

1 women and not men? Why an association with appetite
2 suppressant drugs and not for colds and such when
3 the typical doses given for colds are higher than
4 for appetite suppressants? It wasn't a consistent
5 picture.

6 We also felt that even if an association
7 were real, it's quite clear from this study plus
8 additional data that if there is an increased risk,
9 that has to be weighed against the benefits of these
10 drugs -- and again, we're not sure that an increased
11 risk is present -- but if it is, it seems to be
12 very, very small.

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

1 quite very much on its own.

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

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

10 First, I want to say that when you see
11 up here that this was a failed study, it has
12 absolutely nothing to do with the design, which was
13 outstanding, nor the investigators, who were equally
14 outstanding, but every one of us does failed studies
15 and, if we didn't, then we would basically not
16 understand that we have done failed studies, which
17 would even be worse.

18 Why do we say that this is probably a
19 failed study design or failed study problem? And
20 there are two problems, as I see it. One of them is
21 that only 41 percent of the potential cases are in
22 the study, and you can't say anything about the
23 other cases because you're not really sure what they
24 are. But most important, there's a very substantial
25 problem in selecting the controls, as you'll note.
26 A hundred and fifty one telephone numbers had to be

1 identified to find one potential control and then
2 three eligibles when they did find the potential was
3 basically into the study.

4 To just show you what this could mean in
5 terms of selection bias -- the next one, please. If
6 you look here, they tried to basically match on
7 social class, which is important, or education
8 because education drives a tremendous amount of
9 human behavior, and you can see here that this is
10 just a major, major problem and it's not adjusting
11 for education in the analysis. It's the problem you
12 really don't know what the people are who didn't get
13 into the study, the controls, the ones who didn't
14 answer the telephone and, most important, the ones
15 who did answer the telephones and told you they
16 didn't want to participate and basically when you
17 see this, you get very, very nervous. Twenty
18 percent of your cases with less than high school and
19 only nine percent controls and reverse for college
20 education. And that probably accounts for some of
21 the data which we'll see.

22 Now, very interesting thing to do is to
23 presume that the prevalence of use was similar --
24 and I just put four percent -- was similar to the
25 use in the cases, that is, 3.8 percent in three
26 days, and then say of the 4,200 controls that they

1 didn't get in the study, if their use was four
2 percent, you'd get 168 users and it would turn out
3 that the overall prevalence of use in the controls
4 would be 3.6 percent. We have absolutely no idea
5 what the use rate was in the 4,200 which basically
6 didn't get in and certainly have no idea, even in
7 the larger number, of those 101 telephone calls and
8 there's no way of answering that question. It's
9 just a major question mark, but when they see the
10 small differences that occurred in this study and
11 the small numbers, that is a very worrisome
12 observation that you have this huge number of people
13 who didn't get into the study. Next slide, please.

14 Now, there's also a problem, a rather
15 interesting one, and that is rather if you turn this
16 around, look at the data, why is there greater use
17 in the controls in two weeks to three days prior to
18 the event? If you look at the data here, you get
19 basically the overall use is 5.4 and 4.8, but it's
20 1.7 and 2.5. There's actually more use of controls
21 from three days to two weeks and it's just a little
22 bit of a problem in terms of defining the date of
23 exposure because it doesn't make any sense why you
24 should see something of this magnitude. It's almost
25 as great as the other magnitude. You should note
26 also that the first use, eight and five, is where

1 most of the action is in this whole study. A total
2 of eight and five cases. Next one.

3 Now, the argument was raised that men
4 weren't exposed, but this is not true. Actually,
5 the exposure rate in the controls in the men and
6 women is not significantly different and, if you
7 leave out the appetite suppressant group of women,
8 it turns out basically -- and look just at the nasal
9 decongestant controls, it turns out it's 2.5 percent
10 and 2.1 percent. The only difference in this whole
11 study is the 5.5 percent in the women cases, the men
12 cases. The controls in the men and women are
13 exactly the same, and there should be enough power
14 to test the hypothesis in the men because the use in
15 the controls in the men is the same. The
16 interesting thing. There's no use in the men who are
17 cases. Next.

18 Likewise, it's a rather peculiar
19 phenomenon if we look at cough and cold suppressants
20 that was noted, and this is not a power issue. It
21 turns out that the risk is 1.5 in the women, but
22 it's 0.62 in the men and, again, it's hard to
23 believe that this is a protective in the men. It
24 may be a biological basis related to subarachnoid
25 hemorrhage. The only problem is then if you believe
26 that, as it turns out, there are only four

1 subarachnoid hemorrhage cases in the women who are
2 not hypertensive or cigarette smokers. Every other
3 one of them women with subarachnoid, while a large
4 number of the women that are cases with
5 intracerebral hemorrhage, a larger number, there are
6 very few of them, were neither hypertensive nor
7 cigarette smokers. So this is a subarachnoid
8 hemorrhage phenomenon. Again, it's not internally
9 valid.

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

17 Now, we talked a little bit. Somebody
18 mentioned about the use, and I just want to point
19 out that the nine cases basically in current users
20 within the first three days, and this is in the
21 group in the study that are reported in eight/five
22 controls and just to point this out. One of the
23 women -- this is everybody -- drank 10 cups of
24 coffee a day, one eight and a half cups, one had 10
25 glasses of soda, one had eight glasses of soda a
26 day, one had six glasses of soda a week and a prior

1 history of stroke, one with one glass of soda and a
2 history of stroke, and two of the cases had just
3 prior headache and nothing and, of the five
4 controls, six cups of coffee a day, six glasses of
5 soda, two cups of coffee and one had just a cup of
6 tea. But it's hard. If you look at this, you have
7 eight or nine cases to deal with in your whole study
8 and basically at least four of those people were
9 basically red hot consumers of either coffee or soda
10 in huge amounts per day and they're not typical of
11 the U.S. population by a long shot.

12 Well, thank you very much.

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

24 Some of the concerns. Again, I think
25 based on what the investigators have suggested and
26 the panelists and other comments, I think almost

1 everything has been suggested. I'm very concerned
2 about sample size with respect to dose and every
3 epidemiologist wants to see whether they could grade
4 the exposure, that is, the amount of exposure, and
5 see that there's a lesser effect than those with
6 lesser exposure, and so it would really be nice, for
7 example, if we could look at those separately who
8 were exposed three days prior to the event versus
9 those who are exposed in the 24 hours. And again,
10 it's very, very difficult to do because of the
11 difficulty of capturing that kind of exposure.

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

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

6 Lew has covered control selection, and I
7 think I'll go on. We all face the problems with
8 control selection. As you know, everybody gets
9 telephone solicitations to the point where they
10 screen calls and do all sorts of other things, and
11 it's very hard for us epidemiologists to come along
12 and try to find a population that's referent to the
13 general community because everyone is out there
14 doing it also.

15 I wanted to quickly say -- and it's a
16 point that's probably been made half a dozen times
17 today -- that these cases are different. I think
18 this is really a collection of different kinds of
19 diseases. Now, I'm not going to argue whether
20 they're cousins or distant relatives, but they are
21 at least a little bit different, and I thought
22 Doctor Broderick gave a good explanation talking
23 about mechanisms that may be a little bit different
24 but I'm also worried about risk factors that might
25 be different. My own search of the literature, for
26 example, found very little in the way of risk factor

1 studies of arteriovenous malformations which are
2 part of the case load. Maybe somebody has
3 information, and I would like to see that. But I
4 believe this is a series of closely related diseases
5 that may not be the same, either in their etiology
6 and their mechanism and their genetics and family
7 history and so forth, and it would be really nice if
8 we could look at them separately.

9 Again, a lot of the risk factor
10 questions have been addressed and, in fact, I saw a
11 little bit of information that I wasn't aware of.
12 I'm personally concerned about alcohol use and
13 withdrawal, particularly in that period before the
14 event. I'm very much interested in caffeine use, in
15 part because caffeine in my view does raise blood
16 pressure and Lew pointed out that we're looking at a
17 population, we may be tapping into a population
18 that's a little bit different. I'm amazed. Maybe
19 it's just being simple-minded, but 10 glasses of
20 soda a day or eight and a half or six. That is just
21 a lot and I'm wondering if we're looking at
22 behavioral patterns that we don't in fact fully
23 understand, and I'm also interested in undiagnosed
24 hypertension and we carry around the dogma that half
25 of people with hypertension don't know that they
26 have it and, since hypertension is such a dominant

1 factor in subarachnoid hemorrhage, I'm always
2 worried that in fact there's this reservoir out
3 there that we really don't know how to measure
4 because once they're in the hospital with their
5 events, blood pressure fluctuates a lot and it's
6 very difficult to tell, and I am interested in the
7 cocaine history, as has been mentioned several
8 times. So these are the data that you've already
9 seen that, in fact, Doctor Kernan presented and I
10 hope it looks the same.

11 I'm very concurrent, as Lew was just
12 before me, that there is really an important class
13 difference, social class difference between cases
14 and controls. Some of that may be due to the nature
15 of the disease, but I want to know how much of these
16 differences that we're seeing in fact can be
17 explained by what I think are dramatic differences
18 in social class that are really not explained by
19 ethnicity although, like the one panelist, I did see
20 that Hispanics may have an increased risk,
21 particularly in some counties in the southwest. But
22 I am interested in why there are these differences.

23 For example, a 17-fold difference in the history of
24 cocaine use and issues with respect to caffeine and
25 body mass and so forth.

26 So in summary, for me, this is a

1 logistically extremely difficult and daunting
2 activity and I think personally that there are
3 enough issues left open that it's very hard to make
4 a judgment.

5 DOCTOR GORELICK: Good morning and thank
6 you. Next slide, please. I'm Phil Gorelick and I
7 hail from the great city of Chicago where I serve as
8 professor and Director of the Rush Center for Stroke
9 Research and the section of cerebral vascular
10 disease and neurologic critical care. I am a board
11 certified neurologist and, over the years, I've
12 developed a busy clinical in-patient and office
13 consultative practice. I do have familiarity with
14 case control studies. I have been the PI of four
15 such studies and, as Noel mentioned, I do have a
16 master of public health degree in epidemiology,
17 though my daughter used to refer to it as the miles
18 per hour degree. Next slide, please.

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

25 What I'd like to do in the next several
26 minutes is give you an overview of a clinical

1 neurologist's view of the risk factors for
2 hemorrhagic stroke and key clinical points to
3 consider when evaluating the Hemorrhagic Stroke
4 Project. We will have an opportunity to look at
5 some of the details of these specific cases as I
6 walk you through the ones for appetite suppression.

7 Next slide, please.

8 As you've heard, hemorrhagic stroke
9 makes up about 15 to 20 percent of all strokes. As
10 you've heard previously, there's two types:
11 intracerebral which we abbreviate here as ICH and
12 subarachnoid as SAH. Generally speaking, the
13 intracerebral is more common and usually but not
14 exclusively it's caused by a rupture of a deep
15 artery in the brain and the blood is within the
16 brain tissue. The subarachnoid, as has been
17 previously mentioned, is usually due to a blister on
18 the blood vessel which ruptures and then blood forms
19 around the base of the brain and over the coverings
20 of the brain.

21 The other type of malformation is an AVM
22 or arteriovenous malformation which is an
23 abnormality or tangle of blood vessels that has an
24 abnormal connection directly between the arteries
25 and veins. This can also cause subarachnoid
26 hemorrhage. So as you can see, there are different

1 causes and these may produce different outcomes and
2 we must consider the underlying health status in
3 evaluating the contributors to risk. Next slide,
4 please.

5 Well, here are the hemorrhagic stroke
6 risk factors by sub-type. Intracranial hemorrhage
7 on your left, subarachnoid on your right. And these
8 are from the American Heart Association Risk Factor
9 Panel, of which I was a member of the writing
10 committee, and from other sources. The factors that
11 are highlighted or bolded are the lead factors so,
12 for intracranial hemorrhage, hypertension, heavy
13 alcohol use, anti-coagulants. This problem
14 increases with age so the older are a little higher
15 at risk. There tends to be more men. African
16 Americans and drug abuse has also been implicated,
17 specifically cocaine.

18 On the subarachnoid hemorrhage side for
19 these important risk factors, the one that seems to
20 stand out substantially is cigarette smoking though,
21 again, hypertension, alcohol, heavy alcohol use also
22 come in. This is a disease in which there tends to
23 be a disproportionate amount of subarachnoid
24 hemorrhage in younger person as compared to ischemic
25 stroke and specifically women seem to be a higher
26 target and then again, African Americans have a very

1 high risk. So these are the major risk factors for
2 these two types. You'll see there's some overlap.
3 Next slide, please.

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

17 Let me walk you through this table of
18 the appetite suppressant cases to show you some of
19 my concerns. I'm not showing the cough/cold
20 information, but they also had risk factors, but to
21 simplify the presentation we'll look at this. In
22 the far left hand column you notice that case three
23 had an arteriovenous malformation as the cause. The
24 other five cases had subarachnoid hemorrhage and, of
25 those, an aneurism was identified in one, two, three
26 cases. These UNC cases mean that there was a

1 subarachnoid hemorrhage but no aneurism or other
2 vascular malformation was found.

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

13 Let's look in the alcohol use column.
14 This patient was drinking three drinks per day. We
15 have a patient who had a history of abuse of alcohol
16 but denied use more recently. Here's one who was
17 drinking eight per week and here's one who is
18 drinking 13 per week. So what I'm pointing out here
19 is that all of these cases, generally speaking, had
20 risk or most of them had traditional risk factors
21 for intracerebral hemorrhage or subarachnoid
22 hemorrhage, as you can see here. Next slide,
23 please.

24 Another issue for me has to do with the
25 attributing PPA as a factor here. I've concluded,
26 based on my analysis, that even if the association

1 is real, the number of cases attributed to PPA has
2 to be extremely low and then we're left without a
3 biologically plausible mechanism. Next slide,
4 please.

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

16 Thank you.

17 DOCTOR SOLLER: Thank you very much.

18 I'd like to now introduce Doctor Charles
19 Hennekens.

20 DOCTOR HENNEKENS: Thank you, Doctor
21 Soller. My name is Charles Hennekens. Since last
22 October, I've served as a consultant in epidemiology
23 to the CHPA when I first learned of the Hemorrhagic
24 Stroke Project. Ralph Horwitz and Larry Brass have
25 been colleagues and friends for decades. Since
26 honest scientists have honest differences of

1 opinion, I trust they'll remain so after today.

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

9 My issues relate less to the design but
10 more to the analysis and interpretation of this
11 study. The Independent Expert Panel has presented
12 their cogent joint as well as individual
13 perspectives about the real likelihood that chance,
14 bias and/or uncontrolled confounding each could
15 easily explain the observed findings in the HSP.
16 I'd like to highlight several major issues that
17 derive from the initial epidemiology and
18 biostatistical reviews conducted by myself and Bob
19 Hirsch, who's here in the audience today and is
20 professor of biostatistics and medical statistics at
21 G.W. and also a consultant to CHPA.

22 With respect to chance, this is a large
23 study of over 700 cases and 1,400 controls, but it's
24 crucial to recognize that even the most robust and
25 informative overall test of the hypothesis that PPA
26 is associated with hemorrhagic stroke is based on

1 just 27 exposed cases and 33 exposed controls. This
2 overall finding does not achieve statistical
3 significance, even using what I believe to be an
4 inappropriate one-sided test that yields a p-value
5 of 0.085 which is about one-half of the more
6 appropriate two-sided p-value of 0.17.

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

14 My own view is that regardless of
15 whether the investigators, sponsors, and FDA agree
16 to using one-sided p-values in the design, the most
17 important point in the analysis is that several of
18 these major analyses go from statistical
19 significance to non-significance when one goes from
20 a one- to a two-sided p-value. Further, while the
21 overall finding is based on a total of 60
22 participants, the sub-group of women taking PPA as
23 an appetite suppressant is based on a total of only
24 seven participants, six exposed cases, and one
25 exposed control.

26 Interestingly, one of these six cases

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

13 Indeed, if the primary aim were to study
14 the association between PPA used as an appetite
15 suppressant and hemorrhagic stroke, I would have
16 studied 2,100 women, not 1,153. Perhaps most
17 importantly, chance would remain a plausible
18 alternative explanation, even if this were a
19 randomized double blind placebo-controlled clinical
20 trial of PPA versus placebo. But, in fact, this is
21 a retrospective case control study with additional
22 limitations of bias and uncontrolled and indeed
23 uncontrollable confounding.

24 With regard to bias, selection is an
25 inherent limitation of all case control studies and
26 is a major problem in the HSP because the response

1 rates are low in differential. Parenthetically, I
2 would accept the investigators' estimate of 75
3 percent for cases because I think the failure to
4 enroll the fatalities limits the generalizability,
5 not the validity, of their estimates. However, as
6 has been pointed out, the participation rate and
7 controls is about 35 percent.

8 Observation bias is also likely because
9 cases were hospitalized with hemorrhagic stroke and
10 40 percent were aphasic at the time of the interview
11 and the controls were selected from random digit
12 dialing. Among patients with aphasia, I believe I
13 would not just have more difficulty verifying
14 exposure but an even greater problem with the timing
15 of the use. So the likelihood for noncomparability
16 between cases and controls due to selection and
17 observation bias is substantial and also impossible
18 to assess.

19 With respect to confounding,
20 uncontrolled confounding is clearly present because
21 cases reported a significantly higher prevalence of
22 numerous major and independent risk factors for
23 hemorrhagic stroke. These include race, family
24 history of hemorrhagic stroke, history of
25 hypertension, a major risk factor for intracerebral
26 hemorrhage, cigarette smoking, a major risk factor

1 for subarachnoid hemorrhage, alcohol use, illicit
2 drug use including cocaine, and lower socioeconomic
3 status.

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

20 Further evidence of problem with this
21 sub-group analysis derived from the fact that
22 controls for all these positive confounders in an
23 analysis of a robust sample size would reduce the
24 size of the adjusted relative risk but, in fact,
25 this adjusted estimate was higher than the crude.
26 This, to me, is an unfortunate but logical

1 consequence of the analysis of case control study
2 having one exposed control resulting in a misleading
3 apparently adjusted estimate due to a simple
4 inability to control for confounding in any analyses
5 of data of this sort.

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

18 I certainly understand the intuitive
19 appeal of making a recommendation for a policy
20 statement for a drug use as an appetite suppressant
21 or for cough and cold suppression for which there
22 appears to be other alternatives. It also has some
23 intuitive appeal that a premature recommendation may
24 appear preferable to waiting for a sufficient
25 totality of evidence. Nonetheless, I remain hopeful
26 that sound scientific reasoning will prevail over

1 emotion.

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

11 In conclusion, I urge more research, not
12 any recommendation for a policy statement that is
13 premature and unwarranted based on the current
14 totality of evidence. Mark Twain once said, you can
15 always tell when academics are in dispute because
16 the emotions are so high and the stakes are so low.

17 This may well be true for all of us as speakers
18 here today, but it's certainly not true for you, the
19 Advisory Committee.

20 Thank you very much for your attention.

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

25 FDA's OTC policy is that product
26 availability and labeling should be scientifically

1 documented, clinically significant and important to
2 the safe and effective use of the product by the
3 consumer. The value of this three part policy can
4 not be under-estimated. The first hurdle scientific
5 documentation focused us to look very closely at the
6 quality and strength of the underlying data before
7 reaching clinical or end use conclusions.

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

17 However, prior to the HSP Study,
18 industry was committed to further research on PPA
19 and this commitment remains unchanged. While
20 limited value in terms of its questionable results,
21 the HSP nevertheless shows us that the exposure to
22 PPA among patients with hemorrhagic stroke is small,
23 rare, and it provides insights on possible optimum
24 design for future studies.

25 Hence, we recommend the next three steps
26 to be. Further epidemiologic research. This might

1 be undertaken either in conjunction with PHS or
2 there may be other models to do this and certainly
3 with greater peer input on the design, conduct
4 issues, and analyses, all of which we've been
5 talking about this morning. Second, we think it
6 would be prudent for FDA to finalize the labeling
7 requirements that it has proposed for PPA that
8 include recommendations relating to maximum dosage
9 use, contraindications with specific conditions that
10 are listed, various end use precautions and
11 drug/drug interaction information.

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

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

20 CHAIRMAN BRASS: Thank you very much.
21 Perhaps I'll begin with a couple of clarifications.

22 Would you agree that the HSP can not be used to
23 exonerate PPA as associated with stroke?

24 DOCTOR SOLLER: Well, I think if we look
25 at the questions to the panel with getting ahead,
26 3(c), we think that the association is uncertain.

1 We don't think, 1) that it has been shown and we
2 wouldn't say that it would be C2 in that particular
3 question where you would walk away and say this has
4 demonstrated a negative.

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

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

12 DOCTOR HENNEKENS: We're a little out of
13 synch because I thought I said that absolute
14 estimates are premature and unwarranted. However, I
15 think working with Doctor Hirsch we looked at the
16 HSP data and some outside data and came to some
17 conclusion of a population attributable risk percent
18 estimates of about -- it was between seven and nine
19 percent or something like that, I think it was. But
20 I think these are very treacherous on the base of
21 the available data.

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

24 DOCTOR HENNEKENS: No, I'm not saying
25 you should ignore the extremely low conclusion. I'm
26 saying that if you have an uninterpretable study

1 with a really difficult study to interpret with
2 regard to making assessment of whether there's a
3 valid statistical association, to go further and say
4 that on the basis of even the extremely elevated
5 risks that are seen in some of these sub-groups that
6 using those to assess the impact on the population
7 would be premature and unwarranted.

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

13 DOCTOR HENNEKENS: Well, I'll take a
14 first stab at this and ask Doctor Weiss perhaps to
15 comment. I think the issue is -- and I think one of
16 the major contributions of this study will enhance
17 our quantitative estimates of the risk factors for
18 hemorrhagic stroke, both intracerebral and
19 subarachnoid here, and they are so significantly
20 different. Seven of the major risk factors for
21 hemorrhagic stroke are significantly higher in the
22 cases than in the control, so it's difficult to
23 assess that with noncomparability of this sort that
24 one can begin to achieve control for the differences
25 between the cases and controls when you have only
26 one control to deal with in the analysis.

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

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

11 CHAIRMAN BRASS: Doctor Katz.

12 DOCTOR KATZ: I'll address this question
13 to Doctor Soller or really anybody who wants to
14 answer it. Is there any evidence that the magnitude
15 of weight also that has been documented in
16 adequately controlled trials has any consequences
17 for the public health concerns that we've heard
18 about related to obesity?

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

24 CHAIRMAN BRASS: Doctor D'Agostino.

25 DOCTOR D'AGOSTINO: I want to ask a
26 couple of questions. One is in terms of the

1 statistical -- or make a statement -- in terms of
2 the statistical analyses. You don't necessarily
3 keep going back to square one for your allocation of
4 alpha. I mean I understood from the way this was
5 presented is that there was a hypotheses being
6 driven to set this study up and it was first focused
7 on women, appetite suppressant, first use. There's
8 these procedures called closed procedures. There's
9 the sequential procedures where you do in fact run
10 through a sequence of hypotheses tests at the five
11 percent level and you keep hitting a five percent
12 level until you stop, and that is until you don't
13 get the five percent level to be significant.

14 The way this was set up, I'm not
15 completely convinced that one couldn't have said go
16 through the sequence of hypotheses that are set up
17 at the five percent level for women appetite
18 suppressant, for first use, five percent level, and
19 then to full males plus females and I don't
20 necessarily want to raise a debate here, but I think
21 that the discussion of taking the alpha and dividing
22 it by the number of potential hypotheses is not
23 really where one has to focus on the appropriate
24 hypotheses allocation of alpha. I think that there
25 are many, many other ways of addressing it which
26 would have said that what was done was in fact

1 correct.

2 I have another question after that.

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

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

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

1 correctly.

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

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

15 DOCTOR SOLLER: Brian.

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

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

22 DOCTOR STROM: Again, I'm not a
23 consultant to CPHA. I should also be clear I am not
24 a neurologist. I'm a general internist as well as
25 epidemiologist. There are a lot of people here, I
26 think, who are better qualified to answer than I.

1 But my understanding from my neurology colleagues is
2 these are different diseases and should be treated
3 differently. They may be cousins. They may be
4 related. They may be separate, but when you combine
5 two different diseases into a separate case group,
6 it's problematic. Why that was originally decided
7 and the fact that there were five years and they
8 could change --

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

12 DOCTOR STROM: True, but I think the
13 important thing to realize is these diseases may or
14 may not have different risk factors. PPA may be a
15 risk factor for one and it may be a risk factor for
16 the other, it may be a risk factor for both. If
17 they are different diseases, if it is a risk factor
18 for both, if they really are different diseases,
19 then that is further evidence that it's due to bias
20 rather than biology because you would expect the
21 risk factors for the two things to be potentially
22 different.

23 DOCTOR GORELICK: I think what we found
24 in the case review, as you witnessed, is that in the
25 appetite suppressant group there were five
26 subarachnoids and one AVM and we were dealing with

1 the traditional intracerebral hemorrhage case that
2 we normally would, and so there is some suspicion
3 here that the two things may be different.

4 DOCTOR D'AGOSTINO: Thank you.

5 CHAIRMAN BRASS: Ms. Cohen.

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

12 If a consumer came to me and asked me
13 why PPA is necessary for appetite depressant or for
14 cough, what kind of answer can I give them? My next
15 question is why and how does PPA affect behavior
16 modification? Does it affect the brain cells? Why
17 is it necessary? And lastly, as the wife of a
18 scientist who was at NIH for 41 years, I really need
19 to understand so I can complain to consumers where
20 there's such a strong defense by the scientists of
21 the use of PPA since it's not in the category of an
22 anti-biotic. I really need to understand these
23 things so I can go to a consumer and say, this is
24 what I learned at this meeting and this is what I
25 understand.

26 DOCTOR SOLLER: Let me answer the second

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

15 Now, in terms of necessary, my comment
16 that I made earlier in terms of the policy and the
17 fact that we shouldn't under-estimate it speaks
18 directly to that. There's a susceptibility to move
19 into the second and third part of that policy, and
20 the policy is that the availability of the product,
21 the labeling should be scientifically documented,
22 clinically significant and important to the safe and
23 effective use of the product to the consumer, and
24 you're jumping to the third portion of that. In
25 fact, the importance of this policy in a
26 deliberation like this is to come to an assessment

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1 as to whether the study rises to the level of
2 scientific documentation that would lead you into
3 the second and third phase.

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

14 MS. COHEN: Doctor Brass, may I? Would
15 you permit me? I still don't understand.
16 Indirectly I do understand, but I don't understand
17 how I can answer a consumer saying that PPA is
18 necessary. I don't understand how it's classified,
19 what its efficaciousness is, if you'll pardon the
20 big word, but I don't understand that. And the
21 other thing, in your studies, did you do a study
22 with behavior modification exercise and a low
23 calorie intake versus with the PPA and how long?
24 And I think someone asked here, how long did you
25 follow it after? A year, two years? I still don't
26 think I can go intelligently -- maybe I'm missing

1 something -- and telling consumers what I need to
2 know to answer in an intelligent fashion.

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

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

8 DOCTOR SOLLER: No, but I'm talking
9 about an overall perspective in terms of how you
10 look at the self-care category and you could say,
11 why do you need many of these? You could just
12 tough it out. The point here is that once you look
13 at the information that is supporting or not
14 supporting PPA, you look at the level of scientific
15 documentation and determine whether it rises to the
16 level to suggest a change in availability or
17 alterations in labeling because the benefits that
18 are available in terms of nasal decongestion and
19 appetite suppression are real, and we heard comments
20 earlier today from Doctor Schteingart that related
21 to the demonstration that PPA can reduce weight in
22 both the clinical setting.

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

25 Doctor Gilman.

26 DOCTOR GILMAN: Sid Gilman. I'd like to

1 go to the issue of whether this group was looking at
2 an improper end point by looking at hemorrhagic
3 stroke, so-called. What they were looking at were
4 patients who had extravasation of blood into the
5 spinal fluid or around the brain or into brain
6 tissue. These result, in the case of subarachnoid
7 hemorrhage, from what is called a berry aneurism, a
8 small outpouching of a vessel that is thin and that
9 ruptures. There are risk factors for it, including
10 hypertension and high blood pressure.

11 They're also looking at stroke in the
12 brain. Again, hypertension is a risk factor for it.

13 Those hemorrhages occur from actually little small
14 outpouchings at the branch points of vessels often,
15 but they represent extravasation of blood in brain.

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

26 So I guess I'm a little-- perhaps Doctor

1 Gorelick would clarify this. I don't see that there
2 is an improper rationale in grouping these cases
3 together personally.

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

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

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

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

26 DOCTOR GORELICK: Exactly.

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

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

1 numbers and trying to make heads or tails out of
2 them.

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

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

12 DOCTOR KITTNER: Since the topic of the
13 end point has come up, I'd just like to make a
14 comment. One of the points we'll get to later on in
15 the meeting is that there were a number of a prior
16 reasons why, based on the case report literature,
17 why the study was commissioned. I'm just going to
18 mention one of them, and that is that the case
19 report literature was very heavily weighted towards
20 hemorrhagic stroke, and that kind of a priori
21 evidence, this is in the face of the fact that
22 ischemic stroke is more common than hemorrhagic
23 stroke. So there was a specificity of response
24 which led to the original study.

25 I think that as we're reviewing -- I
26 hope we'll come back to this -- as we're reviewing

1 the data, we can not view this study in isolation
2 independent of the preliminary evidence upon which
3 the study was based. The preliminary evidence
4 suggested diet pill use in women. I'll stop there.

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

8 Doctor Daling.

9 DOCTOR DALING: This is for Doctor
10 Gorelick. In your table where you review the seven
11 cases, six cases and one control, would you comment
12 on the fact that only one of the six cases was what
13 we consider over-weight or even in the upper 25
14 percentile of body weight and two were actually
15 quite thin that would have fallen in the first 15
16 percentile. So why were they taking these drugs if
17 they were very thin?

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

21 CHAIRMAN BRASS: Isn't it BMI?

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

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

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

5 DOCTOR DALING: Whereas the control BMI
6 was 33 so that was clearly someone who was quite
7 obese. That makes you wonder why they were taking
8 these drugs.

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

14 CHAIRMAN BRASS: Doctor Elashoff.

15 DOCTOR ELASHOFF: Yes. In terms of
16 slide 17 which showed how much caffeine use there
17 was, as I recall from reading the stuff prior to
18 initiation of this study, there was a decision to
19 take caffeine out of the appetite suppressants
20 because of its potential to do harm, but it looks
21 like it may not have done any good to take it out if
22 people are drinking that much caffeine during the
23 day.

24 DOCTOR SOLLER: Caffeine was taken out
25 of the products in 1983, in and around that time.
26 There was an abuse issue that was related to things

1 called "black beauties," street-like drugs, and that
2 was all embroiled in that particular issue. It was
3 taken out and now is marketed solely as PPA and I
4 would ask you, Doctor Blackburn or Doctor Hoffman,
5 whether they have any additional comments that they
6 might want to make in regards to caffeine and this
7 issue.

8 DOCTOR HOFFMAN: Brian Hoffman. It's
9 hard for me to say very much. I think caffeine to
10 someone who's never been exposed to caffeine or
11 hasn't been exposed to it recently can have effects
12 on blood pressure, probably in part by stimulating
13 release of catacholamines from the adrenal medulla
14 and possibly the sympathetic nervous system. John
15 Oates and his colleagues at Vanderbilt a number of
16 years ago did some elegant studies on people who
17 take caffeine daily, and my recollection of their
18 work is that after seven to 14 days these effects of
19 caffeine disappear, that we become tolerant to those
20 effects of caffeine.

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

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

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

13 First of all, I'll take you through the
14 format that my presentation will take this morning.

15 I'll give you a historical background of the safety
16 events that led up to this Advisory Committee today.

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

26 And finally, we'll give our overall conclusions.

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

11 In 1991, our office reviewed the
12 postmarketing experience of the spontaneous reports
13 received on hemorrhagic stroke associated with PPA
14 use. Between 1991 and now, we continue to receive
15 reports of hemorrhagic stroke associated with PPA
16 use. I'll spend a little more time discussing
17 O'Neill and Van de Carr's 1984 study.

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

26 The limitations were that in a

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

15 To show you the strength of the signal
16 that we received in our spontaneous reports. The
17 1991 review showed that of all the adverse events
18 reported for PPA use, 14 percent were concerning
19 hemorrhagic stroke with the use of PPA compared to
20 less than one percent of hemorrhagic strokes found
21 as an adverse drug event for all other drugs in our
22 database.

23 The 1991 series went back as far as 1969
24 which is the date on which our database begins and
25 it reviewed all adverse events reported with PPA use
26 up until the end of January 1991. We found that

1 there were 29 domestic cases of stroke associated
2 with PPA use, 22 of which were hemorrhagic stroke.
3 And I must point out, since there has been
4 considerable discussion on whether we should have
5 used intracerebral or subarachnoid hemorrhage that,
6 in fact, the cases represented both intracerebral
7 hemorrhage and subarachnoid hemorrhage. Seventy
8 three percent of the cases at that time were
9 associated with appetite suppressant use and 27
10 percent with cough and cold preparation use. They
11 were predominantly of young age with a median of 27
12 for appetite suppressants and 35 for cough and cold
13 and predominantly females. Fifty five percent of
14 the hemorrhagic strokes occurred with first use of
15 PPA.

16 This led to the generation of the
17 hypothesis that PPA-containing products, both
18 appetite suppressants and cough and cold
19 preparations, particularly first use, are associated
20 with an increased risk of hemorrhagic stroke in
21 young women.

22 As part of our preparation for this
23 Advisory Committee today, we updated the review of
24 cases in our adverse event reporting system. We
25 started on February 1, 1991, which was the date on
26 which the last review ended, and we went up to mid-

1 July of this year. We again found 22 cases of
2 hemorrhagic stroke. There were four well-documented
3 deaths, all of which were in females. Eighty six
4 percent this time were with cough and cold
5 preparations and 14 percent with appetite
6 suppressants. Females still predominated and the
7 median age remained 35.

8 The median time to onset after the last
9 dose was four hours. The median duration of use was
10 24 hours. Eighty two percent of the strokes
11 occurred within three days of PPA use. All cases
12 occurred with preparations containing 75 milligrams
13 of the sustained release of phenylpropanolamine. We
14 note that in this series there is a shift in the
15 demographics with far more cough and cold users than
16 the previous review, the 1991 review, but the median
17 age remains the same.

18 Just to show you a sort of typical case
19 report. We would have a young person, otherwise
20 healthy, who develops a cough or cold. In some
21 cases, a runny nose is what was listed on the form.

22 That person takes a PPA-containing product and
23 within a few days, with absolutely no warning,
24 develops a catastrophic event, a hemorrhagic stroke,
25 is hospitalized and either dies or is permanently
26 disabled.

1 Twenty two cases in the first 20 years,
2 22 cases in the second nine year period, a total of
3 44, might look like an unsubstantial number but I
4 must hasten to point out that there is substantial
5 under-reporting, even for prescription drugs in
6 spontaneous reporting databases such as ours.
7 Perhaps as low as one percent. Further, there is no
8 legal requirement for manufacturers to report non-
9 monograph drug adverse events and many PPA-
10 containing products are in fact non-monograph drugs.

11
12 In addition, there is less attribution
13 of these cases because there is no physician, no
14 learned intermediary, who is aware of the PPA
15 exposure and, in general, under-reporting for over-
16 the-counter products is far less than for
17 prescription products. All these features
18 contribute to the under-reporting and it must be
19 borne in mind that the figure of 44 is literally
20 the very tip of the iceberg.

21 Now we come to the Yale Hemorrhagic
22 Stroke Project which was a case-control study
23 designed to study phenylpropanolamine use and the
24 risk of hemorrhagic stroke. It was sponsored by
25 CHPA and designed and conducted by the HSP Yale
26 group. Our record show, as Doctor Sherman outlined

1 to you this morning, that the protocol was
2 extensively reviewed on many occasions by Yale, CHPA
3 and the agency. It was designed to test the
4 specific hypotheses generated by our data, and this
5 is very important for us to remember as we consider
6 this. It was not data dredging. It was a purpose-
7 designed study.

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

13 The third hypothesis was among women age
14 18 to 49 years to estimate, A) the association
15 between first use of PPA and hemorrhagic stroke and,
16 B) PPA use and appetite suppressants and hemorrhagic
17 stroke. I must again point out from the agency's
18 point of view, this hypothesis #3, parts A and B,
19 was the single most important from our viewpoint as
20 it was generated by our data.

21 The study design was a case control
22 method which, as Doctor Kernan pointed out, is best
23 suited to rare events such as hemorrhagic stroke in
24 young people. It's best suited because it is most
25 efficient in terms of the number of cases required.

26 It can capture all the cases in a specified time

1 period and in a specified population. It's very
2 efficient in terms of timeliness of the results.
3 The results are available much more quickly than
4 with a cohort study and it is far less expensive
5 generally.

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

21 The limitations were in the relatively
22 small sample size and power. As you have heard this
23 morning, it was powered to detect an odds ratio of
24 five or greater. I must hasten to point out that
25 this was not for scientific nor public health
26 reasons but for practical considerations. As it

1 was, the study took longer than six years to
2 complete. From the design stage to the actual
3 handing in of the report was in fact almost eight
4 years. Had it been powered to detect a lower odds
5 ratio, say an odds ratio of two, it would have
6 required a far larger sample size and might have
7 taken 10 or 15 years to complete. We do not think
8 that this was reasonable to wait so long for an
9 answer.

10 Now to address some of CHPA's concerns.

11 They were concerned about the relatively small
12 sample size, that it would give low statistical
13 power to the study, that it made the results subject
14 to exposure misclassification, that the low sample
15 size could introduce important biases and the
16 results might not, therefore, be robust.

17 We counter that by saying that this was
18 the largest study ever of hemorrhagic stroke. Low
19 power normally reduces the probability of detecting
20 a difference if one really exists. In spite of the
21 low power, this study was able to demonstrate a
22 major difference. Bias is usually a product of poor
23 study design and conduct. The Yale Study was well-
24 designed with internal safeguards to protect quality
25 assurance, and the internal consistency in the
26 subset analyses underscores the robustness of the

1 data.

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

14 This slide will demonstrate two things.
15 It shows the internal consistency of the data and
16 the fact that aphasia and hypertension were not in
17 fact significant confounding factors. In the first
18 column, you see the odds ratios as they were
19 presented for appetite suppressants and first use of
20 cough/cold. In the second column, you see the
21 analysis performed on the subset of the subjects
22 without hypertension. You see, in fact, that the
23 odds ratios remain practically the same.

24 In the case of cough and cold, it
25 increases a little bit. In the third column, you
26 see the analysis conducted on subsets without

1 aphasia, and I must point out that the majority of
2 subjects did not have hypertension and were not
3 aphasic. In the column of subjects without aphasia,
4 the odds ratios again remain the same and, in fact,
5 increases with cough and cold suggesting that
6 subjects with aphasia were, in fact, under-reporting
7 their PPA use rather than the converse.

8 They were concerned about
9 misclassification, that it could skew the results
10 and that the areas that they had most concern with
11 were participant recall and product identification.

12 We respond, as Doctor Kernan pointed out, that the
13 subjects were blinded to the exposure of interest so
14 they had no way of knowing what the investigators
15 were after. The interviewers used a highly
16 structured questionnaire and an exposure
17 verification process which included the product
18 identification booklet. Record bias was minimized
19 by the short interval between the event and the
20 interview for both cases and controls, and this was
21 conducted within 30 days.

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

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

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

18 As we pointed out when we showed the
19 earlier slide, aphasic subjects may in fact be
20 under-reporting their PPA exposure. There is no
21 data to suggest that PPA exposure is related to the
22 severity of the stroke or to survival after a
23 stroke, and perhaps the most important point of all
24 is that several epidemiologic studies show that use
25 of surrogate interviews is a major source of bias in
26 epidemiology studies.

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

14 Now we come to the results. The Yale
15 Study supported an increased risk of hemorrhagic
16 stroke associated with PPA use. The findings were
17 statistically significant among appetite
18 suppressants users and first-day users of PPA as a
19 cough/cold remedy, and you will remember that this
20 is what we were interested in from the agency point
21 of view.

22 Now another job of epidemiologists is
23 not just to assess the strength of the association
24 and the relative risk but to assess the public
25 health impact of such a risk, and that's called
26 attributable risk, and that is defined as how much

1 of a disease can be attributed to a certain exposure
2 and, in turn, how much of the risk -- and risk is
3 defined by the number of new cases per year, the
4 incidence of disease -- how much of the risk can we
5 hope to prevent if we were able to eliminate the
6 exposure to the particular agent.

7 Now, before we do that, we thought we'd
8 show you the extent of usage of PPA products in the
9 United States. Take the year 1999, for example.
10 Six billion dose units were sold. Seventy five
11 percent of it was sold in OTC products. In a
12 population of approximately 300 million, as the
13 United States is, six billion doses sold annually
14 translates into 20 dose units for every man, woman,
15 and child in the population. That's extensive use
16 by any standards. We know that this is doses sold,
17 but there must be a correlation between doses sold
18 and doses consumed. Otherwise, they wouldn't keep
19 selling it.

20 This slide shows the distribution of
21 dose units sold annually by indication, and we see
22 here that 98 percent, the lion's share of PPA use
23 sold, is for cough and cold. It's in the
24 preparation for cough and cold remedies, and only
25 two percent for diet preparations. This is
26 important, these figures, when we come to assess the

1 public health impact. In order to assess the public
2 health impact, we extrapolated from the study
3 population to the general U.S. population.

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

17 The total number of hemorrhagic strokes
18 in the study that occurred in the study period was
19 1,714. Various people have pointed out this morning
20 that only 41 percent were actually used as cases.
21 Of the cases, eight cases had first use of PPA as a
22 cough and cold remedy and six cases had PPA use as
23 an appetite suppressant. We went again to the U.S.
24 Census Bureau data to find the exact figure for the
25 population in the 18 to 49 age group and, as of
26 August this year, the estimate was 130 million

1 people in this age group. We went to the published
2 literature to find the background incidence of
3 hemorrhagic stroke, and we got an estimate of eight
4 per 100,000. We took our estimate from population-
5 based incidence stroke studies. Had we used a
6 higher incidence that was quoted this morning of 20
7 per 100,000, our estimate would have been even
8 larger, but we used the more conservative estimate.

9 Combining our incidence estimate and the
10 population estimate, we get 10,400 hemorrhagic
11 strokes per year in the 18 to 49 age group in the
12 U.S. If we'd used the larger figure, it would have
13 been at least twice that number. And this shows our
14 calculations. I must point out that always
15 attributable risk calculations are imprecise. They
16 give you a rough estimate, a ball park figure, and,
17 by our calculations, we found that between 120 and
18 290 strokes could be attributable to PPA use for
19 cough and cold as a first use and 90 to 220 for
20 appetite suppressants. The figures vary depending
21 on whether you correct for the number of cases that
22 actually did occur, the number of cases of
23 hemorrhagic stroke, or whether you just use the
24 number of the cases that were used as cases in the
25 study. This gives you a total number of cases
26 possibly attributable to PPA use of 200 to 500 in

1 the 18 to 49 age group.

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

13 Another function of epidemiologists when
14 an association has been detected is to try to make a
15 causality assessment. The criteria for causal
16 associations include the following. Temporal
17 relationship and, in all our cases reported to the
18 agency, PPA use has preceded the event. It has come
19 before hemorrhagic stroke. So we have that. That's
20 temporal relationship. Strength of the association
21 is measured by the magnitude of the relative risk
22 or, in this case, the odds ratio. And clearly, 16
23 for an odds ratio for appetite suppressant is a
24 large magnitude.

25 3.1 for cough and cold is a lower
26 magnitude but we think that this may result from the

1 wide variety of doses that was experienced in the
2 study. The doses of PPA exposure range from 6.5 to
3 in excess of 150 milligrams, and we do believe that
4 the risk of hemorrhagic stroke is related to the
5 dose so that this odds ratio would represent people
6 taking the low dose diluting the effect of people
7 taking the higher dose.

8 In the Yale Study, dose response is
9 another measure of causal association, another
10 criterion. The Yale Study showed an increased risk
11 of hemorrhagic stroke with doses of PPA above 75
12 milligrams per day. We conducted our own
13 exploratory analyses which did show dose ordering.
14 That is to say that there was an increased risk with
15 doses of PPA greater than 75 milligrams per day. In
16 our current case review, the 2000 case review, all
17 22 reports were with 75 milligram preparations of
18 PPA.

19 Now we come to biological plausibility.

20 PPA is a sympathomimetic amine and common to all
21 sympathomimetic amines is that they have a
22 demonstrated pressor effect. That is to say they
23 raise the blood pressure. They cause hypertension.

24 There is clear cut tachyphylaxis. That is to say
25 that the pressor effect is reduced with continued
26 doses of the drug. The pressor effect is also

1 greater for the sustained release preparations.

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

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

23 Consistency with other knowledge.
24 Again, we believe this criterion is satisfied. We
25 have had numerous case reports in the literature.
26 Just to mention two. Kase in 1987. He reported 10

1 cases, two of which were his own.

2 The Lake Study has already been referred
3 to this morning. Lake reported the largest series
4 of adverse events associated with PPA use, and he
5 reviewed all the cases that had been reported in the
6 literature up to that time. In his series, he found
7 24 cases of intracranial hemorrhage, 15 of
8 hypertensive encephalopathy or seizures, all with
9 onset within 24 hours and most at the 75 milligram
10 per day dose. Then we have O'Neill and Van de
11 Carr's study which, with all its flaws, did show an
12 association, and we have our own in-house case
13 reviews.

14 The only criterion for causality that
15 has not been met is replication of the study, and we
16 have pointed out before that it would take another
17 10 or 15 years to replicate the study. The question
18 that we must ask ourselves is is it in the public
19 health's interest to wait another 10 or 15 years so
20 that this could be replicated or do we have so many
21 other criteria fulfilled for causal association?

22 In summary then, we have a hypothesis of
23 an increased risk of hemorrhagic stroke with early
24 PPA use generated from our case reports. We have a
25 well-designed prospective case control study that
26 strongly supports our hypothesis, and the criteria

1 for causality have largely been fulfilled. We
2 estimate that, at a minimum, 200 to 500 strokes per
3 year in young people are potentially preventable.

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

13 Finally, I'd like to thank the members
14 of the team who all contributed substantially to my
15 presentation this morning. Thank you.

16 CHAIRMAN BRASS: Thank you.

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

19 Yes, Doctor Daling.

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

26 DOCTOR LA GRENADE: This was provided in

1 the study. We used, in fact, the odds ratios that
2 were statistically significant.

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

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

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

14 DOCTOR LA GRENADE: We used the data
15 that we were testing for in our hypothesis generated
16 by the agency and which were also the ones that were
17 found to be statistically significant in the study.

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

21 DOCTOR LA GRENADE: No.

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

24 DOCTOR LA GRENADE: The data do not
25 support, as Doctor Kernan pointed out. We can't use
26 that sort of thing. We have to use what was

1 statistically significant and what were the
2 hypotheses that were generated by our data.

3 CHAIRMAN BRASS: Doctor Cantilena.

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

9 DOCTOR LA GRENADE: I am not aware of
10 gender response in response to this particular drug.

11 I don't know whether anybody on my team has
12 information to that effect. There is one possible
13 contributory explanation in that women are generally
14 smaller than men and we have found in our agency
15 spontaneous reports that more of the adverse events
16 occur in women and it may be that the doses that are
17 prescribed, that are recommended, are the same for
18 men and women and women are a little smaller in body
19 size. That's just one possible explanation.

20 CHAIRMAN BRASS: Doctor Lam.

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

26 DOCTOR LA GRENADE: That is all risk

1 factors.

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

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

7 CHAIRMAN BRASS: Doctor Blewitt.

8 DOCTOR BLEWITT: Yes. In slide 17 and
9 20, you had indicated that it wasn't reasonable to
10 carry the study out any longer, and I frankly
11 wonder, since we're here today, there seems to be a
12 lot of controversy about the results of the study,
13 whether in fact it wouldn't have been reasonable to
14 carry this study over a long enough time so that you
15 could get conclusive results.

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

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

25 DOCTOR LA GRENADE: Not for the two
26 statistically significant odds ratios. I mean the

1 p-value was, in fact, the conventional .05. That's
2 one thing. And while we're on the subject of p-
3 values, I must point out that a p-value of .05 means
4 that the results could have been obtained by chance
5 alone five percent of the time, and that's the
6 conventional statistical cut-off point when we're
7 looking at efficacy. For safety, we don't need to
8 be as certain. We could accept that we could be
9 wrong 10 percent of the time and right 90 percent of
10 the time when we're looking at safety issues or even
11 lower. We could accept, for example, being wrong 20
12 percent of the time on a safety issue.

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

26 In other words, if you get a stomach

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

6 DOCTOR LA GRENADE: Doctor Graham will
7 answer those comments.

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

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

21 In response to the question does
22 publicity about events stimulate reporting to come
23 in, it's been show that you can get stimulation of
24 reports very close to in time to a very major
25 publicity event but that that stimulation wears off
26 within a month and, with PPA, I haven't seen

1 anything in the newspapers over the last seven or
2 eight years that have been beating the drum that PPA
3 causes stroke, so I don't think that one can point
4 to a publicity effect as being responsible for
5 reporting.

6 CHAIRMAN BRASS: Doctor Johnson.

7 DOCTOR JOHNSON: I have a question.
8 It's really just a clarification. Back on slide
9 six. Doctor Lam was just asking about this. So the
10 14 percent versus the .8 percent, can you explain
11 that again? That means that 14 percent of all
12 strokes that were reported?

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

16 DOCTOR JOHNSON: Okay. Thanks.

17 CHAIRMAN BRASS: Doctor Elashoff.

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

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

26 DOCTOR GRAHAM: We do know that we don't

1 have any cases reported from the state of
2 Connecticut where most of the cases in the study
3 occurred.

4 CHAIRMAN BRASS: Doctor Kittner.

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

11 CHAIRMAN BRASS: Thank you for that
12 confession.

13 Lois, could you say something a little
14 more expanding on slide 21. Part of the critique of
15 the cases in controls and the imbalance in the risk
16 factors is described in your slide 20 and you
17 discussed in particular the lack of difference with
18 regard to hypertension or aphasia in terms of what
19 the observed risk factors were. That goes a long
20 way towards saying that there is an imbalance, it's
21 not responsible for what we're likely to be seeing.

22 What occurs for the other potential confounders
23 that people are concerned about and where might
24 there be some residual concern still left?

25 DOCTOR LA GRENADE: Perhaps one member
26 of the team might want to answer that question.

1 Doctor Yi Tsong.

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

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

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

18 Any other comments or questions?

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

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

7 Doctor Ganley.

8 One question while Doctor Ganley gets
9 set up.

10 DOCTOR NEILL: This is for FDA staff. I
11 thought I heard a comment that PPA is also used in
12 non-monograph OTC medications, and that's been my
13 experience when I walk down the street, and I'm
14 curious about the extent to which PPA exists in
15 those medicines, what kinds of places I might find
16 those in, and whether or not any of those kinds of
17 uses are represented in the data in NHSP or in FDA
18 adverse event reporting system. I'm talking about
19 medicines that are not specifically marketed for
20 cough/cold or for appetite suppressant but that sit
21 on the shelf and, because there's no specific claim
22 made except in very vague terms, aren't covered by
23 monograph.

24 DOCTOR KATZ: Well actually, on the
25 shelf there are both monograph and non-monograph
26 products that do contain PPA. There are cough/cold

1 products that are not monograph products that are
2 there. So I don't know if that addresses your
3 question because not all of the cough/cold products
4 that are out on the shelf now are monograph. Some
5 are NDA.

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

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

22 DOCTOR DELAP: I think there are clearly
23 other products out there available to consumers that
24 include PPA in them. I'm thinking of some of the
25 supplements that contain ephedra alkaloid type
26 constituents of which PPA can be grouped as one.

1 Obviously, that's a whole different situation as far
2 as how much we know about those products and how the
3 adverse experiences come in to us.

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

6 DOCTOR SOLLER: Bill Soller, CHPA. I'd
7 just like to comment. The products that you may be
8 thinking about are dietary supplements that contain
9 ephedra and PPA can be a component of ephedra but it
10 represents about 10 percent or so by weight of what
11 the ephedra is in that particular product and, in
12 most products, even less than that. That was
13 discussed at a meeting in August.

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

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

24 DOCTOR SOLLER: It can't be. Wouldn't
25 be a dietary supplement. It would be a drug, and it
26 couldn't be labeled that way or it would be

1 misbranded and action could be taken on that
2 particular product. So there's a regularity --

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

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

18 CHAIRMAN BRASS: Thank you.

19 Doctor Ganley.

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

25 We've developed a group of questions and
26 we've tried to address them in the order that we

1 think is a logical sequence. The first group of
2 questions address the analysis and interpretation of
3 data from the Hemorrhagic Stroke Project. We're
4 particularly interested in looking at this data in
5 totality but also as a function of the condition of
6 use. As Bob Sherman had noted earlier, PPA is
7 involved in two rulemakings here, one for
8 decongestants and one for appetite suppressants.

9 The other is as a function of dose. As
10 Bob Sherman has also noted, there is some
11 differences in the recommendations for dosing for
12 each of those rulemakings, and obviously as a
13 function of first dose which would apply to both
14 rulemakings.

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

21 When we talk about generally recognized
22 as safe, I think reality tells us that drug products
23 do present some risk for consumers and that no
24 product is absolutely safe. To be generally
25 recognized as safe, an ingredient must have a well-
26 characterized, acceptable safety profile under the

1 conditions of use. In the OTC monograph world, when
2 we talk about conditions of use, we're referring to
3 the clinical indication, dosing and labeling. It's
4 totality of the package. I think it's also
5 important to note whether it's the prescription
6 product or an OTC product. The burden of proof and
7 the burden of submitting data falls on the industry
8 to show us that it's safe. It is not the burden of
9 the agency to prove that it's unsafe.

10 I think other considerations to take
11 into account, that adverse events resulting in
12 serious morbidity or mortality are especially
13 concerning, especially for products in the OTC
14 world. We've already heard from numerous
15 individuals already that the OTC adverse event
16 reporting is limited. Companies that market drugs
17 under OTC monographs are not required by regulation
18 to provide safety reports to us and, at a minimum, I
19 think the consumers need to be adequately informed.

20 If there are adverse events associated with the use
21 of a product, they ought to know about them.

22 On the other hand, generally we make
23 risk benefits assessments. There's been some
24 discussion of the benefit of these products and I
25 think we would all acknowledge that PPA treats
26 relatively benign conditions and, although they're

1 very effective, for example, in decongestants, we
2 also have to keep in mind that there is a great
3 public health benefit by providing easy access to
4 medications for self-care.

5 Finally, I just want to point out.
6 There had been some concern about the
7 recommendations in the OPDRA review that that was
8 the position of the agency, and I think that is the
9 position of the reviewers. It's important to us to
10 listen to the Advisory Committee recommendations
11 that will help us to bring closure to the PPA
12 rulemaking. This is the best data that we're going
13 to see pertaining to this issue, and I think we have
14 to realize at that point in time that we do have to
15 make some decisions.

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

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

24 (Whereupon, off the record at 12:34 p.m.
25 to reconvene at 1:30 p.m.)
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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:34 p.m.)

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

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

So I will read the first question and

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

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

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

22 Doctor Gilman.

23 DOCTOR GILMAN: Well, first, I think it
24 might be helpful to address these questions by
25 looking at men because, as I read the data, heard
26 the data presented, I heard nothing to implicate PPA

1 in hemorrhagic stroke in men, probably because there
2 was no exposure to PPA as appetite suppressant and
3 very few people took PPA who were men for cough/cold
4 remedies. So we might be able to first clear the
5 decks, in a way, by just saying well, there's no
6 evidence or evidence is inconclusive that it has any
7 effect in men. Then we could go on to women. That
8 would make the discussion maybe simpler.

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

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

25 CHAIRMAN BRASS: I'm sorry. To my
26 understanding -- well, in my mind, it's not the same

1 to conclude. One might conclude that there is a
2 significant effect in the general population, a
3 significant effect in a sub-group of women, no
4 significant effect in a sub-group of men. With
5 those three observations, it would be inappropriate
6 to say that there is no data in men because the
7 general population is positive.

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

11 CHAIRMAN BRASS: Doctor D'Agostino.

12 DOCTOR D'AGOSTINO: Not to suggest a
13 different strategy and so forth, but in terms of
14 thinking of this first question, I really think that
15 we want to remember the hypotheses that drove the
16 study, and it was very much women. I'm not saying
17 we shouldn't look at the men first and so forth, but
18 it was really driven very much for the females, very
19 much for the appetite suppressant, very much for the
20 first use, and all the questions about alpha and so
21 forth I don't think -- really, I think it's quite
22 really appropriate. I think it's really appropriate
23 to analyze as they did. Now, how we sort of chip
24 away at that is up for discussion, but I think it's
25 the meat of the discussion in terms of where we want
26 to think about things as what's happened in those

1 females.

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

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

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

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

23 DOCTOR GILMAN: Did not. Correct.

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

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

7 CHAIRMAN BRASS: Doctor D'Agostino.

8 DOCTOR D'AGOSTINO: Yes. Just to
9 reiterate what you said this morning in terms of the
10 end point. There was a lot of discussion about the
11 end point being inappropriate. I'm not sure I
12 followed, and I thought your comments were right on
13 target in terms of how I think of clinical trials
14 and being put together. Just to say again what was
15 just said now, I think the study was well-designed,
16 well-executed. There were lots of potential biases.

17 It took 10 years to put together, and no matter
18 what we do. If we say at this point, if we finish
19 saying let's run another study, this study can't be
20 dismissed. I mean we would only be in the position
21 where we may make confirmation of this or not but
22 this study can't be dismissed and so I think
23 chipping away -- and I'm not sure this is the
24 sequence I'd want to chip away at because I think
25 the women who were alpha-type suppressant to first
26 use and then you sort of build up and it isn't

1 necessarily solely driven by alpha of .05/.05 but
2 how do the hypotheses that led to the study lay out
3 and how do the end points get suggested.

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

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

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

23 DOCTOR GILMAN: I think that's eminently
24 reasonable and, again, I think there's good
25 rationale for grouping together subarachnoid
26 hemorrhage with intracerebral hemorrhage with

1 arteriovenous malformations with hemorrhage.
2 Presumably there's some sort of hemorrhagic
3 diathesis connected with use of PPA. So I think
4 there's very good justification for the grouping.
5 And, in addition, this was an hypothesis-driven
6 trial based upon what could be called anecdotal
7 evidence, at least frequent reports, actually quite
8 compelling frequent reports.

9 CHAIRMAN BRASS: Yes, Doctor Daling.

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

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

26 CHAIRMAN BRASS: Doctor Elashoff.

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

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

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

19 DOCTOR DALING: No. Controls.

20 DOCTOR ELASHOFF: Cases versus controls.

21 DOCTOR DALING: They have a table in
22 here.

23 CHAIRMAN BRASS: Use the microphone.

24 DOCTOR DALING: There's only seven PPA
25 users in the whole study -- I mean appetite
26 suppressant one.

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

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

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

26 CHAIRMAN BRASS: So Doctor Daling, so

1 the rates for RDD control recruitment that you cited
2 in terms of expectations, did they include a direct
3 personal interview?

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

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

14 DOCTOR DALING: We get 70 percent or
15 better.

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

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

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

23 DOCTOR DALING: They only had one
24 control to stratify it by. I mean you only had one
25 exposed control, yet if you looked at the exposed
26 controls for weight control, you will see that

1 people who use PPA in general -- I assume these are
2 general population -- that they're more likely to be
3 smokers than are the general population.

4 CHAIRMAN BRASS: I think Doctor --

5 DOCTOR DALING: Why is that wrong?

6 CHAIRMAN BRASS: Because these are in
7 the cases.

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

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

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

14 CHAIRMAN BRASS: Yes.

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

21 CHAIRMAN BRASS: Okay.

22 DOCTOR D'AGOSTINO: The stratification
23 analysis though talked about those who didn't smoke,
24 didn't it?

25 DOCTOR DALING: Well, there was nobody
26 in that strata for weight control. I mean for the

1 smokers, there was only one person in weight control
2 who used it in the controls. That was --

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

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

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

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

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

21 DOCTOR DALING: Yes.

22 DOCTOR D'AGOSTINO: Not more controls.

23 DOCTOR DALING: And they knew at the
24 outset that -- he said that this is exactly what
25 we'd expect, that we would only have one person who
26 used this for weight control who was in the control

1 group, one person. He said .5 of one percent were
2 expected to be using this for weight control.

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

5 DOCTOR DALING: Use of this drug.

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

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

12 DOCTOR D'AGOSTINO: Very, very few.

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

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

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

22 CHAIRMAN BRASS: In terms of the one
23 control who was exposed, the issue of the
24 sensitivity analysis I think is extremely important
25 and to the degree to which having two or three
26 instead of one would have affected the outcome. I

1 understand the FDA did such an analysis. Could you
2 just comment on that sensitivity analysis very
3 briefly just with respect to if that one had been
4 two or three.

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

22 Okay. Let's go to slide 74.

23 CHAIRMAN BRASS: While it's coming up,
24 Doctor D'Agostino, do you want to --

25 DOCTOR D'AGOSTINO: Yes. Again, I think
26 the discussion is that if you made the study bigger

1 and bigger and bigger, you would have started seeing
2 some of the controls with the exposure and the
3 argument or the discussion is that the study wasn't
4 big enough in terms of number of controls, but I
5 think that you do have the sensitivity analysis and
6 I think the sensitivity analysis might bring some
7 clarification on that.

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

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

24 In this one, I give a different
25 scenario. The first column is the probability of
26 misclassification of case exposed and the second

1 column is the probability of misclassification of
2 control exposed and then we have a corrected odds
3 ratio based on our -- data. As you see, if we go to
4 all the misclassification up to 40 percent in the
5 control arm but no misclassification in the case
6 arm, then we still have about the 7.1 correct odds
7 ratio. I think this is extreme misclassification
8 assumption.

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

13 CHAIRMAN BRASS: I understand. Okay.

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

16 CHAIRMAN BRASS: Please wait until
17 you're recognized.

18 DOCTOR HENNEKENS: I wanted to make a
19 comment about my concern about the over-reliance on
20 statistical methods as a way to overcome an
21 inadequate sample and to expand on Doctor Daling's
22 point, you have a comparison of six exposed cases
23 versus one exposed control. That exposed control
24 does not smoke cigarettes and three of the six cases
25 do not smoke cigarettes. So a quote/unquote
26 "stratification analysis" on cigarette smoking leads

1 you that once you adjust for smoking in this
2 analysis, you're comparing three versus one. Not
3 significant.

4 If you're controlling for hypertension,
5 the control did not have hypertension but two of the
6 six cases had hypertension. So you're left in a
7 stratification on hypertension for four versus one.

8 And I think the most extreme example of these data
9 is if you stratify by a BMI of greater than 35. You
10 have none in the cases and one in the controls.
11 This is what happens when you have such small
12 numbers. There is no amount of statistical analysis
13 that can overcome the inadequacy of the sample to
14 control for confounding.

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

21 MS. COHEN: I have a couple of concerns.

22 The end product of this are consumers, and I don't
23 know how one can make a total decision on the safety
24 or efficacy without seeing what the insert is, and I
25 happened to pick something up and it talked about
26 decongestants and they mention thyroid disease,

1 diabetes, prostrate. What about interactions with
2 other disease? I'd like to know about that, but I
3 also want to know if this board, whatever they
4 decide to vote, if they vote that this can continue
5 on the market, I want to see what information is
6 given to consumers. I want to make sure that
7 consumers are safe and understand what they're
8 taking because so far no one has really, to my
9 satisfaction, described to me what PPA does.

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

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

24 CHAIRMAN BRASS: Yes, I can.

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

26 CHAIRMAN BRASS: Would you like the