is, in essence, an actual use study and really those five females but not the male certainly exceeded the last dose but only by a factor of two for an appetite suppressant dose. So it really, in essence, comes down to an extra pill and they ended up on the case list.

So I think the way I'm hearing you, I just wanted to ask you to clarify that because, as I see it, this is really sort of telling you that perhaps the safety margin is not as it should be if you can

just exceed the dose really slightly by a factor of two to two and a half, I guess, in the column for the dose in three days and still end up here on the list. I mean we're talking about an over-the-counter and it's, in essence, sort of an actual use.

DOCTOR BLEWITT: Well, it is a case where a couple of tablets can make a difference. The labeling has been adjusted in fact to bring the total daily dose to the lowest reasonable dose that would not cause side effects. So it initially was somewhere -- it's been backed up. For instance, it's as if you're asking me well, if you took a 400 milligram ibuprofen tablet, wouldn't it be okay to take an 800 milligram, and so there is a point at which you draw the line for medications and I think that that applies here as well.

DOCTOR WEISS: Could I just clarify the issue about the method and the conduct of the random digit dialing. The concern of the Review Committee wasn't that a large number of calls had to be made to identify a matched individual. We understand that process would require a large number. Our concern was that among those persons who are identified as potentially eligible, only approximately 35 percent of them actually were recruited into the study.

The reasons why non-participation is of concern, of course, is that participants and non-participants may differ in a lot of ways that are important to the exposure in question. I'm not saying this actually occurred, but it's conceivable that if a potential control is identified and asked to be participate in an interview but that control has a cold, is not feeling well, they may preferentially choose not to participate. If that does happen, then in the controls that are selected you're going to have an under-representation of the use of PPA.

There is certainly some reassurance in the fact that the proportion of users of PPA was roughly that predicted in advance, but I doubt that that prediction focused on the four geographic areas in the particular age group that was in question. I think there was a good reason to pick some controls and the worry still is that they may not really represent the population at risk for this condition.

CHAIRMAN BRASS: Doctor Kittner.

DOCTOR KITTNER: I think everyone agrees that the study was well-designed and I heard a statement that it was not well-executed. I think that there's no consensus that I've heard around the table that it wasn't well-executed. In fact, I think that

if we were to repeat this study and spend another five years, we'd likely be back around the table here with very similar data and very similar issues. Many of the issues are really inherent. This is actually the largest case control study ever conducted in hemorrhagic stroke and, what's more, it's in a low instance population. We're talking about stroke at any age and here we have a stroke in young adults which is the largest study ever conducted. So I don't think that if we come and redesign and do a study we're necessarily going to be in a better position in five years.

CHAIRMAN BRASS: I think it's important, again just to try to maintain some focus, I think the issue of whether or not we conclude something from HSP needs to be separated, whether we conclude anything or not, help us in the policy decision making, and I think those are two separate issues, and your point, which I agree with, is germane to when we try to extrapolate from HSP into decision making.

Ms. Cohen.

MS. COHEN: I have a question I don't know the answer to. I noticed on the labeling that children 12 years --

CHAIRMAN BRASS: I'm sorry. Only things

related to the HSP interpretation.

MS. COHEN: Well, I think this is important, Doctor Brass, because someone can answer it. It said that children 12 years of age and older and adults can take up to 150 milligrams a day, and I think I need to know if that's a safe amount. This is about safety and consumers.

CHAIRMAN BRASS: Other comments about the HSP.

DOCTOR DELAP: I think we are interested in the comment that was just made, but I'm hoping that we'll get some discussion of the dose a little later on.

CHAIRMAN BRASS: That's correct.

DOCTOR DELAP: I think we have that under question D. I don't want to lose that.

MS. COHEN: Thank you very much.

CHAIRMAN BRASS: Yes.

DOCTOR WARACH: I do have a reservation about the conclusion of the association with the hemorrhage risk for two concerns. One is the problems with adjuster controlling for all the potential reasonable and relevant confounders. The other one that had been mentioned only slightly in passing earlier today was the problem with self-report with

regard to cocaine or other illicit drug use and cocaine is a recognized risk factor for hemorrhage. It's likely to be unreported. Perhaps even more so in the group that suffered the stroke and is feeling a bit guilty about their abuse behavior. So I think the study is very suggestive of this association, but I have that reservation and I would say it's ultimately inconclusive on that point.

CHAIRMAN BRASS: Do the investigators happen to have any information about tox screening on the cases. You'd think that in young patients presenting that it would commonly be done.

DOCTOR KERNAN: We don't have any recorded information on toxicology screens.

CHAIRMAN BRASS: I assume you're going to want votes. Yes, I was afraid you'd say that. Okay.

DOCTOR NEILL: I'm going to save you from voting for a minute. A couple of comments about the study. The first is that with regard to the issue of being able to assess for confounding or not, I've been convinced that this is not a study that can help me control for that and yet to the extent that it's been attempted, it hasn't shown any difference in their results.

To the extent that it was designed to

answer a specific question in the overall population and a co-equal aim in women to answer a specific question, it answered those questions and very clearly overall the answer from this study, however imperfect, is yes, there's an association.

The second comment I'd like to direct to FDA staff, but I've got three comments so don't answer until I get my little third one in. Earlier I was asked by Doctor Soller to use science as a base for my decision and it's my impression that PPA is OTC by virtue of historical accident rather than virtue of science and I wonder if, after my next comment, you could reconcile the expectation that I'm supposed to use the results of the aggregate data to make a decision about OTC safety for this with FDA's statement earlier that the burden of proof for safety is with the manufacturer.

CHAIRMAN BRASS: I'm sorry. I'm going to interrupt again because we're going to get to the issue of how whatever we conclude about HSP is used for decision making.

DOCTOR NEILL: Okay.

CHAIRMAN BRASS: So I really want to stay--

DOCTOR NEILL: Can I move on to my third

comment then?

CHAIRMAN BRASS: Thank you.

DOCTOR NEILL: You can just let that float in the air. With regards to the small numbers that makes it so difficult to control for confounding in men and lack of men using appetite suppressants, I saw some data that suggested that the overall use in the general population is overwhelmingly for cough/cold preparations and I haven't heard anybody comment on what seems to be the massive over-representation of hemorrhagic strokes occurring in people using it for appetite suppressants. I don't have an explanation for why.

Fully a third of these cases come from people using it for that indication when they represent a tiny, tiny percentage of the overall use and, if nothing else, that suggests to me that I ought to believe these fragile results.

DOCTOR SOLLER: Doctor Brass, just quickly. I think what's important here relative to the scientific documentation in that standard is really what we heard a little bit earlier, that maybe there's not an evidentiary standard for safety, that it more becomes well, subjectively, how do I feel about this data set? And I think what the policy

does, it drives us to a much more rigorous view of that.

The comment was the burden of proof for safety is on industry. The agency has acted in approving NDAs and, as far as I know, NDAs for products are approved in the context of safety and effectiveness. I think, therefore, the question here is whether there is a sufficient evidentiary standard and it must be rigorous. That's why you've been brought in because obviously you've got, I think, what the industry looks at is a major polarization within the epidemiologic community and some very important players within that community raising very, very significant concerns. And I think that that's very important. And if you come to a point where you are going to keep the evidentiary standard where it should be, then I think for this study you end up being uncertain that is has shown what you're suggesting it has.

CHAIRMAN BRASS: From the FDA's perspective, before we go into voting, are there issues that you think have not been discussed about HSP that you would like to hear discussed that would be helpful from your perspective?

DOCTOR DELAP: I think the discussion has

been a very good one, and some of the salient points that I've picked up are that the numbers of events on which you're basing a conclusion of an association are relatively small. We knew that that was going to be the case going in, I think, when the study was designed because power was at the margin, even with this fairly ambitious study. I've heard the discussion that it's hard to analyze satisfactorily for confounding in a setting where you don't have so many events to base those kinds of analyses on. I think we hear that, as well.

We're looking at this again from the standpoint of we had some concerns in the early '90s, particularly about women, particularly about weight control products, and this study grew out of that. So we'd like to have your answers as to how we should interpret the results of this study in the setting of all the information that's led up to today.

DOCTOR HENNEKENS: I wanted to respond to Doctor Neill's comment about the overall results. I believe that if one sets aside the concerns that you have a 35 percent articulation rate in controls and an inability to control confounding, especially in the sub-group analyses, if one looks at the overall test of the hypothesis of whether taking PPA for either

cough or cold suppression or appetite suppression is associated with risk of hemorrhagic stroke, the overall analysis, to my thinking, is based on 27 versus 33, and that is not statistically significant.

DOCTOR NEILL: I guess I would respectfully disagree. What I see is an elevated odds ratio with a p-value of .089 which, while it isn't .05, is high enough when considering items of safety to make me concerned about that. I don't think the study was designed to answer the question, but I haven't heard an explanation for why people using this for appetite suppression as an indication would be over-populated in either of the two groups.

DOCTOR HENNEKENS: I certainly agree with your point that you might want a different standard for safety than for efficacy. However, I also feel that my opinion is that if you follow guidelines that are emanating from these data, they'll be lots of drugs you throw off the market when there's nothing wrong with them and lots of drugs you leave on the market that are causing fairly large effects that you're missing because of using rules like this. It goes both ways.

DOCTOR NEILL: I guess one other point that was brought up several times is that in addition

to the very low response rate, there's this unaccounted for dead folk who obviously, by their absence, would tend to make it more difficult to show an effect which is why I remain impressed that there is an effect that's demonstrated despite their absence.

CHAIRMAN BRASS: Doctor Gilliam.

DOCTOR GILLIAM: My concern, I guess, is with the safety, too, and using the figure that are given, about 10,000 people a year in this age group have a stroke, and the FDA was saying that they can attribute -- if you believe the statistics, that there's 200 to 500 strokes in this age group that could potentially be prevented, that's two to five percent of the strokes in this age group. I think that's of concern. Plus also the fact that people are not taking this in the recommended doses.

CHAIRMAN BRASS: I'm almost going to give up but again, it is quite possible to conclude that there's an association based on HSP but when we get to risk versus benefit, etcetera, and vice versa, despite the absence of an association of the trial, one might conclude.

Doctor Gilman.

DOCTOR GILMAN: I think it's a good idea

to go back and take an omnibus position now because this is a trial that was conducted prospectively with a set of hypotheses to test with case control methodology that was superbly followed and the result was significant. As I see those data, they are significant. It's not a feeling. It is what the data show me anyway. So I'm not troubled, as some people in the room seem to be, by the quote "small numbers." They were predictably going to be small numbers. We have what was predicted at the very beginning of the design, and so it should be no surprise to us now that we're dealing with small numbers, but the numbers show a significant risk for hemorrhagic stroke, particularly among first users and in women.

CHAIRMAN BRASS: Doctor Katz.

DOCTOR KATZ: I agree the point of which was the primary outcome and adjusting for multiple comparisons. These are very important issues and we worry about them all the time and overall, given one of the so-called co-equal outcomes, it didn't make it nominally statistically at .08 I guess was the thing. But as Doctor La Grenade said earlier, I just want to reiterate this point. Apparently from the point of view of the FDA, even though there were technically three or five co-equal outcomes apparently, I'm told

that the one outcome in which the agency was specifically interested in as the ultimate primarily-- if I can speak for the team and I really shouldn't, they're here, they can speak for themselves -- was the sub-group in which the statistically significant finding emerged. In other words, women taking it as an appetite suppressant. And that finding, if you consider that to be the primary, if you believe that, holds up to any sort of -- pretty much holds up to any sort of reasonable adjustment procedure for the p-value.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: I think that it's been over and over again and those who are aware of the history know that it's exactly what you just said. You can argue on the other side is that the investigators put a study together and they came up with five hypothesis and gave them all equal weight. I would argue, even in the light of them giving it all equal weight, those significant values using .05 as the cut-off can't be ignored.

CHAIRMAN BRASS: Okay. I'm going to try to synthesize some questions that we can actually vote on. Before we start, I want to remind everybody that Doctors Warach, Blewitt and Kittner are not able to

vote though they're able to participate in the discussion. And all the questions are going to have the following form. They're all going to be about the HSP Study. I'm going to follow my own rule. And there's going to be three options on each question.

So the three options are going to be that the HSP Study suggests that PPA is safe from risk of hemorrhage, that the results suggest that there is an association between PPA and hemorrhagic stroke or 3) inconclusive between those two alternatives. And I'm going to identify populations and uses and we will vote on them individually. So the first option will always be safe, 2) will be associated, 3) will be inclusive. Is that strategy okay? Okay.

So the first population I'm going to ask the question about has to do with women between the age of 18 to 49 using PPA as an appetite suppressant. Safe, associated, inconclusive. All those who feel that, based on the HSP Study alone, that PPA is safe in that population, please raise your hand.

All those who feel that PPA is associated with hemorrhagic stroke in that population, please raise your hand.

DOCTOR TITUS: There are 13 --

CHAIRMAN BRASS: Thirteen. Well, I'll

read it at the end.

And all those who feel the data are inconclusive, please raise your hand.

DOCTOR TITUS: One. So the tally is zero for safe, 13 for there is an association, and one inconclusive.

CHAIRMAN BRASS: The next population will be women between the age of 18 and 49 using the product as a decongestant, and that's any decongestant use. Is that clear? In other words, I'm not talking about first dose only. I'm talking about any exposure as a decongestant. People have that?

All those who feel the product is safe for that group, please raise your hand.

All those who feel there's an association in that group, please raise your hand.

All those who feel it is inconclusive in that group, please raise your hand.

DOCTOR TITUS: So for the females in the 18 to 49 year age for decongestants, there were zero who thought it was safe, there were six who thought there was an association, and there are eight inconclusive.

CHAIRMAN BRASS: Next are women 18 to 49 using any PPA product on first exposure. Okay. Is

that clear? First use risk in women regardless of product class. Okay? All those who feel the product is safe in that group, please raise your hand.

All those who feel that there is an association in that group, please raise your hand.

All those who feel the data are inconclusive in that group, please raise your hand.

DOCTOR TITUS: For females in the ages of 18 through 49 on their first exposure to PPA, we have zero who thought it was safe, we have 13 who thought there was an association, and we have one inconclusive.

CHAIRMAN BRASS: We will now do those same three classes for the general population. So no gender specificity. So without respect to gender, using PPA products as appetite suppressants, those who feel the product -- I'm sorry. It's a clarification question? Please.

DOCTOR GILLIAM: This is just in the 18 to 59 general population or the population as a whole?

CHAIRMAN BRASS: The HSP population, so the 18 to 49. I'm sorry for not clarifying that.

Doctor D'Agostino.

DOCTOR D'AGOSTINO: You want us to vote on the women data, the female data, overwhelming the

combined data?

CHAIRMAN BRASS: That could be an interpretation of what I just said because I think that, again, in terms of the compilation of the data, one of the hypotheses were all exposure.

DOCTOR D'AGOSTINO: Or you could also be saying that there's consistency in males and females and sub-group shows it just on females.

CHAIRMAN BRASS: Well again, in my mind, this goes back to the original hypotheses of the study. One could vote that the result could be significant for women and in the general population, either because the effect is generalizable or in the general cohort the data in women statistically drove it so that it was significant odds ratio. I think which of those occurs has implications for the interpretation of what action should be taken but from a study design primer hypothesis, I thought it would be worth putting on record. But I appreciate the clarification.

Doctor Gilman.

DOCTOR GILMAN: I have concern about doing this though. This is the reason that I suggested that we just eliminate men from the beginning. The problem is that we have a set of hypotheses driven by the

principal question which is about women and stroke and, accordingly, the study was designed with that in mind and now, since there are only two choices, there are men and there are women, we don't have any other choice here, we have to decide whether we want to say, well, I assume there may be some risk to men even though I don't know whether there's risk or not. In other words, go beyond the data as they exist because the trial wasn't designed with this in mind. So I have a problem in trying to vote on this with this question in mind. The study was not really set up or the data do not lend themselves now for me to have clarification as having good rationale for a vote to include in the at risk population because it doesn't look as if men are at risk in this population.

CHAIRMAN BRASS: Let me just read the first study objective from the trial. Specifically to estimate the association between PPA and hemorrhagic stroke among men and women, men and women, not separately, age 18 to 29 and estimate the association by type of PPA exposure in that general population. So that was the rationale, I though, and, while I was concerned because men were not a prospective sub-group, women were, that I thought that addressing the study hypotheses and our conclusion might be helpful.

Doctor Delap.

DOCTOR DELAP: Yes. I think I can understand where Doctor Gilman is coming from. I think there's kind of a logical problem here. I mean it would be hard to say if you're going to ask the question for the whole population, if you feel that there may be a problem in women, how could you say that there's not a problem for the whole population because women are part of that. So I think Doctor Gilman is trying to say, well, we've said what we thought about the women and maybe we should just find out separately what we think about the men and then we can kind of add it up.

CHAIRMAN BRASS: I'm happy to do that, but let me again express my concern that men were not a prospective cohort, that there are reasons to think that if one designed it prospectively for men, one would have designed it differently and that the event rate differences, etcetera, compound that interpretation. But I'm happy to do it that way instead of the total cohort if people are more comfortable doing that.

Doctor Johnson.

DOCTOR JOHNSON: Well, I guess I sort of would follow your suggestions because these are the

aims of the study. Total population, which obviously includes women, and women. I would be uncomfortable voting on men because it wasn't a pre-specified aim and it wasn't designed for that.

CHAIRMAN BRASS: Should we vote on what we're going to vote on?

DOCTOR D'AGOSTINO: I was going to say, again, if the discussion we had at the beginning of this, that one interpretation, if we say yes, is that the female data is the thing that's driving it and so we're not actually necessarily giving an interpretation but just what the data says.

CHAIRMAN BRASS: Yes. Have we convinced you, Doctor Gilman?

DOCTOR GILMAN: No. It's worse than that, Jim. The problem is that if, thinking of my own vote, if I vote that it is associated with risk for the whole population, in my mind, I would be voting on that side of things because the women overwhelm the men but it doesn't mean anything about the men. Yet implicit in this vote is that men are equally at risk, and I don't know if that's true or not. That's the problem with this vote. I don't know how to vote, quite frankly.

CHAIRMAN BRASS: Okay. I am happy to do

a gender, I'm happy to do it by men by that category, and then we can see if it's worth doing a third round. Why don't we do it that way. Doctor Neill.

DOCTOR NEILL: I'm right with Doctor Johnson on this one. The study wasn't designed to answer the question in men. I asked myself the same kinds of questions, and I guess I have no qualms about answering the question as regards to the entire study population because that's what the study was designed to answer and, while it's open to many interpretations, many of which I've gone through in my head -- let's see -- men don't take appetite suppressants, women do, women are the subject of the marketing efforts of these medicines for appetite suppressants. I mean the list goes on and on and on and, while there may not be a risk for men on the drug store shelf, it's not like you're going to say men don't take this. It ain't going to happen.

And so I would strongly urge that we not consider voting for men as a subset since I think we would be implying that we've got data to inform that answer when we don't.

CHAIRMAN BRASS: Here I'm going to take the chicken way out and we're going to do both by male and the total cohort and, because there's an

inconclusive option, everybody will be able to express whether or not they're comfortable voting that way, and it'll be really simple. So let's do it by men. We'll do the men sub-group first. Men between the age of 18 and 49 using the product as an appetite suppressant. All those who feel in that population PPA has been shown to be safe, please raise your hand.

All those who feel that it's been shown to be associated with risk, please raise your hand.

All those who feel the data are inconclusive in that population, please raise your hand.

DOCTOR TITUS: Fourteen inconclusive.

DOCTOR D'AGOSTINO: Can I abstain?

CHAIRMAN BRASS: Let the record show that Doctor D'Agostino is embarrassed to be associated with this vote.

Okay. Men using decongestant. Safe, please raise your hand.

Associated with risk, please raise your hand.

Inconclusive, please raise your hand.

DOCTOR TITUS: I missed somebody's vote. I'm sorry. I don't get the right count. Okay. Fourteen are inconclusive for men on decongestant.

CHAIRMAN BRASS: Okay. Men 18 to 49 with first time exposure to a PPA product, safe, please raise your hand.

Associated with risk, please raise your hand.

Inconclusive, please raise your hand.

DOCTOR TITUS: Fourteen are inconclusive for men 18 to 49 for the first time use.

CHAIRMAN BRASS: Now without gender specificity, the population between the age 18 to 49 using the product for appetite suppressant. All those who feel HSP has demonstrated safety in that population, please raise your hand.

Those who feel that there is an association in that population, please raise your hand.

All those who feel that it's inconclusive, please raise your hand.

DOCTOR TITUS: Okay. In the all population 18 to 49 for appetite suppression, there is zero for it being safe, 13 for there is an association, and one inconclusive.

CHAIRMAN BRASS: Next is the general population 18 to 49 using the product as a decongestant, regardless of timing of exposure. Male

and female 18 to 49. All those who feel HSP demonstrates safety in that, please raise your hand.

All those who feel an association of risk has been demonstrated by HSP in that population, please raise your hand.

All those who feel that it is inconclusive in that population, please raise your hand.

DOCTOR TITUS: The all population for decongestants, we have zero think it's safe, five think there is an association and nine it's inconclusive.

CHAIRMAN BRASS: Next and hopefully finally for this group of votes, 18 to 49, all population with first time exposure to a PPA-containing product. All those who feel HSP establishes safety in that population, please raise your hand.

All those who feel there's an association associated with risk in that population, please raise your hand.

All those who feel that it is inconclusive, please raise your hand.

DOCTOR TITUS: In the 18 to 49 all population first time exposure, zero thought it was safe, 13 through there was an association, and one

thought it was inconclusive.

CHAIRMAN BRASS: Thank you very much. Under A, there's one issue we have not dealt with and that's specifically the question of dose. I'd be interested now in some discussion of, again based on the HSP data, whether or not dose is felt to be a factor in any risk in these populations. Doctor D'Agostino.

DOCTOR D'AGOSTINO: Can I just ask, do you have a summary of what we heard and I'm going to say what I thought it was, that there was some analysis but it wasn't significant but sort of directional. Is that what we basically have before us?

CHAIRMAN BRASS: Doctor Gilman.

DOCTOR GILMAN: I believe it was suggestive but not statistically significant.

CHAIRMAN BRASS: Would any of the presenters disagree with that assessment of the dose data from HSP? That was certainly my impression and that again, it was a secondary analysis. The recall about dose seems to me to be even more problematic in that it was harder to verify. There were strict rules for verifying yes/no, but to verify a dose of exposure would seem to be to introduce an additional variable into that kind of analysis which would be more

problematic.

Doctor Sachs.

DOCTOR SACHS: The only comment I have is kind of a clinical correlation in trying to think about maybe the pathophysiology of this, and it might be a mistake to assume clear linear dose response relationship because there might be a threshold effect, especially if the hypothesis is that there's some kind of pre-existing dimple or blister in the blood vessel that busts after using one of these agents.

CHAIRMAN BRASS: Other comments about dose? Would you like a dose vote? Yes?

DOCTOR DELAP: When we get down to question D, you'll see we have some discussion of dose there and I think it would be fine to skip a vote here. We've heard what I think the consensus is and we can get a little further elaboration in question D.

CHAIRMAN BRASS: Thank you. I love being spared a vote. Okay. The next question is B and, again, focusing on the HSP data, does it provide information on which populations may be at greater or lesser risk? Now, we've defined nine different populations already based on gender and exposure type and implicit in the vote was that women represented a

group of relative risk compared to men and, without doing a statistical analysis on our votes, there was a suggestion that appetite suppressants represented a use population. Are there other population identifications that were gleaned from the presentation which any member of the committee feels is important to highlight?

It appears not to be the case and, again, I think this goes back to the limitations on the sub-group analyses and what stratifications were done did not suggest to me any grouping of the risk by any of the strata so that it did not appear to be unique to underlying hypertension or etcetera but, again, that is clearly based on very small numbers but, in trying to even detect a signal, I don't think there was much basis for reacting to that data. Skip a vote? No vote? Okay.

Now we shift gears and now we will begin--Doctor Cantilena.

DOCTOR CANTILENA: I hate to say this, especially to you, but is it possible to just get a five minute break? I have to answer a page, and this is real important. I don't want to miss it.

CHAIRMAN BRASS: Okay. We will now take the Cantilena break for 10 minutes. Actually, we can

take a 15 minute break. 3:15 please. 3:15.

(Off the record for a 15 minute break at 3:04 p.m.)

CHAIRMAN BRASS: The committee will now continue its discussion and in what follows we will expand upon our earlier discussion in the presentations to look more globally about the use of PPA in the OTC market based not only on the HSP and our comments earlier about the HSP, but the other information that has been compiled and summarized for us, both from spontaneous reporting base and previous published studies.

So the first specific question we'll be discussing is whether or not there's a body of data collected over the years that -- I'm sorry -- there is a body of data collected over the years that has suggested a possible association between PPA use and hemorrhagic stroke. Taking all currently available information into account, do the data support the conclusion that, 1) there is no association between PPA use and hemorrhagic stroke, there is an association between PPA use and hemorrhagic stroke, the association still remains uncertain because of insufficient information.

Who would like to make some initial

comment about that postulate?

DOCTOR GILMAN: I think we have heard data suggesting fairly strongly that there is an association between PPA use and hemorrhagic stroke.

CHAIRMAN BRASS: Again, just to flesh out that, would you comment on what of the available evidence you find most compelling in that conclusion?

DOCTOR GILMAN: It was the comparison of PPA versus all other similar agents that was really striking to me. Fourteen percent with CVA for PPA versus 0.8 percent all other drugs.

CHAIRMAN BRASS: So you're referring to the spontaneous reporting data and what percentage of all PPA adverse events were cerebrovascular versus the overall database and the enrichment of that in the PPA?

DOCTOR GILMAN: Yes.

CHAIRMAN BRASS: Yes, Doctor Sachs.

DOCTOR SACHS: In a supporting statement, the other thing, even back in the adverse reporting from 1977 to 1991, the PPA diet reports of CVA association was 26 percent which was greater than the 20 percent reports of OCPs. That's really compelling.

CHAIRMAN BRASS: Doctor Kittner.

DOCTOR KITTNER: The other thing about

these reports was that they were pretty specific to hemorrhagic stroke and if this was just a background rate or a coincidence of two independent things, you would expect them to be similarly associated with ischemic stroke, and they really weren't. I think some of the other points about the case reports have already been mentioned, that is that there was a relationship to first dose and often within the first six hours which is consistent with the pharmacologic effect on blood pressure and the diminished effect with repeated doses.

Another point in the case report and which we also see in the case control study seems to me an association with excess use of a PPA.

One final point that I observed in reviewing the case report literature was that the cases of intracerebral hemorrhage were not really entirely typical. There were reports showing bilateral hemorrhage, two cases of bilateral hemorrhage at that time, and 11 cases showing angiographic features of vasculopathy, at least, or angiographic features that would be consistent with vasculitis and I thought that's relevant in view of the fact that PPA has close structural and pharmacologic similarities to amphetamine where drug-

induced vasculopathy with intracerebral hemorrhage has been well-documented. So I think it speaks a little bit to the potential biological plausibility.

CHAIRMAN BRASS: I noted that in some of your earlier writings and, frankly, I got a little confused because how could there simultaneously be an acute first dose six hour effect and then the development of a vasculopathy? Those seem to be exclusive.

DOCTOR KITTNER: Notice I didn't say vasculitis, which is an inflammatory condition of the blood vessels. I mean many things can cause angiographic changes in the blood vessels, eclampsia and so on, so that the pathological underpinnings of those angiographic changes are not necessarily inflammatory.

CHAIRMAN BRASS: Doctor D'Agostino.

DOCTOR D'AGOSTINO: I want to make sure I understand this question. This question is saying the data that was accumulated over the years, in addition to the study we just looked at, the hemorrhagic stroke project.

CHAIRMAN BRASS: That is correct.

DOCTOR D'AGOSTINO: Right. And so that being the case, the idea of gathering a fair amount of

data on spontaneous reports and other sources and then actually putting the study together, that in a very real way confirmed what was being shown with a lot of the spontaneous data and other collected data I think is a very compelling scenario.

CHAIRMAN BRASS: Doctor Johnson.

DOCTOR JOHNSON: Yes. I agree that it's sort of the consistency of the data, the case reports led to this study and the results really sort of fell out the way that it might have been anticipated. But also, as Doctor Sachs mentioned, some of the data about other drugs, comparisons with other drugs, both in the spontaneous reporting system and also within the HSP Study where there didn't seem to be associations with other drugs, those things all together really just sort of strengthen the evidence in my mind.

CHAIRMAN BRASS: Other comments about that. Would somebody, because the issue has been raised multiple times, comment on whether or not the nature and limitations of the spontaneous reporting base database influence your confidence in those other data sets as we address this question? Doctor Cantilena, would you comment on that, please?

DOCTOR CANTILENA: I think you're still

trying to punish me for the break. I would say that I think this is an example of where you see something that might be a signal in the spontaneous system, and then you go ahead with the HSP Study which I view for the subsets that we've already discussed as confirmatory of signal. But I guess I get uncomfortable when people want to hold up the spontaneous reporting system or MedWatch, as it's now known, as strong evidence for there not being a problem. I just think it's not as sensitive as some of us have heard, but I think it certainly was used appropriately, in my opinion, in this setting where we spotted something, we thought it was a signal and then we went ahead with the HSP Study.

CHAIRMAN BRASS: The other issue related to this that I'd be interested in some comments on, particularly from our neurology consultants, is the issue of biologic plausibility, that again, when one is trying to build the pieces together, it has been suggested by some that there is and by others that there's no biologic plausibility for an association between phenylpropanolamine and hemorrhagic stroke. Would one of our neurologists comment on that, please.

DOCTOR GILMAN: May I comment on the previous question?

CHAIRMAN BRASS: Most certainly.

DOCTOR GILMAN: The reported data on association of hemorrhagic stroke with PPA use is not only just suggestive. I think it must be vastly under-reported for many reasons. The principal reason is because it's not that easy to report for second. In today's hospitals, there is enormous pressure to see patients. Getting a full history of all drug exposures is difficult, time-consuming, and one has to keep in mind that PPA may not necessarily be the drug on a clinician's mind when one sees a young person with hemorrhagic stroke. There are many other issues. Is the patient going to herniate? Do I need to watch this patient, put the patient in ICU, etcetera, etcetera? Do we call the neurosurgeon? Is this a berry aneurism that may need treatment? There are many, many other issues. So I think the fact that there are so many reports is very strong suggestive evidence.

CHAIRMAN BRASS: What about the issue of biologic plausibility?

DOCTOR GILMAN: Well, I commented on this a bit earlier. What we have in common is a hemorrhagic diathesis affecting the brain, the blood vessels of the brain. Those vessels, some of them,

are outside of brain substance itself. That is, in the Circle of Wil or some of the arteries that are on the surface of the brain which account for the subarachnoid hemorrhage component of this. Others are within the substance of the brain and that includes arteriovenous malformations. In other words, three somewhat different kinds of pathologies are implicated.

So the biological plausibility that comes to my mind is that there is some factor related to clotting of blood or to hemorrhaging of blood, perhaps something related to blood pressure levels or some other phenomenon. But yes, it is entirely biologically plausible because I can think of a common mechanism accounting for all of these three different kinds of hemorrhagic stroke pathologies.

CHAIRMAN BRASS: Any other comments or observations? Doctor Hoffman.

DOCTOR HOFFMAN: Can I just comment as a person who directs a hypertension clinic. I find some of this a bit difficult to grasp. There was a comment made that perhaps there was no dose response relationship because only a tiny amount of PPA would be necessary to rupture an aneurism. In the blood pressure studies that I'm familiar with, the typical

responses in blood pressure to PPA were very small. In some studies have been negative. We should all remember that in the day-to-day affairs our blood pressure may fluctuate 50, 70 or 100 millimeters of mercury. So I find it a bit difficult to grasp how one could be so confident that potentially very small or nonexistent changes in blood pressure due to PPA would ultimately lead to a stroke.

And I'd like to comment on the issue of hemorrhage. I think it's well known from the work of Walter Cannon in the 1930s that part of the stress report mediated by catacholamines is actually to have subtle effects to make the blood easier to clot. These are from the days when we confronted sabre-tooth tigers. I'm ont aware of any evidence that catacholamines would promote hemorrhage.

CHAIRMAN BRASS: I think one of the issues that confounds both sides of the statement are that we're clearly dealing with a very rare event and that we're not dealing with a predictable blood pressure response. And then I think it was in the FDA presentation that we do not have a large enough database to identify whether or not there's a subset that response to PPA exposure differentially with respect to either blood pressure or even selective

cerebral hemodynamic effects. And so I think that is clearly why it doesn't happen to everybody who takes PPA.

The question though remains whether or not there may be mechanisms which apply to a rare individual who's susceptible, either because of their CNS anatomy, an underlying risk factor, or a differential population response to the exposure.

DOCTOR HOFFMAN: I think that's certainly true, and you can't exclude that. But it is interesting, as far as I know, in many people who study autonomic nervous system, sympathetic function, basal constriction and so forth, not particularly with PPA. As far as I know, these types of individuals have really not been described, at least as far as I'm aware.

CHAIRMAN BRASS: Doctor Cantilena.

DOCTOR CANTILENA: I guess I would just follow with at comment that while we're in essence trying to extrapolate the results of extremely closely controlled, clinical setting in terms of the hypertensive response from the product, I think that this again is sort of an actual use, all comers, and when someone pops their diet pill and goes home or is on the way home and someone cuts them off on the

highway or their two year old pitches a fit on the kitchen floor, which happened to me this morning, it's sort of the issue of how does it actually fit in?

So I think that if even a small increase in the average in the clinical study, in that average there are clearly outliers and then if you have that individual in an actual use out of the hospital or out of the Phase One unit setting, you can certainly see that it's possible that you can have an exaggerated response.

DOCTOR HOFFMAN: I don't want to be argumentative, but pharmacologically that's not an obvious conclusion because in some animal studies which have been more extensively done than in humans, PPA is a partial agonist. So in the setting of low autonomic function, partial agonist may tend to raise blood pressure but in the setting that you described of stress and high activation to sympathetic function, one could predict that the hypertensive response would be blunted. I mean that's the logic behind partial agonists for beta receptor antagonists. They may even raise heart rate at rest but blunt rapid heart rate that occurs with exercise.

So I just comment that I don't think it's a foregone conclusion that that's what would happen.

DOCTOR CANTILENA: Certainly I understand your comment, but I think when a lot of the data sort of points at the first dose and perhaps those effects happen after tolerance, I also think the whole issue of drug/drug interactions, which are not controlled for in an actual use study, is significant. So I'm not as familiar with the data as you are, but I would hazard a guess that there could be settings in the actual use which that's not the case, and that's the whole point of my comment.

DOCTOR HOFFMAN: Yes, thank you. Can I just make one comment. The issue of tolerance to PPA has been referred to very extensively. I was just curious to what data people were referring to when they use that to explain plausibility of a first dose effect.

DOCTOR BLACKBURN: I'm George Blackburn from the Harvard Medical School, and I did do a first dose study, large study of 881 healthy individuals published in *JAMA*, and we did find that the independent factor of PPA was less than four millimeters, even though, as you point out, 10 percent of the population had a large response but it was equally distributed for all this fright that you talked about. It was during the placebo, the 25

milligram given three times and the sustained release and other determinants were base-line blood pressure in these individuals and individuals who were higher BMI.

So it does support that, you know, there is some defense that there's a large indigenous autonomic sympathetic tone at the time you take the first dose and so there is an even distribution and we had, using Yates analysis, we could find that the age, the gender, the BMI were the major contributors to this area and then followed by the baseline blood pressure and only less than four millimeters could be independently attributed to PPA.

CHAIRMAN BRASS: Thank you.

Are there other comments about question C before we put it to a vote? Doctor Gilman.

DOCTOR GILMAN: I just wanted to comment that what we're talking about now is the reason for going into Phase IV clinical trials because after one has completed a Phase III double blind placebo controlled trial to see the effects of a drug at a particular population against placebo, one wants to know what this drug is like in the real world when given to people who are taking polypharmacy at times including people who may have untoward reactions to a

drug and there may be one person in the 100. In this situation, it may be just those people who have a berry aneurism or just those people who are quote "ready to have their stroke" in various other ways.

CHAIRMAN BRASS: Other comments. If not, we will now vote on Question C which I will read again. There is a body of data collected over the years that has suggested a possible association between PPA use and hemorrhagic stroke. Taking all currently available information into account, do the data support the conclusion that -- so you can vote for either 1) that there's no association, 2) there is an association, or 3) that the association still remains uncertain. All those who feel that there is not an association, please raise your hand.

All those who feel that there is an association, please raise your hand.

All those who feel that the association still remains uncertain, please raise your hand.

DOCTOR TITUS: There were zero votes for no relationship, there were 13 yes associations and one uncertain.

CHAIRMAN BRASS: We now move on to Question D. Considering your answer to Question C, can PPA be considered to be generally recognized as

safe for use as a decongestant, an appetite suppressant? When answering this question, please address whether dose is an important consideration. Maybe I'll start the discussion this time myself because the issue of dose is, I think, an interesting one. While we concluded that we could draw no dose conclusion from HSP, that in the same way we lumped the data when we look at the spontaneous reporting base and the HSP, one might be concerned that in fact there is a dose relationship that does exist though clearly the data do not provide sufficient evidence to make that conclusively.

The other point I'd like to make is actually taken off one of Doctor Ganley's slides actually, is that no drug is absolutely safe and that we have a number of drugs that are available over the counter that we know are associated with rare adverse events, some of them very serious. We know that there are even more drugs available which, when taken other than as directed by the label, particularly in excessive doses, may be associated with serious adverse events so that the definition of generally recognized as safe I think isn't just out of a vacuum but it's against a background of risk and, while the question isolates that from the efficacy concern with

the degree of efficacy that may exist, ultimately I think the decision is going to have to be made on a risk to benefit ratio.

So while our discussion will focus on risk, I think it's important to recognize that we're not talking about absolutely safe but trying to provide some context for whatever safety concerns we have, both with respect to what's been generally acceptable as safe in the past as well as any issues that are unique to this product.

Doctor Johnson.

DOCTOR JOHNSON: I guess for me the issue of risk/benefit is what really sort of makes this whole question easy. The way I view this -- and I'll do decongestant and then appetite suppressant -- is that what does the consumer lose if this product is taken off the market? There are a lot of other decongestants. I understand that the members of CHPA are going to lose money, but that's not really our concern. They are marginally effective drugs, I think, for problems that aren't life-threatening, and so there really are no huge long-term outcome benefits such that really I think any degree of risk becomes much less tolerable.

And so in both the situations, I guess I

view this risk, even though it's rare, as being one that is not upset by benefits because I view the benefits of this product as fairly marginal.

CHAIRMAN BRASS: Doctor Gilman.

DOCTOR GILMAN: I agree with what Doctor Johnson said, but just specifically to address the issue of appetite suppression. Doctor Schteingart showed us what an effective drug PPA seems to be over the short-term. I asked him during the break -- I don't know if he's still here. Yes, he is. -- what is the long-term outcome with those patients, and his response was, well, 95 percent of people who take medications for weight loss wind up with the same weight back again within some years. There has, however, been no study -- I believe I'm quoting him correctly -- there's been no study on the efficacy of PPA over many years. Say five years, six years, 10 years.

So I agree with what Doctor Johnson said. The benefits are marginal and short-lived with respect to weight loss and, for decongestants, I agree there are other products that are equally good.

CHAIRMAN BRASS: If you'd like to comment, please come to a microphone.

DOCTOR WALSON: Yes. I'm Doctor Phil

Walson from the University of Cincinnati, and I'm a paid consultant for CHPA. Well, I'm tempted to say a lot of things including the fact that it's difficult to comment on something when I personally think you're mixing up causation with association. 1) you're making assumptions from a study that clearly wasn't powered or designed to answer certain questions. For example, in the population I represent, you wouldn't even bother to include them. That is, children. And they all go to those hospitals where you were collecting data.

I'm also a medical toxicologist and I'm appalled that you could even talk about collecting data on cocaine use without something we can measure months past exposure reliably.

CHAIRMAN BRASS: If you could focus on the question.

DOCTOR WALSON: I'll focus on the question. But it does all come down to risk and benefit, and you made the comment. One is that not everyone responds to any decongestant, one, and I want to go back. There were two points on Doctor Ganley's slide and one is that there are benefits to consumer accessibility to short-term medications that offer symptom relief. I don't want to get off on weight

control because I think it would be better to stick to decongestants. And these products, I am worried that when you do remove them you are forgetting a risk and that is what are your consumers going to turn to? And we're already seeing them turn in both cases, you're going to see them turn to products that are neither regulated, quality controlled nor studied at all. At least this product does have data showing it's efficacious for short-term use. That is true for both, and you're going to turn patients to ephedra compounds. You're going to turn them to other things.

So I think that to say there's no benefit, I think you have to weigh risk and benefit. That's what you're doing --

DOCTOR JOHNSON: I didn't say there was no benefit. I said I believe the benefit was marginal and that, particularly for cough and cold, there were other acceptable products on the market.

DOCTOR WALSON: Yes, there are other choices, but one of the things that I think consumers would tell you is that -- and I don't have the plausible explanation -- that some consumers prefer one product to the other. I'm not sure that the other products on the market are either more effective or safer. So I think that, at least in terms of patients

that were not included in the study, which this study speaks nothing to. I mean the reason they didn't do children is because their own data, including the FDA data, would show that any adverse event in childhood is so rare that they would never have been able to power any study to find it so that I am concerned about the population that I represent, that at least you need to make sure that you don't deny our pediatric population access to something that wasn't even studied.

CHAIRMAN BRASS: Doctor Schteingart, you wanted to make a very brief comment, please.

DOCTOR SCHTEINGART: Yes. I'd like to make the comment that it's been well agreed that obesity is a chronic, serious medical condition. It's not a benign condition and that treatment actually has major improvement in the co-morbidity associated with obesity. There is no effective long-term treatment of obesity. There is usually a combination of the things I mentioned before: diet, exercise, behavior therapy, and medication. I use medication as an aid in helping the patients actually stay on their diets, even for moderately shorter periods of time. We don't have treatment that has been validated for long-term use like it's been for hypertension or diabetes, which are

extremely effective in normalizing whatever the treatment is supposed to normalize.

However, for short periods of time, the administration of appetite suppressants or any other anti-obesity drugs can help the patient lose enough weight to improve their co-morbidities and also to help them behaviorally continue to adhere to a weight reduction program. But it's true, as Doctor Gilman has indicated, there is no validated long-term use for PPA because that's not the way it's been approved by the FDA. Not, for example, the way that cybutramine or orlistat have been approved for indefinite use.

CHAIRMAN BRASS: Part of the consideration, in my mind, for generally recognized as safe, as I indicated earlier, relates to the use as per the label. And to the degree that information could be placed on a label which would mitigate the risk, that I think becomes an important consideration.

Now, having posed that, I'm concerned that whether there is or not on the basis of two things. First of all, we have failed to identify any clear sub-groups that we identified them, other than women, but that we could steer use away from and 2) this has, to my eye, provided a very interesting actual use study on how consumers use products and this label

clearly says "Consult your physician if you have high blood pressure" and we ended up with a cohort that was quite rich in hypertensives. And so the degree to which if a label warning, even if one could conceive of an effective one, the degree to which it actually would be effective in steering away at risk populations would remain a concern in my mind.

Yes, Ms. Cohen.

MS. COHEN: I was referring to the FDA report on page eight and nine and talking about 75 milligrams and what happened as a result of that, and I am concerned because I did look at the label and the label, I will repeat myself and forgive me, for 12 years old and older and adults, twice a day they can take 75 milligrams twice a day. That's 150 milligrams and, if we're worried about consumers over-dosing, this really boggles my mind.

In terms of I would like to respond to the pediatrician. Advertising, advertising, advertising. So when you talk about what consumers buy, it's the one that's advertised the most or on the shelf or where they place it on the shelf. So I don't know how much -- goes on in a pharmacy when you go to buy a cough medicine. I bought one yesterday and, believe me, I read the label. But I've had some experience

reading this information. So I think this report, I am satisfied with the statistics and what's been done and I'm satisfied that as a result of 75 milligrams there's a good chance for hemorrhagic stroke and really, 150 milligrams just boggles my mind.

CHAIRMAN BRASS: Other comments from the panel with respect to Question D?

DOCTOR SACHS: As a pediatrician, I actually have a different interpretation of some of the information that you presented. I think there are very good studies in children that show these medicines are safe and effective or efficacious to begin with and that if you look at placebo controlled studies and also studies that look at duration of cold symptoms, the colds last 10 days if you take something, they last 10 days if you don't take something. The placebo effect is very great. I know in our population when we talk about over-the-counter remedies for cold and cough, we actively discourage them.

One other reason which was not really emphasized today was the risk of arrhythmias, especially in children who receive some of these things. So now having read all the background data and all the HSP Study data, I mean even though the

incidence of stroke in a young person is rare, I would be greatly concerned about adolescents who might choose to use these as either cough and cold remedies or appetite suppressants, particularly in the populations that might be on OCPs. I mean you start having to label and label and label. That becomes superfluous.

DOCTOR WALSON: Let me respond. A lot of things. One is that, briefly, it's for short symptomatic control and it's relative to -- I'm sure you also counsel against use of antibiotics but the fact is if a child goes to a physician, the odds are overwhelming they will get an antibiotic for a viral infection. That has been shown. If the child can stay home, to not visit your office, they will decrease it. So there is in fact a benefit and that's been shown in terms of symptomatic relief, even though I also don't use them when someone gets to the hospital. So I think that's important.

The second thing. I think that there's an assumption in your comment about dose that's really not shown out and that is the risk goes down with age, not up, despite the fact that the doses may not go down very much, and that's because children in fact are resistant. I also ran a pediatric hypertension

lab. They tolerate blood pressure changes different.

And then one final comment. I'm a little concerned with this call of first time use because I'm not sure there are too many children who make it to 18 without a use of one of these products.

CHAIRMAN BRASS: First time use was not defined as first life time use.

DOCTOR WALSON: Yes, I know.

CHAIRMAN BRASS: Doctor Cantilena.

DOCTOR CANTILENA: Just to comment in terms of Doctor Ganley's slide where he asked us to consider the dose issues. I think, as I commented before, sort of when you look at the dose that, at least in our study, seems to cause trouble, it's not several-fold over the recommended dose. So again sort of getting back to the point of margin of safety. I think the cases that we've seen and the cases that we heard about from the spontaneous reporting are not massive overdoses. We're really talking about individuals who I frankly don't understand who they are. They're obviously females but in terms of how come they get in trouble, I mean I obviously don't have a clear idea of why that is. But I think the key for me is that they're not significantly out of. It's really we're talking about one or two extra pills.

Clearly, the other sort of alarming issue is even though the label seemed to be in the right format, if that was the same label that was in effect during the study, it doesn't seem to be extremely effective and I think that's a significant concern.

CHAIRMAN BRASS: Other comments before we put this question to a vote? If not, the question on the table is considering your answer to Question C, can PPA be considered to be generally recognized as safe for use as, first, a decongestant? The answer will be yes or no. All those who think that it can be generally recognized as safe for use as a decongestant voting yes, please raise your hand at this time.

Abstain is an option this time. All those who feel the answer is no, please raise your hand.

All those abstaining, please raise your hand.

DOCTOR TITUS: We have zero for yes, 12 noes and two abstentions.

CHAIRMAN BRASS: Same question for appetite suppressant. Considered generally recognized as safe for use as an appetite suppressant. Voting yes, please raise your hand.

Voting no, please raise your hand.

Abstaining, please raise your hand.

DOCTOR TITUS: For appetite suppressants, there were zero for yes, 13 noes and one abstention.

CHAIRMAN BRASS: Thank you. The next question is a little too open-ended for me. Who knows what may come up? But anyway, we'll ask it. Does the committee have any additional recommendations? Let's try to limit it to PPA.

Are there issues from the agency that we haven't touched on or that you'd like to see expansion of the discussion on?

DOCTOR DELAP: No. Thank you very much.

CHAIRMAN BRASS: On that basis, I'd like to thank all who participated in the discussion today. The presenters did an excellent job of staying on time. Thanks to all the committee members, and we are adjourned.

(The meeting was concluded at 3:57 p.m.)

C E R T I F I C A T E

This is to certify that the foregoing transcript in the matter of: MEETING ON SAFETY ISSUES OF PHENYLPROPANOLAMINE (PPA) IN OVER-THE-COUNTER DRUG PRODUCTS

Before: FDA / CDER / NDAC

Date: OCTOBER 19, 2000

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis