

1 conditions or Parkinson disease for two weeks after
2 stopping the MAOI drug. If you do not know if your
3 prescription contains an MAOI, ask a doctor or
4 pharmacist before taking the product. Ask a doctor
5 before use if you have high blood pressure, thyroid
6 disease, heart disease, diabetes, glaucoma, or
7 breathing problems such as emphysema or chronic
8 bronchitis, difficulty urinating due to enlargement
9 of the prostate gland or have been reading too fast.

10 (Laughter)

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

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

15 CHAIRMAN BRASS: Please.

16 DOCTOR SOLLER: I will mention that FDA
17 has proposed labeling and that the products that
18 we've reviewed have essential elements of that
19 labeling and, ma'am, we take this labeling very
20 seriously. It's important that it be driven by the
21 information that we have. I think it's relevant
22 that there is a statement that tells consumers not
23 to take more than the recommended dose and it's
24 accompanied by a statement that says taking more can
25 be harmful.

26 For PPA weight control products, there's

1 a statement that it shouldn't be used by people
2 under 18 years of age. There are statements about
3 appropriate drug/drug interactions that should be
4 looked out for and potential contraindications. And
5 that's not unlike other labeling in other categories
6 of OTC medicines. It's entirely consistent in its
7 construct and the kinds of concepts that are being
8 conveyed to consumers.

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

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

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

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

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

22 CHAIRMAN BRASS: Doctor Soller.

23 DOCTOR SOLLER: Well, Lou, I would have
24 to look side-by-side, but I can say to you that I
25 think it's probably the same one that was going on
26 when the study was initiated. You're asking me to

1 look at what's here and comparing up there. What it
2 looked to me was the one that was on the major PPA-
3 containing products, national brands as well as the
4 house brands. I mean if you want me to take a look
5 more closely and report back to you during this
6 meeting, I can do that.

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

10 DOCTOR SOLLER: Basically they were
11 there. Yes.

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

16 DOCTOR SOLLER: I would say reasonably
17 similar for the major brands and at least one of
18 those had something that was in drug facts-type of
19 format. The house brands and at least one other
20 national brand was not in that kind of format, so
21 there were differences in the labeling and it was
22 not across the board entirely consistent with what
23 was proposed by FDA, the reason that we suggested
24 that there be a push to standardize that particular
25 labeling. When that happens, it would also be
26 standardized into the format that I know you're

1 familiar with, the panel ANDAC has reviewed, that's
2 the new OTC label format.

3 DOCTOR CANTILENA: Okay. Thank you.

4 CHAIRMAN BRASS: Doctor Elashoff.

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

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

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

23 CHAIRMAN BRASS: Does that elicit any
24 comment? I just want to follow up I think on
25 something that Doctor D'Agostino was suggesting and
26 actually was prompted by the comment from the CHPA

1 group, and that is I endorse the concept that one
2 has to be very careful about getting into sub-group
3 analyses and to the degree they can be helpful,
4 that's fine but when the sub-group analyses get even
5 smaller, people are concerned about the small
6 numbers in the primary end points which were
7 prospectively defined adequately powered to address
8 those issues and then confuse how sub-group analyses
9 aren't clear. I think that's not surprising and,
10 while it is okay to talk about them, I think that
11 one has to focus the primary conclusions on the
12 primary hypotheses that were posed by the study
13 which, in fact, included women prospectively as a
14 sub-group and the general population and the degree
15 to which confounders were not balanced, one has to
16 rely on overall general principles to assess whether
17 or not they mitigate the response.

18 DOCTOR D'AGOSTINO: Again, I think the
19 issue is that if this were a clinical trial in other
20 settings or epidemiologic case control, you say you
21 look at the global and then you look for consistency
22 across the sub-groups. You don't look for
23 statistical significance across the sub-groups. I
24 think the concern that's being raised is that some
25 of these sub-groups and some of these variables,
26 these confounders, may be what's driving the

1 analysis. When you look at the sub-groups, none of
2 them are inconsistent but we don't have the ability
3 to perform a test that, as Janet just said, it's
4 going to be everyone's satisfaction. But I think it
5 is a good point to bring this back to what the study
6 was designed to actually do and see what happens at
7 that level.

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

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

12 DOCTOR KULLER: Can I make a comment?

13 CHAIRMAN BRASS: Please.

14 DOCTOR KULLER: I think there's two
15 questions here which still need to be resolved.
16 First, this man/woman situation. The use of PPA in
17 the control group in the men and the women is
18 exactly the same. It is not statistically
19 different. It is not low use of PPA in the men, and
20 the number of cases in the study is very similar for
21 men and women so that yes, subarachnoid hemorrhage
22 may be more common, as we know, in women but in this
23 study, the number of cases in men and women is not
24 terribly different and the use of PPA, especially if
25 you exclude the use in obesity drug, is 2.5 percent
26 versus 2.1 percent in the controls.

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

6 The second problem, which hasn't been
7 resolved and was pointed out by Doctor Daling a few
8 moments ago, is that internally the study is superb
9 but I just don't understand how one can resolve the
10 issue that the controls are almost the same as
11 basically going on a street corner and asking people
12 whether they took PPA or not. I mean when you have
13 that small a control group, when you have to make
14 100 and some phone calls to find one potential
15 control and then only one out of three who you
16 actually find ever get into your study, I don't
17 understand how you can possibly interpret the
18 control group in terms of the use of PPA when the
19 whole study is based on eight cases that use PPA
20 versus five controls. This is not a twelve-fold
21 risk across the population. It's eight versus five,
22 and when you have that much of a problem with
23 selection of controls, even though the rest of the
24 study is superb and it is and everything they talked
25 about and the FDA presentation, we all agree. But
26 the problem is you still have the controls are just

1 like doing a survey by asking people on the street
2 who you're going to vote for or what do you think of
3 something. That's not the way we do studies and,
4 when you have that problem, it's almost impossible
5 to interpret the results.

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

10 DOCTOR KULLER: It's 2.5 percent versus
11 2.1 percent if you exclude the women who were taking
12 the appetite suppressant and, if you don't, then
13 it's 2.7 versus 2.1 and that is not even close to
14 statistically significantly different. It is
15 strikingly different among the cases. 5.1 in the
16 women and 1.9 percent in the men, but that has
17 nothing to do with PPA in the community. It has to
18 do with the use of the drug in male cases versus
19 female cases and the number of cases is 319 men and
20 383 women in the study. So it's not a function of
21 there aren't any men in the study. This is not a
22 power issue in men. It's a very interesting
23 observation that men are essentially protected and
24 women basically have what's reported to be a risk in
25 the study. But you can't attribute this to low use
26 of PPA in men or basically to not enough stroke

1 cases in the men to interpret the data.

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

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

22 DOCTOR KULLER: But Ralph, you have to
23 admit you only have four women who are first
24 exposures in the controls, also, so you have one man
25 and four women in the entire study and that would be
26 a little shaky in terms of interpretation. There's

1 only four women in the control group that are first
2 users and there's one man, so that's your entire
3 presumption.

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

13 DOCTOR HORWITZ: I've learned over the
14 years not to try and get into a dispute with Doctor
15 Kuller. The emotion would be high and the stakes
16 would be low, I'm sure. I did, however, want to
17 point out that when we said with regard to first use
18 in women the .5 percent, Doctor Daling, that we had
19 referred to earlier had to do with the expected
20 exposure prevalence for first use among women of .5
21 percent. You may feel, Doctor Kuller, and I
22 understand that, that the four exposed women in that
23 category represents a small number. It was the
24 anticipated number that led to the sample size
25 estimation that .5 percent was what we anticipated
26 from the market data, that .5 percent was what we

1 found in actually conducting the study. Those four
2 exposed controls-- you and I may wish there were
3 more -- nevertheless were the basis for the sample
4 size estimations that we used in the planning of the
5 study.

6 CHAIRMAN BRASS: Doctor Gilman.

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

12 CHAIRMAN BRASS: Doctor Blewitt.

13 DOCTOR BLEWITT: I propose that we go
14 back to your question, question A, and I'd like to
15 step back from all the details of this issue and
16 just make a few comments if I may. First, it's my
17 belief that the study results are not conclusive.
18 Now, that's not to say, however, that there isn't
19 useful information that can be potentially gathered
20 from a study of this size. I personally don't think
21 that we're going to-- for the committee's sake, I
22 don't think we're going to resolve the
23 epidemiological and statistical debate that's been
24 going on here. It's just not possible, particularly
25 where the data are described as fragile, some of the
26 results appear to be inconsistent.

1 My own reading, general reading of it,
2 not being an expert, is that I really felt that the
3 populations differed significantly as to make them
4 non-comparable. I felt that comparing hospitalized
5 versus non-hospitalized was not wholly appropriate.

6 I felt that the cases differing significantly on
7 seven different factors was important. I felt that
8 there was a substantial difference in the patterns
9 of use of the drug in cases in controls and so
10 forth.

11 So my approach was to basically pretend
12 that 27 cases were brought to me to take a look at,
13 27 charts, and say what do you think about these?
14 There's a concern that maybe phenylpropanolamine is
15 the culprit in all of this, and give us your
16 feeling. And my approach to that would be to take
17 each of the cases and to look at the dose that was
18 given, the timing of the dose, what concomitant
19 medications might be taken, what concomitant disease
20 states might be present and the general
21 demographics.

22 And so I went to page 37, Table 6 here,
23 and without getting into too much detail because I'm
24 not looking at hospital charts. This is the study
25 report manuscript. But just in what I could perhaps
26 gather from looking at this chart compared to what I

1 might be able to get if I were able to look at the
2 cases in some depth and I found that if I looked at
3 the case group, there were, in addition to what's
4 been said about smoking and hypertension and so on,
5 a lot of cases where the dose in three days was
6 exceeded. I see a 600, I see an 890, a 480, 640,
7 600. I see the last dose in some cases being 150,
8 150, 150. I also see one which is low as 20.

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

25 CHAIRMAN BRASS: Doctor D'Agostino.

26 DOCTOR D'AGOSTINO: I think what was

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

22 And so what I'm suggesting is that let's
23 remember that this was a case control study that was
24 prospectively put together and I think we need to
25 look and we should look at how the hypotheses played
26 out and then certainly for interpretation, if we

1 think there's a relationship, to do exactly what you
2 said. I think we have to be compelled to do what
3 you said.

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

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

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

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

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

7 CHAIRMAN BRASS: Thank you.

8 Doctor Cantilena.

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

22 So I think the way I'm hearing you, I just
23 wanted to ask you to clarify that because, as I see
24 it, this is really sort of telling you that perhaps
25 the safety margin is not as it should be if you can
26 just exceed the dose really slightly by a factor of

1 two to two and a half, I guess, in the column for
2 the dose in three days and still end up here on the
3 list. I mean we're talking about an over-the-
4 counter and it's, in essence, sort of an actual use.

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

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

26 The reasons why non-participation is of

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

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

20 CHAIRMAN BRASS: Doctor Kittner.

21 DOCTOR KITTNER: I think everyone agrees
22 that the study was well-designed and I heard a
23 statement that it was not well-executed. I think
24 that there's no consensus that I've heard around the
25 table that it wasn't well-executed. In fact, I
26 think that if we were to repeat this study and spend

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

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

21 Ms. Cohen.

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

25 CHAIRMAN BRASS: I'm sorry. Only things
26 related to the HSP interpretation.

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

7 CHAIRMAN BRASS: Other comments about
8 the HSP.

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

13 CHAIRMAN BRASS: That's correct.

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

16 MS. COHEN: Thank you very much.

17 CHAIRMAN BRASS: Yes.

18 DOCTOR WARACH: I do have a reservation
19 about the conclusion of the association with the
20 hemorrhage risk for two concerns. One is the
21 problems with adjuster controlling for all the
22 potential reasonable and relevant confounders. The
23 other one that had been mentioned only slightly in
24 passing earlier today was the problem with self-
25 report with regard to cocaine or other illicit drug
26 use and cocaine is a recognized risk factor for

1 hemorrhage. It's likely to be unreported. Perhaps
2 even more so in the group that suffered the stroke
3 and is feeling a bit guilty about their abuse
4 behavior. So I think the study is very suggestive
5 of this association, but I have that reservation and
6 I would say it's ultimately inconclusive on that
7 point.

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

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

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

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

25 To the extent that it was designed to
26 answer a specific question in the overall population

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

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

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

21 DOCTOR NEILL: Okay.

22 CHAIRMAN BRASS: So I really want to
23 stay--

24 DOCTOR NEILL: Can I move on to my third
25 comment then?

26 CHAIRMAN BRASS: Thank you.

1 DOCTOR NEILL: You can just let that
2 float in the air. With regards to the small numbers
3 that makes it so difficult to control for
4 confounding in men and lack of men using appetite
5 suppressants, I saw some data that suggested that
6 the overall use in the general population is
7 overwhelmingly for cough/cold preparations and I
8 haven't heard anybody comment on what seems to be
9 the massive over-representation of hemorrhagic
10 strokes occurring in people using it for appetite
11 suppressants. I don't have an explanation for why.
12

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

18 DOCTOR SOLLER: Doctor Brass, just
19 quickly. I think what's important here relative to
20 the scientific documentation in that standard is
21 really what we heard a little bit earlier, that
22 maybe there's not an evidentiary standard for
23 safety, that it more becomes well, subjectively, how
24 do I feel about this data set? And I think what the
25 policy does, it drives us to a much more rigorous
26 view of that.

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

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

23 DOCTOR DELAP: I think the discussion
24 has been a very good one, and some of the salient
25 points that I've picked up are that the numbers of
26 events on which you're basing a conclusion of an

1 association are relatively small. We knew that that
2 was going to be the case going in, I think, when the
3 study was designed because power was at the margin,
4 even with this fairly ambitious study. I've heard
5 the discussion that it's hard to analyze
6 satisfactorily for confounding in a setting where
7 you don't have so many events to base those kinds of
8 analyses on. I think we hear that, as well.

9 We're looking at this again from the
10 standpoint of we had some concerns in the early
11 '90s, particularly about women, particularly about
12 weight control products, and this study grew out of
13 that. So we'd like to have your answers as to how
14 we should interpret the results of this study in the
15 setting of all the information that's led up to
16 today.

17 DOCTOR HENNEKENS: I wanted to respond
18 to Doctor Neill's comment about the overall results.

19 I believe that if one sets aside the concerns that
20 you have a 35 percent articulation rate in controls
21 and an inability to control confounding, especially
22 in the sub-group analyses, if one looks at the
23 overall test of the hypothesis of whether taking PPA
24 for either cough or cold suppression or appetite
25 suppression is associated with risk of hemorrhagic
26 stroke, the overall analysis, to my thinking, is

1 based on 27 versus 33, and that is not statistically
2 significant.

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

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

22 DOCTOR NEILL: I guess one other point
23 that was brought up several times is that in
24 addition to the very low response rate, there's this
25 unaccounted for dead folk who obviously, by their
26 absence, would tend to make it more difficult to

1 show an effect which is why I remain impressed that
2 there is an effect that's demonstrated despite their
3 absence.

4 CHAIRMAN BRASS: Doctor Gilliam.

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

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

21 Doctor Gilman.

22 DOCTOR GILMAN: I think it's a good idea
23 to go back and take an omnibus position now because
24 this is a trial that was conducted prospectively
25 with a set of hypotheses to test with case control
26 methodology that was superbly followed and the

1 result was significant. As I see those data, they
2 are significant. It's not a feeling. It is what
3 the data show me anyway. So I'm not troubled, as
4 some people in the room seem to be, by the quote
5 "small numbers." They were predictably going to be
6 small numbers. We have what was predicted at the
7 very beginning of the design, and so it should be no
8 surprise to us now that we're dealing with small
9 numbers, but the numbers show a significant risk for
10 hemorrhagic stroke, particularly among first users
11 and in women.

12 CHAIRMAN BRASS: Doctor Katz.

13 DOCTOR KATZ: I agree the point of which
14 was the primary outcome and adjusting for multiple
15 comparisons. These are very important issues and we
16 worry about them all the time and overall, given one
17 of the so-called co-equal outcomes, it didn't make
18 it nominally statistically at .08 I guess was the
19 thing. But as Doctor La Grenade said earlier, I
20 just want to reiterate this point. Apparently from
21 the point of view of the FDA, even though there were
22 technically three or five co-equal outcomes
23 apparently, I'm told that the one outcome in which
24 the agency was specifically interested in as the
25 ultimate primarily-- if I can speak for the team and
26 I really shouldn't, they're here, they can speak for

1 themselves -- was the sub-group in which the
2 statistically significant finding emerged. In other
3 words, women taking it as an appetite suppressant.
4 And that finding, if you consider that to be the
5 primary, if you believe that, holds up to any sort
6 of -- pretty much holds up to any sort of reasonable
7 adjustment procedure for the p-value.

8 CHAIRMAN BRASS: Doctor D'Agostino.

9 DOCTOR D'AGOSTINO: I think that it's
10 been over and over again and those who are aware of
11 the history know that it's exactly what you just
12 said. You can argue on the other side is that the
13 investigators put a study together and they came up
14 with five hypothesis and gave them all equal weight.

15 I would argue, even in the light of them giving it
16 all equal weight, those significant values using .05
17 as the cut-off can't be ignored.

18 CHAIRMAN BRASS: Okay. I'm going to try
19 to synthesize some questions that we can actually
20 vote on. Before we start, I want to remind
21 everybody that Doctors Warach, Blewitt and Kittner
22 are not able to vote though they're able to
23 participate in the discussion. And all the
24 questions are going to have the following form.
25 They're all going to be about the HSP Study. I'm
26 going to follow my own rule. And there's going to

1 be three options on each question.

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

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

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

22 DOCTOR TITUS: There are 13 --

23 CHAIRMAN BRASS: Thirteen. Well, I'll
24 read it at the end.

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

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

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

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

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

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

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

22 CHAIRMAN BRASS: Next are women 18 to 49
23 using any PPA product on first exposure. Okay. Is
24 that clear? First use risk in women regardless of
25 product class. Okay? All those who feel the
26 product is safe in that group, please raise your

1 hand.

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

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

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

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

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

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

22 Doctor D'Agostino.

23 DOCTOR D'AGOSTINO: You want us to vote
24 on the women data, the female data, overwhelming the
25 combined data?

26 CHAIRMAN BRASS: That could be an

1 interpretation of what I just said because I think
2 that, again, in terms of the compilation of the
3 data, one of the hypotheses were all exposure.

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

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

19 Doctor Gilman.

20 DOCTOR GILMAN: I have concern about
21 doing this though. This is the reason that I
22 suggested that we just eliminate men from the
23 beginning. The problem is that we have a set of
24 hypotheses driven by the principal question which is
25 about women and stroke and, accordingly, the study
26 was designed with that in mind and now, since there

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

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

25 DOCTOR DELAP: Yes. I think I can
26 understand where Doctor Gilman is coming from. I

1 think there's kind of a logical problem here. I
2 mean it would be hard to say if you're going to ask
3 the question for the whole population, if you feel
4 that there may be a problem in women, how could you
5 say that there's not a problem for the whole
6 population because women are part of that. So I
7 think Doctor Gilman is trying to say, well, we've
8 said what we thought about the women and maybe we
9 should just find out separately what we think about
10 the men and then we can kind of add it up.

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

20 Doctor Johnson.

21 DOCTOR JOHNSON: Well, I guess I sort of
22 would follow your suggestions because these are the
23 aims of the study. Total population, which
24 obviously includes women, and women. I would be
25 uncomfortable voting on men because it wasn't a pre-
26 specified aim and it wasn't designed for that.

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

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

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

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

21 CHAIRMAN BRASS: Okay. I am happy to do
22 a gender, I'm happy to do it by men by that
23 category, and then we can see if it's worth doing a
24 third round. Why don't we do it that way. Doctor
25 Neill.

26 DOCTOR NEILL: I'm right with Doctor

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

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

20 CHAIRMAN BRASS: Here I'm going to take
21 the chicken way out and we're going to do both by
22 male and the total cohort and, because there's an
23 inconclusive option, everybody will be able to
24 express whether or not they're comfortable voting
25 that way, and it'll be really simple. So let's do
26 it by men. We'll do the men sub-group first. Men

1 between the age of 18 and 49 using the product as an
2 appetite suppressant. All those who feel in that
3 population PPA has been shown to be safe, please
4 raise your hand.

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

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

10 DOCTOR TITUS: Fourteen inconclusive.

11 DOCTOR D'AGOSTINO: Can I abstain?

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

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

17 Associated with risk, please raise your
18 hand.

19 Inconclusive, please raise your hand.

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

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

26 Associated with risk, please raise your

1 hand.

2 Inconclusive, please raise your hand.

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

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

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

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

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

19 CHAIRMAN BRASS: Next is the general
20 population 18 to 49 using the product as a
21 decongestant, regardless of timing of exposure.
22 Male and female 18 to 49. All those who feel HSP
23 demonstrates safety in that, please raise your hand.

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

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

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

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

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

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

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

23 CHAIRMAN BRASS: Thank you very much.
24 Under A, there's one issue we have not dealt with
25 and that's specifically the question of dose. I'd
26 be interested now in some discussion of, again based

1 on the HSP data, whether or not dose is felt to be a
2 factor in any risk in these populations. Doctor
3 D'Agostino.

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

10 CHAIRMAN BRASS: Doctor Gilman.

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

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

23 Doctor Sachs.

24 DOCTOR SACHS: The only comment I have
25 is kind of a clinical correlation in trying to think
26 about maybe the pathophysiology of this, and it

1 might be a mistake to assume clear linear dose
2 response relationship because there might be a
3 threshold effect, especially if the hypothesis is
4 that there's some kind of pre-existing dimple or
5 blister in the blood vessel that busts after using
6 one of these agents.

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

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

15 CHAIRMAN BRASS: Thank you. I love
16 being spared a vote. Okay. The next question is B
17 and, again, focusing on the HSP data, does it
18 provide information on which populations may be at
19 greater or lesser risk? Now, we've defined nine
20 different populations already based on gender and
21 exposure type and implicit in the vote was that
22 women represented a group of relative risk compared
23 to men and, without doing a statistical analysis on
24 our votes, there was a suggestion that appetite
25 suppressants represented a use population. Are
26 there other population identifications that were

1 gleaned from the presentation which any member of
2 the committee feels is important to highlight?

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

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

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

19 CHAIRMAN BRASS: Okay. We will now take
20 the Cantilena break for 10 minutes. Actually, we
21 can take a 15 minute break. 3:15 please. 3:15.

22 (Off the record for a 15 minute break at
23 3:04 p.m.)

24 CHAIRMAN BRASS: The committee will now
25 continue its discussion and in what follows we will
26 expand upon our earlier discussion in the

1 presentations to look more globally about the use of
2 PPA in the OTC market based not only on the HSP and
3 our comments earlier about the HSP, but the other
4 information that has been compiled and summarized
5 for us, both from spontaneous reporting base and
6 previous published studies.

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

19 Who would like to make some initial
20 comment about that postulate?

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

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

1 conclusion?

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

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

11 DOCTOR GILMAN: Yes.

12 CHAIRMAN BRASS: Yes, Doctor Sachs.

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

19 CHAIRMAN BRASS: Doctor Kittner.

20 DOCTOR KITTNER: The other thing about
21 these reports was that they were pretty specific to
22 hemorrhagic stroke and if this was just a background
23 rate or a coincidence of two independent things, you
24 would expect them to be similarly associated with
25 ischemic stroke, and they really weren't. I think
26 some of the other points about the case reports have

1 already been mentioned, that is that there was a
2 relationship to first dose and often within the
3 first six hours which is consistent with the
4 pharmacologic effect on blood pressure and the
5 diminished effect with repeated doses.

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

9 One final point that I observed in
10 reviewing the case report literature was that the
11 cases of intracerebral hemorrhage were not really
12 entirely typical. There were reports showing
13 bilateral hemorrhage, two cases of bilateral
14 hemorrhage at that time, and 11 cases showing
15 angiographic features of vasculopathy, at least, or
16 angiographic features that would be consistent with
17 vasculitis and I thought that's relevant in view of
18 the fact that PPA has close structural and
19 pharmacologic similarities to amphetamine where
20 drug-induced vasculopathy with intracerebral
21 hemorrhage has been well-documented. So I think it
22 speaks a little bit to the potential biological
23 plausibility.

24 CHAIRMAN BRASS: I noted that in some of
25 your earlier writings and, frankly, I got a little
26 confused because how could there simultaneously be

1 an acute first dose six hour effect and then the
2 development of a vasculopathy? Those seem to be
3 exclusive.

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

11 CHAIRMAN BRASS: Doctor D'Agostino.

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

17 CHAIRMAN BRASS: That is correct.

18 DOCTOR D'AGOSTINO: Right. And so that
19 being the case, the idea of gathering a fair amount
20 of data on spontaneous reports and other sources and
21 then actually putting the study together, that in a
22 very real way confirmed what was being shown with a
23 lot of the spontaneous data and other collected data
24 I think is a very compelling scenario.

25 CHAIRMAN BRASS: Doctor Johnson.

26 DOCTOR JOHNSON: Yes. I agree that it's

1 sort of the consistency of the data, the case
2 reports led to this study and the results really
3 sort of fell out the way that it might have been
4 anticipated. But also, as Doctor Sachs mentioned,
5 some of the data about other drugs, comparisons with
6 other drugs, both in the spontaneous reporting
7 system and also within the HSP Study where there
8 didn't seem to be associations with other drugs,
9 those things all together really just sort of
10 strengthen the evidence in my mind.

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

18 DOCTOR CANTILENA: I think you're still
19 trying to punish me for the break. I would say that
20 I think this is an example of where you see
21 something that might be a signal in the spontaneous
22 system, and then you go ahead with the HSP Study
23 which I view for the subsets that we've already
24 discussed as confirmatory of signal. But I guess I
25 get uncomfortable when people want to hold up the
26 spontaneous reporting system or MedWatch, as it's

1 now known, as strong evidence for there not being a
2 problem. I just think it's not as sensitive as some
3 of us have heard, but I think it certainly was used
4 appropriately, in my opinion, in this setting where
5 we spotted something, we thought it was a signal and
6 then we went ahead with the HSP Study.

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

15 Would one of our neurologists comment on that,
16 please.

17 DOCTOR GILMAN: May I comment on the
18 previous question?

19 CHAIRMAN BRASS: Most certainly.

20 DOCTOR GILMAN: The reported data on
21 association of hemorrhagic stroke with PPA use is
22 not only just suggestive. I think it must be vastly
23 under-reported for many reasons. The principal
24 reason is because it's not that easy to report for
25 second. In today's hospitals, there is enormous
26 pressure to see patients. Getting a full history of

1 all drug exposures is difficult, time-consuming, and
2 one has to keep in mind that PPA may not necessarily
3 be the drug on a clinician's mind when one sees a
4 young person with hemorrhagic stroke. There are
5 many other issues. Is the patient going to
6 herniate? Do I need to watch this patient, put the
7 patient in ICU, etcetera, etcetera? Do we call the
8 neurosurgeon? Is this a berry aneurism that may
9 need treatment? There are many, many other issues.

10 So I think the fact that there are so many reports
11 is very strong suggestive evidence.

12 CHAIRMAN BRASS: What about the issue of
13 biologic plausibility?

14 DOCTOR GILMAN: Well, I commented on
15 this a bit earlier. What we have in common is a
16 hemorrhagic diathesis affecting the brain, the blood
17 vessels of the brain. Those vessels, some of them,
18 are outside of brain substance itself. That is, in
19 the Circle of Wil or some of the arteries that are
20 on the surface of the brain which account for the
21 subarachnoid hemorrhage component of this. Others
22 are within the substance of the brain and that
23 includes arteriovenous malformations. In other
24 words, three somewhat different kinds of pathologies
25 are implicated.

26 So the biological plausibility that

1 comes to my mind is that there is some factor
2 related to clotting of blood or to hemorrhaging of
3 blood, perhaps something related to blood pressure
4 levels or some other phenomenon. But yes, it is
5 entirely biologically plausible because I can think
6 of a common mechanism accounting for all of these
7 three different kinds of hemorrhagic stroke
8 pathologies.

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

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

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

26 And I'd like to comment on the issue of

1 hemorrhage. I think it's well known from the work
2 of Walter Cannon in the 1930s that part of the
3 stress report mediated by catacholamines is actually
4 to have subtle effects to make the blood easier to
5 clot. These are from the days when we confronted
6 sabre-tooth tigers. I'm ont aware of any evidence
7 that catacholamines would promote hemorrhage.

8 CHAIRMAN BRASS: I think one of the
9 issues that confounds both sides of the statement
10 are that we're clearly dealing with a very rare
11 event and that we're not dealing with a predictable
12 blood pressure response. And then I think it was in
13 the FDA presentation that we do not have a large
14 enough database to identify whether or not there's a
15 subset that response to PPA exposure differentially
16 with respect to either blood pressure or even
17 selective cerebral hemodynamic effects. And so I
18 think that is clearly why it doesn't happen to
19 everybody whotakes PPA.

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

25 DOCTOR HOFFMAN: I think that's
26 certainly true, and you can't exclude that. But it

1 is interesting, as far as I know, in many people who
2 study autonomic nervous system, sympathetic
3 function, basal constriction and so forth, not
4 particularly with PPA. As far as I know, these
5 types of individuals have really not been described,
6 at least as far as I'm aware.

7 CHAIRMAN BRASS: Doctor Cantilena.

8 DOCTOR CANTILENA: I guess I would just
9 follow with a comment that while we're in essence
10 trying to extrapolate the results of extremely
11 closely controlled, clinical setting in terms of the
12 hypertensive response from the product, I think that
13 this again is sort of an actual use, all comers, and
14 when someone pops their diet pill and goes home or
15 is on the way home and someone cuts them off on the
16 highway or their two year old pitches a fit on the
17 kitchen floor, which happened to me this morning,
18 it's sort of the issue of how does it actually fit
19 in?

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

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

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

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

1 that's not the case, and that's the whole point of
2 my comment.

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

9 DOCTOR BLACKBURN: I'm George Blackburn
10 from the Harvard Medical School, and I did do a
11 first dose study, large study of 881 healthy
12 individuals published in *JAMA*, and we did find that
13 the independent factor of PPA was less than four
14 millimeters, even though, as you point out, 10
15 percent of the population had a large response but
16 it was equally distributed for all this fright that
17 you talked about. It was during the placebo, the 25
18 milligram given three times and the sustained
19 release and other determinants were base-line blood
20 pressure in these individuals and individuals who
21 were higher BMI.

22 So it does support that, you know,
23 there is some defense that there's a large
24 indigenous autonomic sympathetic tone at the time
25 you take the first dose and so there is an even
26 distribution and we had, using Yates analysis, we

1 could find that the age, the gender, the BMI were
2 the major contributors to this area and then
3 followed by the baseline blood pressure and only
4 less than four millimeters could be independently
5 attributed to PPA.

6 CHAIRMAN BRASS: Thank you.

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

9 DOCTOR GILMAN: I just wanted to comment
10 that what we're talking about now is the reason for
11 going into Phase IV clinical trials because after
12 one has completed a Phase III double blind placebo
13 controlled trial to see the effects of a drug at a
14 particular population against placebo, one wants to
15 know what this drug is like in the real world when
16 given to people who are taking polypharmacy at times
17 including people who may have untoward reactions to
18 a drug and there may be one person in the 100. In
19 this situation, it may be just those people who have
20 a berry aneurism or just those people who are quote
21 "ready to have their stroke" in various other ways.

22 CHAIRMAN BRASS: Other comments. If
23 not, we will now vote on Question C which I will
24 read again. There is a body of data collected over
25 the years that has suggested a possible association
26 between PPA use and hemorrhagic stroke. Taking all

1 currently available information into account, do the
2 data support the conclusion that -- so you can vote
3 for either 1) that there's no association, 2) there
4 is an association, or 3) that the association still
5 remains uncertain. All those who feel that there is
6 not an association, please raise your hand.

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

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

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

14 CHAIRMAN BRASS: We now move on to
15 Question D. Considering your answer to Question C,
16 can PPA be considered to be generally recognized as
17 safe for use as a decongestant, an appetite
18 suppressant? When answering this question, please
19 address whether dose is an important consideration.

20 Maybe I'll start the discussion this time myself
21 because the issue of dose is, I think, an
22 interesting one. While we concluded that we could
23 draw no dose conclusion from HSP, that in the same
24 way we lumped the data when we look at the
25 spontaneous reporting base and the HSP, one might be
26 concerned that in fact there is a dose relationship

1 that does exist though clearly the data do not
2 provide sufficient evidence to make that
3 conclusively.

4 The other point I'd like to make is
5 actually taken off one of Doctor Ganley's slides
6 actually, is that no drug is absolutely safe and
7 that we have a number of drugs that are available
8 over the counter that we know are associated with
9 rare adverse events, some of them very serious. We
10 know that there are even more drugs available which,
11 when taken other than as directed by the label,
12 particularly in excessive doses, may be associated
13 with serious adverse events so that the definition
14 of generally recognized as safe I think isn't just
15 out of a vacuum but it's against a background of
16 risk and, while the question isolates that from the
17 efficacy concern with the degree of efficacy that
18 may exist, ultimately I think the decision is going
19 to have to be made on a risk to benefit ratio.

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

1 Doctor Johnson.

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

15 And so in both the situations, I guess I
16 view this risk, even though it's rare, as being one
17 that is not upset by benefits because I view the
18 benefits of this product as fairly marginal.

19 CHAIRMAN BRASS: Doctor Gilman.

20 DOCTOR GILMAN: I agree with what Doctor
21 Johnson said, but just specifically to address the
22 issue of appetite suppression. Doctor Schteingart
23 showed us what an effective drug PPA seems to be
24 over the short-term. I asked him during the break -
25 - I don't know if he's still here. Yes, he is. --
26 what is the long-term outcome with those patients,

1 and his response was, well, 95 percent of people who
2 take medications for weight loss wind up with the
3 same weight back again within some years. There
4 has, however, been no study -- I believe I'm quoting
5 him correctly -- there's been no study on the
6 efficacy of PPA over many years. Say five years,
7 six years, 10 years.

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

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

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

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

5 CHAIRMAN BRASS: If you could focus on
6 the question.

7 DOCTOR WALSON: I'll focus on the
8 question. But it does all come down to risk and
9 benefit, and you made the comment. One is that not
10 everyone responds to any decongestant, one, and I
11 want to go back. There were two points on Doctor
12 Ganley's slide and one is that there are benefits to
13 consumer accessibility to short-term medications
14 that offer symptom relief. I don't want to get off
15 on weight control because I think it would be better
16 to stick to decongestants. And these products, I am
17 worried that when you do remove them you are
18 forgetting a risk and that is what are your
19 consumers going to turn to? And we're already
20 seeing them turn in both cases, you're going to see
21 them turn to products that are neither regulated,
22 quality controlled nor studied at all. At least
23 this product does have data showing it's efficacious
24 for short-term use. That is true for both, and
25 you're going to turn patients to ephedra compounds.
26 You're going to turn them to other things.

1 So I think that to say there's no
2 benefit, I think you have to weigh risk and benefit.

3 That's what you're doing --

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

8 DOCTOR WALSON: Yes, there are other
9 choices, but one of the things that I think
10 consumers would tell you is that -- and I don't have
11 the plausible explanation -- that some consumers
12 prefer one product to the other. I'm not sure that
13 the other products on the market are either more
14 effective or safer. So I think that, at least in
15 terms of patients that were not included in the
16 study, which this study speaks nothing to. I mean
17 the reason they didn't do children is because their
18 own data, including the FDA data, would show that
19 any adverse event in childhood is so rare that they
20 would never have been able to power any study to
21 find it so that I am concerned about the population
22 that I represent, that at least you need to make
23 sure that you don't deny our pediatric population
24 access to something that wasn't even studied.

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

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

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

1 indefinite use.

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

9 Now, having posed that, I'm concerned
10 that whether there is or not on the basis of two
11 things. First of all, we have failed to identify
12 any clear sub-groups that we identified them, other
13 than women, but that we could steer use away from
14 and 2) this has, to my eye, provided a very
15 interesting actual use study on how consumers use
16 products and this label clearly says "Consult your
17 physician if you have high blood pressure" and we
18 ended up with a cohort that was quite rich in
19 hypertensives. And so the degree to which if a
20 label warning, even if one could conceive of an
21 effective one, the degree to which it actually would
22 be effective in steering away at risk populations
23 would remain a concern in my mind.

24 Yes, Ms. Cohen.

25 MS. COHEN: I was referring to the FDA
26 report on page eight and nine and talking about 75

1 milligrams and what happened as a result of that,
2 and I am concerned because I did look at the label
3 and the label, I will repeat myself and forgive me,
4 for 12 years old and older and adults, twice a day
5 they can take 75 milligrams twice a day. That's 150
6 milligrams and, if we're worried about consumers
7 over-dosing, this really boggles my mind.

8 In terms of I would like to respond to
9 the pediatrician. Advertising, advertising,
10 advertising. So when you talk about what consumers
11 buy, it's the one that's advertised the most or on
12 the shelf or where they place it on the shelf. So I
13 don't know how much -- goes on in a pharmacy when
14 you go to buy a cough medicine. I bought one
15 yesterday and, believe me, I read the label. But
16 I've had some experience reading this information.
17 So I think this report, I am satisfied with the
18 statistics and what's been done and I'm satisfied
19 that as a result of 75 milligrams there's a good
20 chance for hemorrhagic stroke and really, 150
21 milligrams just boggles my mind.

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

24 DOCTOR SACHS: As a pediatrician, I
25 actually have a different interpretation of some of
26 the information that you presented. I think there

1 are very good studies in children that show these
2 medicines are safe and effective or efficacious to
3 begin with and that if you look at placebo
4 controlled studies and also studies that look at
5 duration of cold symptoms, the colds last 10 days if
6 you take something, they last 10 days if you don't
7 take something. The placebo effect is very great.
8 I know in our population when we talk about over-
9 the-counter remedies for cold and cough, we actively
10 discourage them.

11 One other reason which was not really
12 emphasized today was the risk of arrhythmias,
13 especially in children who receive some of these
14 things. So now having read all the background data
15 and all the HSP Study data, I mean even though the
16 incidence of stroke in a young person is rare, I
17 would be greatly concerned about adolescents who
18 might choose to use these as either cough and cold
19 remedies or appetite suppressants, particularly in
20 the populations that might be on OCPs. I mean you
21 start having to label and label and label. That
22 becomes superfluous.

23 DOCTOR WALSON: Let me respond. A lot
24 of things. One is that, briefly, it's for short
25 symptomatic control and it's relative to -- I'm sure
26 you also counsel against use of antibiotics but the

1 fact is if a child goes to a physician, the odds are
2 overwhelming they will get an antibiotic for a viral
3 infection. That has been shown. If the child can
4 stay home, to not visit your office, they will
5 decrease it. So there is in fact a benefit and
6 that's been shown in terms of symptomatic relief,
7 even though I also don't use them when someone gets
8 to the hospital. So I think that's important.

9 The second thing. I think that there's
10 an assumption in your comment about dose that's
11 really not shown out and that is the risk goes down
12 with age, not up, despite the fact that the doses
13 may not go down very much, and that's because
14 children in fact are resistant. I also ran a
15 pediatric hypertension lab. They tolerate blood
16 pressure changes different.

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

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

24 DOCTOR WALSON: Yes, I know.

25 CHAIRMAN BRASS: Doctor Cantilena.

26 DOCTOR CANTILENA: Just to comment in

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

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

23 CHAIRMAN BRASS: Other comments before
24 we put this question to a vote? If not, the
25 question on the table is considering your answer to
26 Question C, can PPA be considered to be generally

1 recognized as safe for use as, first, a
2 decongestant? The answer will be yes or no. All
3 those who think that it can be generally recognized
4 as safe for use as a decongestant voting yes, please
5 raise your hand at this time.

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

9 All those abstaining, please raise your
10 hand.

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

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

17 Voting no, please raise your hand.

18 Abstaining, please raise your hand.

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

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

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

4 DOCTOR DELAP: No. Thank you very much.

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

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

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