

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DRUG ABUSE ADVISORY COMMITTEE
WITH REPRESENTATION FROM THE
NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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OPEN PUBLIC HEARING

ON

IMPROVING THE PRESCRIPTION LABELING
OF SMOKING CESSATION PRODUCTS

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Monday, June 9, 1997

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The hearing was held in the Versailles Room at the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 9:00 a.m., Doctor Eric C. Strain, Chair of the Committee, presiding.

PRESENT:

DOCTOR ERIC C. STRAIN, Chair

DOCTOR KAREN M. TEMPLETON-SOMERS, Executive
Secretary

DOCTOR ELIZABETH KHURI, Member

DOCTOR ALICE M. YOUNG, Member

DOCTOR ANNE ANDORN, Member

DOCTOR HARRIET de WIT, Member

DOCTOR CAROL L. FALKOWSKI, Member

DOCTOR LLYN A. LLOYD, Member

DOCTOR ROGER E. MEYER, Member

DOLORES YAROMA, Member

DOCTOR RALPH D'AGOSTINO, NDAC Member

DOCTOR THEODORE G. TONG, NDAC Member

DOCTOR PIPPA M. SIMPSON, PDAC Member

ALSO PRESENT:

DOCTOR NORMAN A. DREZIN, FDA

DOCTOR CELIA JAFFE WINCHELL, FDA

DOCTOR CURTIS WRIGHT, FDA

A-G-E-N-D-A

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1 P-R-O-C-E-E-D-I-N-G-S

2 9:07 a.m.

3 CHAIR STRAIN: Let's go ahead and get
4 started. My name is Eric Strain. I'll be chairing
5 this meeting. Let me introduce Karen Templeton-
6 Somers, the Executive Secretary, who will review the
7 Conflict of Interest Statement.

8 Oh, before we start that, let's take a
9 moment and go around the table and introduce
10 ourselves to each other. Maybe if we could start at
11 this end, please.

12 DOCTOR TONG: Good morning. I'm Ted
13 Tong. I'm from the University of Arizona, Professor
14 of Pharmacology/Toxicology, and I'm a member of the
15 Nonprescription Drug Advisory Committee for the FDA.

16 DOCTOR D'AGOSTINO: Ralph D'Agostino from
17 Boston University. I'm also a member of the
18 Nonprescription Drug Advisory Committee.

19 MS. YAROMA: Dolores Yaroma, Registered
20 Nurse at Second Genesis in Rockville, Maryland, a
21 long-term drug and alcohol abuse facility, treatment
22 facility.

23 DOCTOR YOUNG: I'm Alice Young, Professor
24 of Psychology and of Psychiatry in Behavioral
25 Neuroscience at Wayne State University in Detroit,

1 and a member of the Drug Abuse Advisory Committee.

2 DOCTOR ANDORN: Anne Andorn, Acting
3 Assistant Chief of Staff for Mental Health, St.
4 Louis VA, and I'm also Associate Professor and Vice-
5 Chair of the Department of Psychiatry of St. Louis
6 University School of Medicine.

7 CHAIR STRAIN: I'm Eric Strain. I'm from
8 Baltimore.

9 EXECUTIVE SECRETARY TEMPLETON-SOMERS:
10 Karen Templeton-Somers, Executive Secretary, Drug
11 Abuse Advisory Committee, FDA.

12 DOCTOR KHURI: I'm Elizabeth Khuri. I'm
13 at Cornell New York Hospital, New York City,
14 Associate Professor of Public Health Pediatrics, and
15 Director of the Adolescent Development Program,
16 which is a research demonstration methadone
17 maintenance clinic for young people developed by
18 Dole and Neisswinder.

19 DOCTOR de WIT: I'm Harriet de Wit, I'm
20 in the Department of Psychiatry at the University of
21 Chicago, and I'm a member of the Drug Abuse Advisory
22 Committee.

23 DOCTOR SIMPSON: I'm Pippa Simpson. I'm
24 Associate Professor at Wayne State University, and
25 I'm a biostatistician.

1 DOCTOR FALKOWSKI: I'm Carol Falkowski.
2 I'm with the State Alcohol and Drug Abuse Agency for
3 the State of Minnesota, and a member of the Drug and
4 Alcohol Advisory Committee.

5 DOCTOR LLOYD: I'm Llyn Lloyd with the
6 Arizona State Board of Pharmacy and a member of this
7 committee.

8 DOCTOR DREZIN: I'm Norman Drezin. I'm
9 the Deputy Director and Supervisory Regulatory
10 Counsel for the Division of Drug Marketing,
11 Advertising and Communications.

12 DOCTOR WINCHELL: I'm Celia Winchell.
13 I'm the Medical Team Leader for the Addiction Drug
14 Products part of the Division of Anesthetic,
15 Critical Care and Addiction Drug Products at FDA.

16 DOCTOR WRIGHT: Curtis Wright, Acting
17 Director for the Division.

18 CHAIR STRAIN: Thank you.

19 And now, Ms. Templeton-Somers will read
20 the Conflict of Interest Statement.

21 EXECUTIVE SECRETARY TEMPLETON-SOMERS:
22 The following announcement address the issue of
23 conflict of interest with regard to this meeting and
24 is made a part of the record to preclude even the
25 appearance of such at this meeting.

1 Based on the submitted agenda and
2 information provided by the participants, the Agency
3 has determined that all reported interests and firms
4 regulated by the Center for Drug Evaluation and
5 Research present no potential for a conflict of
6 interest at this meeting with the following
7 exceptions.

8 In accordance with 18 USC 208(b)(3) a
9 full waiver has been granted to Doctor Elizabeth
10 Khuri. A copy of this waiver statement may be
11 obtained from the Agency's Freedom of Information
12 Office, Room 12A-30, Parklawn Building.

13 In addition, we would like to disclose
14 for the record that Doctor Murray Jarvik has
15 excluded himself from today's discussions on
16 labeling for smoking cessation products.

17 In the event that the discussions
18 involve any other products or firms not already on
19 the agenda, for which an FDA participant has a
20 financial interest, the participants are aware of
21 the need to exclude themselves from such involvement
22 and their exclusion will be noted for the record.

23 With respect to all other participants,
24 we ask that in the interest of fairness that they
25 address any current or previous financial

1 involvement with any firm whose products they may
2 wish to comment upon.

3 Thank you.

4 I'd also like to announce for the
5 benefit of the people in the audience that if you do
6 address the committee in any way that you come up
7 and use the microphone, either at the podium or many
8 of the open public hearing speakers will be using
9 the podium at the front of the room. If you are not
10 at the table, please do state your name, your
11 affiliation, and any industry support that you have.

12 Thank you.

13 DOCTOR WRIGHT: Mr. Chairman?

14 CHAIR STRAIN: Yes.

15 DOCTOR WRIGHT: Doctor Winchell will
16 make the first presentation on behalf of the Food
17 and Drug Administration.

18 CHAIR STRAIN: Yes, thank you.

19 DOCTOR WINCHELL: Good morning, I'm
20 Celia Winchell, I'm the Medical Team Leader for the
21 group that has responsibility for the smoking
22 cessation products. Thank you for being with us
23 today.

24 The topic we'll address today is the
25 prescription labeling of smoking cessation products,

1 and we hope to have a discussion on how the labeling
2 might be improved. It's our hope that we'll come
3 away from this meeting with some ideas for secondary
4 efficacy measures that could be added to current
5 labeling in order to improve the information we
6 provide to clinicians.

7 Let me say, for a minute or two, a
8 couple of words about what we are not going to talk
9 about. We are not planning to discuss at this
10 meeting either reconsidering the primary outcome
11 variable used to define success in clinical trials,
12 smoking cessation products, or to discuss other
13 indications of these products besides smoking
14 cessation.

15 We are very aware that these subjects
16 are of great interest to many people here, and many
17 more people who are not here, and I want to assure
18 you that these topics will be taken up in due time.

19 Many issues are complex and wide
20 reaching. However, we like to think that the
21 prescription labeling of smoking cessation products
22 is a narrow enough area that we at the division
23 level can reach some tangible conclusions and
24 recommendations in a single meeting.

25 This is actually where this all began,

1 in this very room, if I am not mistaken. Here we
2 were considering the NDA for bupropion SR, which we
3 recently approved as ZYBAN for smoking cessation,
4 and it was at this meeting where we became aware
5 that we had developed certain traditions in writing
6 prescription labels and didn't question them until
7 this particular meeting.

8 We had allowed Glaxo-Wellcome to present
9 in their briefing package and in their presentation
10 several secondary efficacy measures, but we didn't
11 comment on them, and we didn't include them in the
12 labeling. And, at that meeting, members of the
13 committee suggested that this information would
14 actually be useful to clinicians and that we should
15 consider adding more efficacy information to the
16 label.

17 And, the following day similar questions
18 arose in the discussion of the Nicotrol inhaler NDA,
19 and the result was that a working group of committee
20 members was formed to help us consider various
21 questions relating to the efficacy outcomes for
22 these products. The first task of the assignment
23 was to prepare for this meeting.

24 Let me say a word of thanks to this
25 group, Doctor Andorn, who has served as the Chair,

1 Doctor Snyder, who has been unable to be with us
2 today but works very hard on this, getting it ready,
3 and passed his input along, and Doctor Strain.
4 Doctor Andorn will be speaking shortly.

5 And, in a moment I'll describe the
6 process that we used to gather information for this
7 meeting, but first I'd like to give you some
8 historical background.

9 Many of you may know that the pilot drug
10 evaluation staff was the group responsible for the
11 review and evaluation of products to treat smoking
12 cessation, among other addictive disorders, prior to
13 the establishment of our division, HFG-170, in the
14 fall of 1995. The pilot drug evaluation staff
15 approved no fewer than five smoking cessation
16 products in the course of about a year over 1991 to
17 1992, Nicorette 4 milligram gum, the 2 milligram gum
18 had already been on the market for several years,
19 the Habitrol patch, NicoDerm patch, Nicotrol and
20 Prostep patches. They used a common team of
21 reviewers they called the Nico Team, and they had
22 established this common team so that they could work
23 together to provide the proverbial level playing
24 field in writing the labels. They emphasized
25 commonalities wherever possible. They used common

1 language wherever possible, and the aim of this was
2 to try to prevent those minor differences in
3 labeling that result in the spurious promotional
4 claims we are so familiar with from ads now on
5 television.

6 One of the things they did was to meet
7 in September of 1991, to come to closure on writing
8 a consistent label for three products then under
9 consideration, so that they could establish a
10 template that would be used for all three of those,
11 as well as for future products. I've been reviewing
12 the records from this meeting and from labeling
13 meetings that preceded it, gaining a new
14 appreciation for the importance of the
15 administrative record, and I can see from these
16 records that the question of how to present the
17 efficacy of these products was a difficult one, even
18 then, and that the template we've been using since
19 was arrived at, really, through careful
20 consideration by the review team.

21 Some of the decisions are documented in
22 the record, others are available to us only through
23 the oral tradition, but having written it all down
24 now I guess we have the tomlit of smoking cessation
25 product labeling, so hopefully those decisions which

1 anybody -- that I don't remember how it happened, if
2 anybody else does they can let us know.

3 Basically, there were six specific items
4 that I could identify that were addressed by the
5 pilot drug review team in choosing how to label
6 these products. The first decision was to include a
7 range of quit rates across centers, rather than a
8 single number that represented the efficacy for the
9 study. The second issue was that only one
10 definition of abstinence, the protocol defined
11 definition, was that it included for analysis the
12 quit rates that were reported which were based on a
13 specified four-week period, they didn't include one-
14 week quit rates, that's the measure that sometimes
15 we call point prevalence rates, and they did not
16 include data on the number of cigarettes smoked by
17 non-quitters, although that data was available, and
18 although various withdrawal symptoms were measured
19 in different studies, only craving was reported in
20 the labeling.

21 I'm going to run through these one at a
22 time and tell you what I could divine regarding how
23 these decisions were made. The quit rate ranges,
24 these products were all tested in multi-center
25 studies, and the reviewers noted a very wide range

1 of quit rates across centers, in both the treatment
2 group and the placebo group, and, in fact, the
3 attributable quit rate, the number of percentage
4 points by which the treatment differed from the
5 placebo group, varied from up to 30 percent to small
6 negative numbers in studies where the placebo group
7 beat the treatment group. And, the reviewers
8 ultimately said they wanted to give the clinician a
9 feel for the expected quit rate and also the
10 variability across clinics, and that including a
11 range of quit rates seemed like the best way to do
12 this.

13 This also had the effect of preventing
14 promotion of the products based on overall quit
15 rates, which they felt were going to turn out
16 slightly different for spurious reasons, because
17 they really felt that all the products had about the
18 same efficacy, and they wanted to prevent this.

19 This choice also resulted in, without
20 making a very complicated graph, it seemed like the
21 only way to present these ranges, was in a tabular
22 format, and that was another side effect of this
23 decision.

24 Next was the definition of abstinence.
25 We've been rather consistent about this. In smoking

1 cessation trials, and in all the protocols,
2 abstinence is defined as the patient reports smoking
3 zero cigarettes since the previous reference point,
4 the patient appears at the study site during a
5 specified window of time to provide a biological
6 sample suitable for the detection of smoking,
7 usually that's breath, carbon monoxide, and produces
8 a sample that's below the cutoff specified, in the
9 case of CO usually it's about ten parts per million.
10 And, people have criticized this, that it's too
11 stringent and it underestimates quit rates, but it's
12 what we've been using.

13 After submission, the sponsor sometimes
14 suggested that we could consider annualizing the
15 quit rates using some more liberal definitions, like
16 abstinence with slips, or smoking on no more than
17 two days during the period of abstinence
18 determination, but, again, this returns to the idea
19 that all they were going to present was a range of
20 quit rates. So, when they looked at this and they
21 said that these secondary analyses did not produce a
22 change in the statistical relationships between the
23 treatments, in other words, the study one on the
24 strictest definition, since they didn't really want
25 to put a bunch of different quit rates in the label

1 anyway there was no reason to include these.

2 This slide is wrong. It says abstinence
3 defined as weeks through six, but actually what I
4 meant was, success defined as abstinence during
5 weeks three through six inclusive, and I'll remind
6 you that the notion that success should be quit for
7 a month came out an advisory meeting similar to this
8 one. Basically, the advisory committee thought that
9 to be considered successful somebody ought to be
10 able to quit for a month, and this was translated in
11 clinical trials into, generally, there would be a
12 week or so of grace after the quit date, and then
13 efficacy would be determined six weeks after the
14 quit date, at which time the person had to say
15 they'd been abstinent for a month.

16 I should just say, there's probably a
17 little confusion, because sometimes this is called
18 weeks two through six, which means the end of week
19 two to the end of week six, and sometimes it's
20 called weeks three through six, which means the
21 beginning of week three through the end of week six,
22 it's all the same thing. In fact, in other studies
23 where, for example, the drug is supposed to be taken
24 for a little while before you try to quit, sometimes
25 it says weeks four through seven. It really doesn't

1 matter.

2 You may ask, why do they choose to
3 analyze the data this way. This was a conscious
4 choice, because actually it wasn't the protocol
5 definition of success in every trial, although now
6 it is, I mean we've really kind of come to some
7 agreement on this, and the products we're getting in
8 now this is the protocol definition, but there was
9 one that defined it as any four of eight and was
10 reanalyzed using weeks four through six. And, the
11 sponsor suggested some alternative analyses,
12 additional alternative analyses, using things like
13 any four of seven, or abstinence since quit date,
14 but, again, the administrative record shows that the
15 motivation was to provide a level playing field, and
16 they explained why they reanalyzed this data saying,
17 this was purposes of consistency of labeling across
18 approved nicotine patches.

19 The next thing that was considered was
20 these one-week quit rates. I've been asked by my
21 grammar and usage consultant to put in a word
22 against the term point prevalence rates, that it is
23 triply redundant, in that prevalence is both at a
24 point and a rate. You might consider what we want
25 to call this, I called it one-week quit rates.

1 Actually, the reviewers looked at this,
2 they requested this analysis, and they wanted to
3 look at this, this is defined as the percentage of
4 subjects who have been abstinent for seven days
5 preceding that measurement, and they looked at this
6 in the hope that it would help them to decide how
7 long to keep trying on the treatment in the case of
8 a patient who was not able to quit. They concluded
9 that the design of the trial rendered this
10 uninformative. It said, examination of the week-at-
11 a-glance quit rates suggest that most patients who
12 will quit had done so by week three. Unfortunately,
13 this is probably an artifact of the two-week grace
14 period which the subjects were allowed in order to
15 be still eligible for the weaning protocol.

16 Nevertheless, this is an analysis that
17 still retains a certain amount of popularity, and we
18 are interested in knowing what people think of it.

19 Smoking reduction was another thing that
20 they took a look at. They examined the number of
21 cigarettes smoked by non-quitters, and they actually
22 recommended an additional analysis to the sponsors,
23 because the initial analysis compared the treatment
24 group and the control groups with respect to the
25 absolute numbers of cigarettes per day, and it

1 turned out to be statistically significant, but the
2 groups were different by only a few cigarettes per
3 day, and they just didn't think that was clinically
4 meaningful, so they suggested this categorical
5 analysis, in which the definition of reduction was
6 being able to reduce to half pack per day.

7 But, upon examining this, first of all,
8 they said that they felt there was a distinct
9 paucity of evidence supporting the health benefits
10 of reduction, and also, they were concerned about
11 the impact on cessation attempts of endorsing this
12 as an indication. This was of sufficient concern
13 that it was taken to the Drug Abuse Advisory
14 Committee in 1991, and it was also discussed at
15 other venues, such as the CPDD meeting, and input
16 was obtained from the American Lung Association, and
17 there was concern that endorsing reduction as also
18 an option would have a negative impact on cessation
19 attempts, and since this worrisome hypothesis had
20 not been disproved, and has yet to be, smoking
21 reduction, although demonstrated in clinical trials,
22 was not included.

23 Next was the decision to include craving
24 as an index measure of withdrawal symptoms. The
25 different trials included different measures of

1 withdrawal symptoms, some had the patients rate the
2 severity of seven different DSM-III withdrawal
3 symptoms, in others they rated only craving, only
4 withdrawal. Other trials were done in Swedish, we
5 don't really know what they were rated, only what
6 the translator tells us which one was craving.
7 However, the reviewers elected to include only
8 craving, and anecdotally my understanding is they
9 wanted to choose a single cardinal symptom of
10 withdrawal, about which they had data for all of the
11 products, and they commented, "The concurrence of
12 the craving reduction and the quit rate does not
13 prove it as a causative factor, but the logical link
14 between reduction of craving and quitting is easily
15 appreciated."

16 The sponsors did want, in some cases, to
17 present other single measures, but they were not
18 permitted to do so because in the case where there
19 are a panel of measures it was felt to be
20 inappropriate to just pick the ones that had turned
21 out statistically significant, multiple endpoint
22 problem.

23 Another little side effect here was
24 that, although there's data for craving across
25 studies, they didn't all use the same measure, so

1 that, the artifact of this is the little diagram in
2 the labels that shows craving, but doesn't have any
3 labels on the Y axis, because we wanted to -- it was
4 hard to know how to compare them across studies, so
5 that's what they did to manage that.

6 So, this is what we've been doing to
7 date. After the advisory committee called our
8 attention to these issues last December, we decided
9 to take a hard look at what we've been doing and see
10 whether it's time to make a change. Already we have
11 approval on label that includes overall quit rates
12 for two multi-center studies, because we felt that
13 the overall rate was a pretty good representation of
14 the efficacy.

15 So, we need your input to decide what
16 other changes to consider, and this meeting is the
17 first step. In preparation for our discussions
18 today, we solicited input from a variety of sources.
19 As you know, the members of the committed were
20 polled for their responses and for their suggestions
21 on what members of the research community should be
22 asked for input, and then a phone survey of
23 researchers was conducted by our working group
24 members. We sent a letter to commercial sponsors
25 asking them how they would like to have seen their

1 label differ or how they'd like to change their
2 labels, and we sent letters to organizations and
3 agencies with an interest in this matter, like SRNT,
4 and American Lung Association, NIDA and so on.

5 We tried to broadly publicize the
6 meeting and its topic and the availability of a
7 public docket for submissions through Federal
8 Register Notice, through our press office, it's made
9 its way into a number of industry publications, and
10 some researchers were kind enough to help us out by
11 posting this inquiry on their group's WEB site or
12 mailing list.

13 We are very fortunately, actually, that
14 a number of the people who responded to the docket
15 or the phone survey were sufficiently interested in
16 this issue to come here today to speak to you in
17 open public session. We expect to have a lively
18 group of presentations and an interesting
19 discussion.

20 This is the question we'll be posing to
21 you this afternoon, after our presentations. Of the
22 suggestions mentioned today, which additional
23 efficacy measures do you believe might be clinically
24 meaningful and would offer useful information to the
25 clinician, such that we should consider adding them

1 to the prescription labeling for smoking cessation
2 products. I'd like you to keep it in mind as we
3 proceed through the agenda.

4 I've provided some historical background
5 and next you'll hear from Norm Drezin, who is the
6 Deputy Director for the Division of Drug Marketing,
7 Advertising and Communications, which we call DMAC,
8 and Norm will help us understand how labeling and
9 promotion are linked, what is in the jurisdiction of
10 DMAC and what is not, and what options exist for
11 communicating information to clinicians.

12 After that, Doctor Andorn will present
13 the information she received from the process of the
14 phone poll, and then we'll hear from speakers in
15 open public session, and Doctor Strain will
16 summarize some of the commonalities he saw across
17 those comments, then we'll have a discussion.

18 Thanks a lot.

19 CHAIR STRAIN: Thank you, Doctor
20 Winchell.

21 We'll next hear from Doctor Drezin. As
22 he's coming up -- yes, do you want to go ahead and
23 make an announcement?

24 EXECUTIVE SECRETARY TEMPLETON-SOMERS:
25 As part of the active recruitment of public response

1 to this topic, we have a lengthy open public hearing
2 scheduled for 10:30. At this time, however, we'd
3 like to invite any members of the audience who have
4 not signed up previously to make brief comments if
5 they would like. Are there any requests for time at
6 the open public hearing, at the brief one?

7 Thank you.

8 DOCTOR DREZIN: Good morning. It's a
9 pleasure to be here today. I'm going to be talking
10 about some issues that are generally not things that
11 are discussed by an advisory committee or topics
12 that you usually would have reason to be involved
13 in. And so, I hope that, you know, I'm going to try
14 to explain it as clearly as I can.

15 The agenda for today is to discuss the
16 relationship between labeling and promotion, the
17 labeling requirements and the advertising
18 requirements. I want to start off with what the
19 Agency's authority is.

20 The Agency is responsible for the
21 labeling of all drug products, prescription drug and
22 over-the-counter drug products, and is also
23 responsible, primarily, for prescription drug
24 advertising. The Federal Trade Commission has
25 primary responsibility for over-the-counter

1 advertising.

2 Now, when FDA became involved in drug
3 advertising back in the '60s, there was some
4 discussion of how the different areas were to be
5 divided under the legislation, and in the early
6 1970s there was a memorandum of understanding
7 between the FTC and the FDA, in which they basically
8 came to the conclusion that FTC would have primary
9 responsibility for over-the-counter advertising and
10 FDA would have primary responsibility for
11 prescription drug advertising. I say primary
12 responsibility, bear in mind that that doesn't
13 exclude either agency from either product area, and
14 there are some areas at times when FDA may be
15 involved in OTC issues and the FTC may wish to be
16 involved in prescription issues.

17 Another issue that's very important for
18 this panel to understand is that unlike the approval
19 process for prescription drugs, where nothing
20 happens until the product is approved in a proactive
21 way by the Agency, promotion does not have that
22 advantage. The FDA does not require promotion
23 materials to be precleared, as a matter of fact the
24 statute prohibits that except in extraordinary
25 circumstances. And, there are very few

1 circumstances in which that has actually come about.

2 Primarily, the one area that you may be
3 aware of in which promotion materials must be
4 submitted to the agency prior to being used are for
5 products that have been approved under the
6 accelerated approval process, which offer drugs for
7 life-threatening and serious illnesses.

8 With that point, where do practitioners
9 get information about prescription drugs, and
10 primarily the approved product labeling is a primary
11 source, also publications, peer review journals,
12 continuing medical education, in pharmacy and
13 nursing education programs, and promotion, which is
14 probably where they see most of it, brochures, ads,
15 videos, seminars, dinner meetings, et cetera, and
16 there's a tremendous amount of that information.

17 Now, the statute actually requires, it
18 defines labeling to mean all labels and other
19 written, printed or graphic matter upon any article
20 or any of its containers or wrappings, or
21 accompanying such article. Now, that last -- that
22 second phrase, accompanying such article, is a very
23 key issue in regulating prescription drug promotion,
24 because what that did, by a Supreme Court decision
25 in 1948, was, basically, to say that the material

1 that a manufacturer or sponsor hands out to the
2 practitioner in their office or in the health care
3 setting, even though it's not with the product, is
4 still labeling.

5 So, what is the purpose of labeling?

6 Let me just, to clarify some language here first
7 off, when we talk about labeling for this part of
8 the talk we are going to be talking about the
9 approved product labeling or package insert, and
10 that is the labeling that the agency approves that
11 everybody is familiar with, it has specific sections
12 and specific layout. There's also the concept of
13 promotional labeling, though that's not defined in
14 the statute, and that is something that I will use
15 to describe everything else from the pen that has
16 the name of the drug, to the video, to a product
17 monograph that might be 75 or 100 pages long and
18 describe everything else known about the drug.

19 And then, there's advertising, and I'll
20 describe the difference between advertising and
21 promotional labeling a little later.

22 So, the purpose of labeling is to inform
23 health care providers about the drug, and that is
24 primarily for the agency the key issue. I'm going
25 to refer to a Federal Register statement that issued

1 in October of 1995, describing a public meeting
2 about the revamping of the package insert, and in
3 that Federal Register statement the agency said,
4 "The major purpose of prescription drug product
5 labeling is to help ensure that prescribing health
6 care professionals have the information necessary to
7 prescribe products in a safe and effective manner."
8 They go on to say, "The approved labeling
9 communicates the conclusions of FDA review of the
10 data, of the product's new drug application." And
11 finally they say, "The approved labeling also serves
12 as the basis for product promotion. FDA's
13 regulations specify that all advertising claims made
14 about a product be consistent with approved
15 labeling."

16 But, remember that the labeling, when
17 approved by the agency, has another function too, to
18 the industry, that's the license that enables them
19 to put this product on the market, promote it and
20 sell it, and there are distinctions because there
21 are different interests. The agency has a very
22 specific interest in its mandate about providing
23 information to health care providers about the
24 drugs, so that they can be used in a safe and
25 effective way. The industry wants to do that, they

1 also want to sell a lot of product, and what that
2 labeling says and how they can use it makes a big
3 difference in the marketing of their product.

4 So, when you talk about prescription
5 drug labeling, as you see I learned how to use clip
6 art when I was playing with these slides. I was
7 having a little fun with them. The issue about
8 labeling is going to be misbranding. That's the
9 violation, a prohibited act under the statute is if
10 a product is misbranded, and the product can be
11 misbranded because it's false and misleading, the
12 labeling or advertising is false or misleading in
13 any particular, and that applies to both the
14 approved product labeling and the promotional
15 labeling for the product.

16 Now, what I want to do here, and I want
17 to impress upon you, is the fact that all these
18 things are treated the same way under the statute
19 and regulations. For example, in the prescription
20 drug labeling regulations, Section 201.100(c)(1),
21 and I'll try not to do that too often, giving
22 citations, labeling, being that which is on or
23 within the package, must have adequate information
24 for its use, for all intended purposes, and for all
25 purposes for which it is advertised or represented,

1 and that's a summary of that section.

2 But, the next section in the same
3 regulation, 100(d)(1), talks about any labeling,
4 whether or not it is on or within the drug package,
5 whether it's distributed by the manufacturer, or
6 sponsor, or somebody on their behalf, and then sets
7 out the very same identical language and uses. So,
8 there's no distinction between that which can be
9 given in the package insert and that which can be
10 given in the promotional labeling, brochures, slim
11 jims or any type of other product literature that is
12 dropped off or mailed to your office.

13 Now, what is the labeling? Under the
14 regulations, it's a summary of the scientific
15 information for the safe and effective use of the
16 drug. The approved product labeling or package
17 insert should be informative and accurate, and
18 neither promotional in tone nor false or misleading
19 in any particular. And, the any particular is nice,
20 broad language, I mean it covers just about anything
21 and everything you want to say, and statements that
22 may be in there about a drug.

23 Now, this is very important because in
24 the development of labeling, both between the agency
25 and the sponsors, sponsors usually have a plan for

1 how they are going to market their product. This is
2 all thought out beforehand, and when they come to
3 the agency they know how they want to strategically
4 place their product in the marketplace, both amongst
5 competitive products and amongst other uses or other
6 treatment modalities. And so, they are always
7 trying to find a way of having language in that
8 label that gives them the basis to go forward with
9 this strategic plan, and that's very important to
10 them. Whether or not it meets the agency's criteria
11 is another issue.

12 Under the more specific requirements of
13 the labeling, it has to be safe and effective, and
14 one of the areas where you find a lot of
15 differentiation in labeling is based on patient
16 subgroups, the subpopulations, be in age or agenda,
17 or concomitant conditions, or severity of disease,
18 and that makes a very important distinction when you
19 are talking about a drug that's used in a second
20 line situation, because it has efficacy but because
21 of its adverse events it shouldn't be used in
22 certain patients, or it's only been tested in mild
23 disease and we don't know what would happen in the
24 severe cases, or it's never been tested in a patient
25 that had a recent MI, and are there any differences

1 when you use a product in that patient population or
2 any other specific concomitant disease patient
3 population than the patient population in which the
4 drug was studied, and what are those differences.

5 There are also limitations in the
6 labeling requirements that address the product being
7 refractory to other drugs, so that it's used only
8 when other drugs were shown to be ineffective, or
9 short-term use, the drug was only studied in four or
10 six weeks, and it's going to be used chronically,
11 it's going to be used for the rest of the patient's
12 lifetime. Or, very key is when not to use the
13 product, and that also can be in the labeling and
14 could be part of the recommendations for labeling.

15 Now, when I mentioned before promotional
16 labeling, I started to give a definition. It's not
17 really defined, but the advertising regulations list
18 a rather long list of examples, which includes
19 brochures, booklets, mailing pieces, file cards,
20 bulletins, calendars, price lists, catalogues,
21 letters, videos, et cetera. It includes baseball
22 caps and tee shirts, it includes pens and coffee
23 mugs, and anything else that is apt to be putting
24 the product before you.

25 On the other hand, advertising is

1 considered to be published journals, magazines,
2 newspapers, that which is broadcast through media,
3 such as TV and even telephone communications, and as
4 you know there are a lot of communications now about
5 calling 800 numbers and getting into rather lengthy
6 discussions.

7 The key difference between promotional
8 labeling and advertising is that labeling must have
9 the full approved package insert with it,
10 advertising can have something called a brief
11 summary, which is best described as neither brief
12 nor a summary, but it basically contains all of the
13 risk information that accompanies the product and is
14 in the labeling. You see this most often in either
15 professional journals or most recently in the lay
16 press, where you see a product ad and then there's a
17 page or a half page of extremely small, blurred type
18 that's almost impossible to read.

19 The key is that these two materials, or
20 types of materials, or types of promotion, are
21 treated the same under the statute. Section 201 in
22 the statute talks about it in terms of the
23 representations made or suggested in labeling or
24 advertising, omissions of material fact, these are
25 ways that the products can be misbranded and

1 considered false or misleading, and that is in the
2 representations made or suggested even in a positive
3 sense, or by omitting significant information. And,
4 a part of the statute that's very unique is that
5 they also talk about the consequences that may
6 result from the use of the drug.

7 So, the standard for labeling and
8 advertising is that it can recommend and suggest the
9 drug only for those uses contained in the approved
10 product labeling, they may not be false, lacking in
11 fair balance, which is something I'll talk about a
12 little more in a minute, or otherwise misleading.

13 Prescription drugs are unique. The law
14 requires disclosure of the consequences of using the
15 drug, consequences being fair balance. Drugs have a
16 beneficial result, and that's why we are using them.
17 They also have a lot of negatives, and that's what
18 takes up most of the space in the product labeling,
19 and that also needs to be communicated.

20 When you buy a car, and they don't have
21 to tell you that it's going to break down or might
22 break down, you use a drug and they need to tell you
23 that it may cause a granular citosis, or it may
24 cause nausea and vomiting, or something along those
25 lines.

1 In an article back in 1990, before
2 becoming commissioner, Doctor Kessler wrote in the
3 JAMA a fair balance test, and that is that the
4 advertisement, or labeling as the case may be,
5 viewed in its entirety to determine whether it
6 presents a balanced account of all clinically
7 relevant information, the risks and benefits that
8 can affect the physician's prescribing decision.

9 Now, this is important in the sense of
10 this panel is going to be considering labeling, and
11 what more we need to tell physicians, and that could
12 be all that we need to tell the providers, whether
13 it be positive for greater use or great benefit of
14 the product, as well as things we need to call out
15 to their attention that are negative about that
16 patient population of that use.

17 The advertising regulations provide
18 specifically that it would be false or misleading if
19 an ad contained a representation or suggestion not
20 approved or permitted in labeling, that a product
21 was more effective than was stated in the labeling,
22 and that frequently may come up because the labeling
23 says that the drug was effective in 30 percent of
24 the patients treated, and out comes some article or
25 some promotional material that talks about 70, 80,

1 90 percent, 110 percent, I don't know, going upward,
2 a broader range of conditions or patients that may
3 be based on patient subpopulations, it could be
4 based on severity of disease, concomitant disease,
5 or altogether unrelated conditions, or that it's
6 safer than is described in the labeling, and that
7 commonly comes about in some situations in which the
8 labeling says, has a high incidence of some adverse
9 event and they are trying to make it appear safer by
10 talking about something that gave some data about a
11 lower incidence. So, it's better, more effective,
12 broader range of conditions of patients, or safer,
13 fewer side effects, less incidence, or less serious.

14 Now, another issue comes up with
15 comparative claims, and in the marketplace we've got
16 to consider, and I think Celia spoke earlier about
17 the number of nicotine patches, and just think about
18 all the other drug products, the number of -- there
19 are ten ace inhibitors, there are a number of
20 calcium channel blockers, everybody is looking to
21 find a niche against this competition, and to find a
22 comparative claim that says my drug is better than
23 your drug, or my competitor's drug. It contains a
24 comparison that represents or suggests that a drug
25 is safer or more effective than another drug in some

1 particular, when it's not been demonstrated to be
2 safer or more effective.

3 Now, this is the advertising
4 regulations, but let me talk about the labeling
5 regulations.

6 In 201.57, the specific regulations lays
7 out the specific requirements for each section of
8 the labeling, in V, let's see, I guess it's 3-V,
9 "Any statements comparing the safety or
10 effectiveness, either greater or less, of the drug
11 with other agents for the same indications shall be
12 supported by adequate and well-controlled studies as
13 defined in Section 314.126(b) or unless this
14 requirement is waived." So, when you are looking at
15 labeling and you are seeing studies, there's a
16 question of whether the comparative information in
17 there actually meets the standard to say that this
18 drug is better than the other drug. There may be
19 some data, there may be some either a trend or there
20 may even be, you know, some higher level of
21 persuasive data, but does it meet the standard for
22 comparison between those two products or two or more
23 products.

24 In general, we look to see that
25 comparative claims are supported by substantial

1 evidence, and that's usually described as at least
2 two adequate and one controlled studies, and that
3 they use the products compared in the claims, and
4 that may sound a little obvious, but often times we
5 see studies that do not compare the products.
6 Perhaps it was a foreign study, and the product
7 that's actually being marketed and sold in Europe is
8 not the same product that's going to be marketed and
9 sold in the United States. It must be within
10 labeling for all products, sometimes that could be
11 within the uses or the patient populations, or that
12 they use appropriate dosages and doses of all
13 products.

14 Some of the things that we've seen in an
15 attempt to support comparative claims are things
16 like that a comparison is made but the comparative
17 product is not actually administered in the dosage
18 formulation, the dose or the route of administration
19 that would be used in the United States, or that
20 it's not an appropriate dosage. For example, one
21 way of showing efficacy is to use a high dose of one
22 product and a low dose of the other product, or for
23 adverse events and safety, do the converse. So,
24 these have to be looked at very carefully to make
25 sure when you are looking at comparative data that

1 they are using the same part of the dosage range,
2 the correct products, the correct route of
3 administration, because that recommendation, if it
4 appears in labeling, it will appear in promotions,
5 it will appear on billboards, it will appear
6 everywhere you see the product, and it may or may
7 not be supportable, it may not be validated, and we
8 need to know that, you need to consider it.

9 And, with that, I think I'll close and
10 open it up to any questions that you may have.

11 CHAIR STRAIN: Thank you, Doctor Drezin.

12 We'll now take a few minutes for
13 questions from the committee for Doctor Drezin.

14 Doctor Lloyd.

15 DOCTOR LLOYD: What can you tell us
16 about the oral presentation and things that are not
17 printed or in media presentations, things that are
18 just made orally in promotions and advertising?

19 DOCTOR DREZIN: Well, the great wish to
20 be the fly on the wall, if we could only be so. We
21 considered oral presentations to be advertising,
22 because they are not written, printed or graphic,
23 and to the extent that we can bring an action, this
24 is retrospective, because in the promotional sense
25 it's always retrospective. Something has to happen,

1 we have to have evidence, we have to be informed
2 about it, and we have to then be able to develop
3 enough evidence to bring an action.

4 The most recent, or I should say one of
5 the most major cases we brought involving that was
6 issues involving Abby Pharmacia a few years ago, for
7 the promotion of dipentum for ulcerative colitis.
8 In that situation, we had evidence, both from people
9 who received information as well as from company
10 programs in which they were training and critiquing
11 people about -- sales reps about how they made the
12 presentations in order to know what took place in
13 the oral. They actually took the oral presentations
14 and had written documentation about them.

15 But, we also had oral evidence of
16 people, both from people who made presentations, as
17 well as people who received presentations, and in
18 that case we wound up in a permanent injunction.
19 But, it's difficult, we need practitioners to tell
20 us what's happening, we need sales reps or former
21 sales reps who were unhappy about being forced into
22 making such presentations, and then we can develop
23 the case.

24 And, the other thing is that for
25 practitioners, when, you know, you are being told

1 things, be skeptical and challenge what you are
2 being told, and if you feel it's inappropriate, give
3 us a call, call the Med-Watch line, you know, call
4 the agency, or even complain to the company, but I
5 would suggest you call us, we'd really like that.

6 CHAIR STRAIN: Yes.

7 DOCTOR TONG: What interest does the FDA
8 have with the materials on the Internet, as we see
9 increasing materials, company sponsored and others,
10 dealing with particular products? Are they
11 considered promotion? Are they considered
12 advertising, or just what?

13 DOCTOR DREZIN: They are considered
14 promotion when they are put on by the company, or
15 someone on behalf of the company. We have not come
16 upon a decision or guidance yet that we are working
17 on to make a determination of whether it's labeling
18 or advertising, but at this time we are saying,
19 really, for our purposes and for current purposes
20 the industry should treat it as one or the other and
21 follow the rules.

22 It really doesn't make a lot of
23 difference between whether you put up the full
24 product information or whether you put up the brief
25 summary, since the Internet is not limited in space

1 or cost for that purpose, I can't imagine why
2 anybody would want to put up the brief summary
3 instead of the full prescribing information because
4 the difference is positive information, the full
5 prescribing information would have the clinical
6 trials and the clinical pharmacology sections, and
7 the full indications section, the brief summary is
8 not required to have that.

9 So, most companies that I'm aware of
10 that use the Internet are putting on their full
11 prescribing information with it, and it is looked
12 at, we do monitor it, obviously, we don't have the
13 resources to spend a lot of time surfing the WEB
14 from company to company, but I assure you that in
15 most instances competitors do an ample job for us,
16 and we find out what's going on on the Internet and
17 have acted appropriately, but it is promotion.

18 CHAIR STRAIN: Other questions?

19 Yes, Doctor Winchell.

20 DOCTOR WINCHELL: Let me just ask you to
21 comment on direct-to-consumer advertising, because I
22 know a lot of times when we think about what would
23 be useful to the clinician, at the same time we
24 think what might be confusing to the consumer. And,
25 if you can just let people know about how direct-to-

1 consumer advertising is regulated.

2 DOCTOR DREZIN: Direct-to-consumer
3 advertising is regulated the same way that
4 professional advertising is regulated. It requires
5 fair balance. It can't be false or misleading.
6 Often times it may be a little difficult to come up
7 with adequate information in what we call consumer
8 friendly language. A brief summary is still
9 required, and appears, if you look at Parade
10 magazine, or any of the other lay publications,
11 Time, Newsweek, or whatever, and you see
12 prescription drug ads, flip the page and you'll see
13 the brief summary.

14 But, looking at the proliferation of it,
15 it certainly has grown and those requirements have
16 not hampered that growth, you know, totally. How
17 much would be without that requirement we don't
18 know.

19 The real issue is what can consumers get
20 out of it, and that depends on how much effort the
21 sponsor wishes to make. The information doesn't
22 hurt consumers. There's a big difference now
23 between the amount of information that consumers
24 want or demand and the amount that they used to want
25 or demand.

1 I go back to the time when I was in
2 pharmacy school, a few hundred years ago, and we
3 look at that time, it was actually unlawful for a
4 pharmacist to put the name of the drug on the label
5 of the bottle. Patients did not know what drugs
6 they were taking, and they really didn't ask, they
7 didn't want to know.

8 In the late '60s or early '70s, a change
9 was made in that pharmacists were able to put the
10 name of the drug on the label if the doctor checked
11 a box on the prescription that said "label."

12 We've come a long way now, just go to
13 Borders, or any of the book stores, and you'll find
14 entire sections on prescription drug compendia that
15 people are buying because they want information.

16 I was at Price Club a couple of months
17 ago, they were selling PDRs, they had a very large
18 stack of PDRs in the middle of the floor. People
19 want information, and considering the fact that we
20 hear a lot about consumers saying, you know, the
21 brief summary, nobody wants this information, why
22 are they buying PDRs, that is the epitome of the
23 information, they want information, they are asking
24 for information, they want to know what the drugs
25 are for, they also want to know the adverse events

1 about the drug.

2 CHAIR STRAIN: Doctor Lloyd?

3 DOCTOR LLOYD: Do you have any comments
4 on off-label use in promotional activities or
5 unapproved use promotional activities?

6 DOCTOR DREZIN: Well, if there are
7 promotional activities, I wish you'd tell me about
8 those when they are going on, because, clearly, that
9 is against the regulations.

10 The whole concept, the whole process
11 that we have committees like this, and the review
12 process since 1962, is for those indications to be
13 determined to be safe and effective and to be placed
14 on the label.

15 And, when you have off-label uses you
16 are circumventing that system. The label is
17 basically the only data that has been independently
18 evaluated to determine whether, in fact, it's valid
19 and that the drug is safe and effective for those
20 conditions.

21 There is off-label information out
22 there, certainly the agency has never attempted to
23 stop health care providers from using products for a
24 variety of uses, though the regulations apply to the
25 sponsors as far as giving out information, and even

1 there the agency has waived a little bit to the
2 extent that if a provider wishes information and
3 calls a company, or asks the company, can I get
4 information about such and such, the agency does not
5 interfere with that provision of that information.
6 But, the agency says, number one, that information
7 should not be prompted by the company, practitioners
8 should say, I have a patient, I have a problem, what
9 do you know about something, rather than, wouldn't
10 you like to have some information about -- you know,
11 sign this card, or if you want this information I'll
12 be happy to pass this forward to the company and we
13 can send it to you, and that's prompted, that's
14 solicited, and that's not appropriate.

15 But, on unsolicited requests, the agency
16 has not sought to interfere with the provision of
17 what we consider to be a scientific exchange of
18 information.

19 CHAIR STRAIN: Doctor Khuri.

20 DOCTOR KHURI: I simply would like to
21 underline the importance of Doctor Winchell's
22 remark. I imagine it's fair to say that the
23 regulations governing advertising in People magazine
24 are, perhaps, less stringent than the actual
25 labeling on the product, in that the pictures, for

1 example, that you can use that transmit the
2 messages, whether sex or pleasure, we all know the
3 complexities of advertising and marketing, and
4 convincing the consumer to buy one product over
5 another, whether it's laundry soap or an
6 antihistamine, that this is really a major factor
7 because increasingly, as we know following up on
8 your remarks, patients come in to doctors telling
9 them what they want them to prescribe, that they
10 know from their reading that Habitrol is better than
11 NicoDerm, and that's what they want. And, how they
12 got that impression is very often from the trade
13 magazines and not the labeling.

14 I just wanted to underline that point.

15 CHAIR STRAIN: Thank you.

16 Doctor de Wit?

17 DOCTOR de WIT: You mentioned the
18 advertising of prescription medications is the
19 jurisdiction of FDA, but advertising of OTC is the
20 jurisdiction of the Federal Trade Commission, is
21 that right?

22 DOCTOR DREZIN: Correct.

23 DOCTOR de WIT: So, when something
24 changes from prescription to over the counter are
25 there any immediate concerns, or is there going to

1 be any action to change the advertising to fit in
2 with the Federal Trade Commission? Can you tell us
3 something about when something changes from one to
4 the other?

5 DOCTOR DREZIN: When there is a switch
6 about to take place, well, first off, one thing
7 that's important to recognize is the fact that these
8 agencies don't exist in a vacuum. We know those
9 folks very well, they know us, we talk to each other
10 very often, we meet and so each other. So, it's not
11 a vacuum. As a matter of fact, some of them attend
12 advisory committee meetings for the OTC products,
13 and they are aware of the switches, to the extent
14 that they need information that's of a medical,
15 technical or scientific nature they ask and we
16 provide. To the extent that we have some concerns,
17 we are not shy about discussing it with them.

18 So, there is a very good interaction
19 that takes place constantly. It's not something
20 that needs to be started or adjusted.

21 Does that help you?

22 DOCTOR de WIT: Is there anything
23 different about the rules of the Federal Trade
24 Commission versus FDA, and what wording, or how they
25 advertise?

1 DOCTOR DREZIN: Yes, I mean, there's a
2 significant difference in the way the two agencies
3 operate, by their statutes. The standard is fairly
4 the same, their deception and our misleading are
5 fairly close.

6 The issue is that they don't get
7 materials submitted. One of the issues in the
8 prescription drug advertising and promotional area
9 is that sponsors are required to submit every ad or
10 promotional piece that they use at the time they
11 start to use it. So, a promotional material, at the
12 time they initially disseminate it, and advertising
13 at the time of its initial publication. The same ad
14 may run in 30 journals, they only have to submit it
15 once.

16 The FTC does not have any such
17 requirement. Their case generation is usually based
18 on them seeing something or receiving a complaint
19 about it and generating the case and making a
20 determination that they ought to look at it. They
21 may wind up getting information from us, they may
22 wind up getting information from consumers, or
23 health care providers, and they are very receptive
24 to receiving that information, but they do not have
25 the same type of reporting requirement. And their

1 process, which is now in some modification to giving
2 more advice to industry, but at least up until now
3 has been, here's the law, you know the law, you
4 break the law and then we'll take an action, without
5 any specific oversight, because, remember, not only
6 do they look at over-the-counter drug ads, but they
7 are looking at cars, and perfumes, and clothing,
8 they have the entire gamut of everything else but
9 prescription drug advertising. It's a resource issue
10 as well.

11 CHAIR STRAIN: Other questions?

12 Thank you, Doctor Drezin.

13 We'll now hear from Doctor Andorn, the
14 Chair of the working group, who will provide a
15 summary of the telephone survey of academicians
16 conducted by the working group.

17 Doctor Andorn.

18 DOCTOR ANDORN: Some of this may seem a
19 little redundant with some of the things said by
20 previous speakers, because we didn't coordinate very
21 well, but I think we may also have a different spin
22 on some of the same words.

23 When I first talked to some of the
24 individuals and asked our questions, it became
25 obvious that the discussion became rambling the

1 minute I said the word label, and often, as my
2 students will tell you, when that happens I figure
3 that it's because we don't all have the same
4 definition.

5 So, I went back to Webster's, this is
6 out of my own book shelf so you can see how often I
7 replace my Webster's, but the 1986 Webster said that
8 a label is, "A slip of paper or other material to
9 designate or describe, indicate nature, ownership,
10 destination of an article." The 1966 definition is
11 very similar but includes "...other appropriate
12 information."

13 I think where we come to in the labeling
14 of prescription products is the narrow 1986
15 definition, put the minimum in there obtained by the
16 sponsor, whereas, the intent of the statute may have
17 been a little closer to the 1966 version which said,
18 "... include other appropriate information." And,
19 with that in mind, I think we are in the middle of a
20 pendulum swing, because what we are doing today is
21 looking at what other appropriate information needs
22 to be included in the label.

23 And, from the same statute that we have
24 just heard, a little paraphrasing, but the label
25 shall contain the summation of essential scientific

1 information, and the underlines are mine. It
2 doesn't say the summation of essential scientific
3 information obtained by the sponsor, it says the
4 summation of essential scientific information for
5 the safe and effective use of the drug. The label
6 shall be informative, and it's hard to be
7 informative if you restrict too much what you put in
8 the label, and accurate, neither promotional, nor
9 false.

10 And, importantly, that no implied claims
11 or suggestions of drug use may be made if there is
12 inadequate evidence of safety or there's a lack of
13 evidence of effectiveness. And, for those of us
14 stuck in the HMO managed care battles, I wanted to
15 point out the word effectiveness is the key word,
16 not efficacy.

17 So, really, as we've already heard, the
18 obligations of the label are to give the indications
19 for the use of the product, to give the evidence of
20 effectiveness, not efficacy, and that, of course,
21 includes the mechanism if it's known, and to also
22 state what is known about the safety of the
23 compound, that includes everything from dose ranges
24 to toxicity, side effects and so forth.

25 Now, what do physicians really want?

1 And, if I listen to my staff at staff meetings, or
2 my residents haranguing me with questions about
3 drugs, what it sounds like the physician really
4 wants is, tell me who in this label should get the
5 drug? How high can I push the dose, particularly in
6 the case of a non-responsive patient, and how do the
7 sponsor findings relate to the general body of
8 literature? What's the rational basis I should use
9 to pick this drug over any other drug?

10 And, please, please, in this label,
11 relieve me of the liability, and that includes for
12 alternative uses, that includes for prescribing in
13 obstetric cases, and the chronic use of a short-term
14 study compound.

15 Now, some of those wishes may be
16 unrealistic, given the statute, but some of the
17 people we talked to have come up with some creative
18 ideas for meeting some of those wishes.

19 Now, can the label be changed, and I
20 think that's an issue that the committee needs to
21 think about. Certainly it can, a label can be
22 changed at any time. It can be changed at the
23 request of the sponsor, who may have additional
24 findings, say, from Phase IV trials, new
25 information, new indications, as we've seen recently

1 with Wellbutrin. It can be changed at the request
2 of the agency, if the agency gets new safety
3 information, develops warnings based on input, or
4 new findings reported in the academic journals
5 concerning the compounds.

6 And, I think what's really progressive
7 is what this particular branch of the FDA is doing,
8 is being sensitive to the customer, and customer
9 satisfaction with the label and what this meeting
10 really is also about is what is the consumer, the
11 health care provider consumer, input to modifying
12 the labels for smoking cessation products.

13 Now, the method we used to tap into our
14 academic colleagues in the smoking cessation arena
15 was very informal. We had a very short time
16 turnaround, so we couldn't do anything formal, and
17 it was very non-random.

18 What we did, as Doctor Somers generated
19 us a list of NIH grantees, I went through that
20 current list and anybody who had smoking cessation
21 in the title of their grant got a chit next to their
22 name and we attempted to contact them. Those
23 individuals then suggested other individuals, and we
24 also had suggested names from the board members.

25 The cohort was actually limited to those

1 who returned our calls, and in my case at least, I
2 made only two attempts to contact people. I just
3 didn't have enough time to do more than that.

4 We reported the results as a consensus,
5 and a consensus is the majority of respondents.

6 Now, I know Salient really doesn't want
7 us to talk about design, but when you approach
8 academic researchers in this area it is very
9 difficult for them, although the FDA sees these two
10 events as separate processes, they seem inseparable
11 to most academicians. I really didn't want to throw
12 away some of the good ideas that were shared by our
13 colleagues, so I will give two seconds to the issue
14 of some of their suggestions about design.

15 Consensus was that a one-month quit rate
16 is just not realistic in the real world of
17 treatment. It is just not realistic, particularly,
18 for nicotine. But, if that's the standard, they
19 understand that. They would recommend changing
20 design to a longer-term treatment, six to 12 months
21 were the time periods most people mentioned.

22 Quit rates for one month may be useful,
23 both useful clinically to let the patient know they
24 are on the right track, but they really -- the
25 consensus was these drugs have been studied for too

1 short a period.

2 Quit rates for a day were considered
3 useless, a useless piece of information to get from
4 a study, and that total abstinence really is the
5 gold standard, that reduction in use is misleading,
6 both to the provider and the patient. I think it
7 was Doctor O'Brien who state that it's well known
8 that even if reduction occurs for a short time
9 period, there's rapid escalation back to the
10 previous dose, and so treatment outcome of reduction
11 is not fair to the patient.

12 Some of the comments, and these are
13 individual comments made, smoking cessation and
14 relapse prevention are two important aspects of
15 treatment, the current design only addresses
16 cessation. The success rate in nicotine addiction
17 is lower than alcohol, cocaine and heroin, where
18 long-term treatments are applied and are the
19 standard. A methadone-type model might be
20 therapeutically useful, i.e., long-term chronic use
21 of a nicotine substitution product, and that a
22 current design is illogical by applying a low dose
23 for a short period of time. And, finally, that the
24 issue of restarting a cessation program after failed
25 abstinence is also not addressed by current design.

1 Now, there were some consensus ideas for
2 changes in the label, assuming design stays the same
3 as it is. The academicians did want point
4 prevalence data included, but they wanted it
5 explained carefully, and I kept hearing that, you
6 know, you have to be simple to the providers, and
7 pretty soon I was beginning to get the feeling that
8 once you graduate and finish your residency and go
9 out in the field you lose IQ points, and that's not
10 the issue. The issue is that you are no longer
11 speaking the language of statistics every day, and
12 if you don't use the language you lose the
13 vocabulary. And so, we need to be very careful,
14 that kept coming through, in how we label, how we
15 use language in the label, so that it's easily
16 understood by the provider.

17 The academicians wanted six month and
18 one year abstinence data included. They also wanted
19 the specified adjunct treatments applied. If it was
20 a behavioral treatment that was also given to the
21 patients, what did it consist of? How many
22 sessions, group, individual, so forth.

23 The consensus was that all data should
24 be explained, even what statisticians think is
25 readily understandable to the consuming public, it

1 should be explained in simple language, and limit
2 the discussion in the label to the achievement of
3 abstinence, and not reduction in smoking.

4 There was an overwhelming consensus to
5 add published safety data that is already available,
6 whether it was obtained by the sponsor or not. For
7 instance, the study by Murray, which looked at 3,000
8 patients who continued to use Nicorette gum long
9 after short-term use would have terminated, and
10 several respondents suggested that a generic
11 statement concerning the need for long-term use
12 based on the literature should be added.

13 Some suggested formats, one from Doctor
14 Young, to kind of explain some point prevalence data
15 in a simple language. We studied blank, how many
16 smokers for blank number of days or months, and
17 during the study such a percent abstained from
18 cigarettes for at least one month at some time
19 during the study, and another percent were abstinent
20 at the end of the study, which was for however many
21 months.

22 One of the more creative suggestions for
23 a change in format was add a discussion section to
24 labels, and include relevant literature and other
25 reported, and that meant literature reported

1 experience, and discussions, not just of relative
2 risks, but, for instance, harm reduction, that it is
3 well known in the literature that smoking is harmful
4 to fetuses, nicotine is less harmful, if harmful at
5 all, to the fetus, and, therefore, a patch might
6 reduce the harm, even though that hasn't been
7 studied. This kind of idea could be included in a
8 discussion section, and could even include
9 discussion from advisory board meetings, and be done
10 in a format very similar to the neurobiology of
11 aging, where data is presented and then two or three
12 people discuss very briefly that data and the impact
13 of it on outcomes.

14 Some of the specific comments made
15 address which stage of change the product is best
16 used, is it useful in the pre-contemplative stage,
17 is it useful only in the action stage?

18 Specify the effects on specific
19 withdrawal symptoms, not just craving, which some
20 people said was useless anyway, but the specific
21 withdrawal symptoms being those that the consumer is
22 most interested in, irritability, weight gain, et
23 cetera.

24 Include rates of relapse upon
25 discontinuation from the study, not just rates of

1 abstinence, but what practitioners need to talk to
2 their patients about are rates of relapse, and
3 include the information on the number of prior quit
4 attempts by the study cohort. Were these all
5 patients that this was their first attempt, or for
6 some was this third and fourth attempt, and were
7 there differences in their response, since it is
8 well known it takes multiple attempts to quit
9 smoking.

10 Two researchers that were polled opposed
11 changing the label, although they suggested lots of
12 good changes, because changes might confuse
13 providers who are used to the present standard and
14 might be unfair to some products that are already
15 out there to change the labels at this late date.

16 Two other researchers suggested the use
17 of a generic statement that encourages the use of
18 clinical judgment, a blanket statement like,
19 although these data would support short-term use,
20 the literature supports long-term use, and we
21 encourage the clinician to make a treatment plan
22 based on the needs of his or her patient, some
23 generic statement.

24 So, in summary, the academicians
25 suggested changing design to include longer-term

1 treatment, and change the label to include what
2 long-term data has been obtained, point prevalence
3 data, and literature data on long-term safety and
4 treatment, literature data on relapse prevention,
5 and to specify the role of the product in the
6 overall treatment plan for the patient.

7 That's it. If there are any quick
8 questions before the break?

9 CHAIR STRAIN: Yes, let's take a few
10 minutes to see if the committee has questions.

11 Yes, Doctor D'Agostino.

12 DOCTOR D'AGOSTINO: Were there any
13 comments about comparative statements with the
14 placebo? One of the difficulties I had in terms of
15 reviewing this material in general is that, if you
16 look at the individual centers and you start talking
17 about the rates, and you introduce the range, you
18 start getting overlap with the drug versus the
19 placebo and so forth. And, one of the ways of
20 addressing this, not only in terms of secondary
21 measures, but even the primary measures, might be to
22 emphasize more the comparative statements with the
23 placebo or other control groups. Has anything like
24 that come up in the discussion?

25 DOCTOR ANDORN: Only from one individual

1 did the issue of placebo even come up, because I was
2 pretty rigid and said, let's not talk about design.
3 You are given the design we have, how would you
4 change the label?

5 DOCTOR D'AGOSTINO: No, I'm talking in
6 terms of presenting the material.

7 DOCTOR ANDORN: Right, but nobody
8 discussed it.

9 DOCTOR D'AGOSTINO: Nobody discussed it.

10 CHAIR STRAIN: Doctor Winchell.

11 DOCTOR WINCHELL: I just wanted to
12 clarify, when you mentioned using -- including point
13 prevalence data in the label, from your presentation
14 I surmised that you meant across time to present how
15 many people were able to abstain for a month, not
16 necessarily the month that was specified.

17 DOCTOR ANDORN: There were two pieces of
18 that. One is, not necessarily the month, they felt
19 that if there were patients that did abstain for a
20 month this is useful information, whether it was the
21 month or not. But, the second issue was, if you
22 took a point in time, how many people were
23 abstaining at that time point, whether or not they
24 had abstained in that month.

25 DOCTOR WINCHELL: But, you are saying

1 those who are abstaining at that time point would be
2 defined as abstaining for how long prior to that
3 determination?

4 DOCTOR ANDORN: How long it ever turned
5 out for that individual.

6 DOCTOR WINCHELL: So, either a month or
7 five minutes.

8 DOCTOR ANDORN: You take the point in
9 time and then you retrospectively look at how long
10 that patient or person had been abstaining.

11 DOCTOR WINCHELL: Okay.

12 CHAIR STRAIN: Other questions for
13 Doctor Andorn?

14 Thank you.

15 We are running a little bit behind, but
16 why don't we go ahead and still take a 15-minute
17 break at this point, plan on reconvening here at
18 10:45.

19 (Whereupon, at 10:28 a.m., a recess was
20 taken until 10:51 a.m.)

21 CHAIR STRAIN: If I could ask the
22 committee members to take their seats, please.
23 Let's go ahead and get started.

24 Before we get started with the open
25 public hearing, I'd like to take a moment and

1 introduce Doctor Roger Meyer, who has joined the
2 committee, to the committee members and the
3 audience.

4 I'd like to explain that we are now
5 moving into the open public hearing. We have a
6 series of speakers who will be making comments over
7 the course of the remainder of this morning. Each
8 one has been allotted up to 20 minutes, I understand
9 not all anticipate taking 20 minutes, but they have
10 20 minutes allowed, and I will keep an eye on the
11 clock.

12 The way we'd like to do this is, allow
13 the committee an opportunity to ask a few questions
14 of speakers if they so desire after each speaker has
15 completed their presentation. Some speakers do need
16 to move on after their presentation, so they won't
17 be here necessarily for the remainder of the day.
18 So, with the speaker's permission, and with the
19 committee's willingness, we will proceed in that
20 manner.

21 We'll begin then with Doctor John
22 Hughes, who will be our first speaker. It's your
23 choice, Doctor Hughes, which podium you wish to use.

24 DOCTOR HUGHES: Thank you, Doctor
25 Strain.

1 CHAIR STRAIN: If you could identify
2 yourself and your institution at the beginning of
3 your presentation, thank you.

4 DOCTOR HUGHES: All right.

5 I'm John Hughes. I'm a Professor at the
6 University of Vermont, and I'm here speaking on my
7 own behalf. I would like to make three points
8 today, three recommendations.

9 The first is that you not making any
10 decisions about labeling today whatsoever. The
11 second is that you not let the issue of labeling
12 divert you from what I understand was the major
13 issue in the last couple meetings, which is,
14 reconsideration of approval criteria. And then
15 thirdly, that you, before you making decisions, that
16 you join with some other organization in having a
17 scientific meeting on this issue.

18 The major rationale for this is that of
19 all the issues that come before you I would say that
20 smoking cessation is the most important, and because
21 of that I don't see any reason to rush to decision,
22 and we need much more data before making a decision.

23 I would like for you not to make a
24 decision today for two reasons. One is, I don't
25 think you are going to have the benefit of full

1 information. Although we have a lot of people here,
2 I would note that there are not public
3 representatives of NCI, of NIDA, CPED, of the
4 American Lung Association, so, clearly, you are not
5 getting all the benefit of discussion today that you
6 could.

7 Secondly, there was a short notice of
8 only about a month. Now, I know of nine meta-
9 analytic data sets that could be mine for discussion
10 on these, but none of the people that I talked to in
11 the last month were willing to rush and try to get
12 some data together for this meeting here. So,
13 there's lots of data out there that you could use to
14 make decisions that you are not going to have the
15 benefit of today.

16 Secondly is, I think that making
17 decisions on labeling is putting the cart before the
18 horse. In my letter to you, I predicted that much
19 of today's meeting would not be around labeling, but
20 would be around approval criteria. I was heartened
21 to see that Doctor Winchell and Doctor Andorn both
22 confirmed my prediction.

23 So, to make a decision on labeling
24 without making a decision on approval criteria, you
25 just can't do it. What happens is one of two

1 things. You either back into an approval criteria,
2 without fully considering it, or you end up with two
3 standards, one standard for approval and one
4 standard for advertising. That puts independent
5 scientists like myself into a bad position, because
6 we have two different criteria.

7 You've got to remember that FDA
8 decisions have very big impacts on our field. The
9 one-month and six-weeks criteria is now appearing in
10 the scientific literature quite a bit. So, what you
11 decide today influences my field greatly, and to
12 make those decisions without having adequate input
13 from my colleagues I think is a disservice, not only
14 to the FDA, but to the field in general. This is a
15 big decision.

16 Let me just give you an example. We've
17 heard talk about craving, well if we make a decision
18 on craving, how are we going to do that? For
19 example, are we going to use an intent-to-treat
20 analysis, or are we only going to look at cravers
21 who are abstinent? Are we going to look at peak
22 craving, are we going to look at duration to not
23 craving? Are we going to look at area under the
24 curve? Is craving the first week important or
25 craving the first four weeks that's important?

1 So, all of those, you may say, well, all
2 that's approval stuff, but you've got to decide that
3 for labeling too. There's no way to make a decision
4 on craving about labeling without addressing those
5 four issues. I mean, you can't do it without
6 reconsidering approval.

7 Secondly, let's say you make a decision
8 on marketing about craving you can advertise this
9 way, the next pharmaceutical company that comes to
10 you with an indication of craving, I'm not saying my
11 drug is cessation, I just want craving, they are
12 going to point at that advertising decision that you
13 made and back you into a corner of using that as an
14 approval criteria.

15 Secondly, I was very encouraged that the
16 DAAC was interested in making my field relook at
17 approval criteria. I think this was a great service
18 that you've done to us. We've had lots of debates
19 in our field, but never had anybody really say,
20 look, stop the bandwagon, tradition is not quite
21 enough, let's do it.

22 I think we need a full discussion of
23 this. I think -- I'm very pleased with your survey,
24 I think that's a very systematic way to go about
25 that, but surveys are consensus, and they don't

1 necessarily reflect validity. Okay. If I wanted to
2 have a survey of what works in the chemical
3 dependency field and I survey chemical dependency
4 counselors, they may not give me the most valid
5 decision.

6 So, I would again urge you to consider a
7 conference. This could be sponsored by SRNT, by
8 NCI, by NIDA, by the American Lung Association,
9 AHCPH, and if you could have it by the fall, and I
10 think that if you asked these people that have these
11 nine data sets, for example, they could look at some
12 very interesting questions. For example, what's the
13 relationship between point prevalence and continuous
14 abstinence?

15 My view on this is, I can make the point
16 prevalence rates go up very easily. I just choose
17 people that are very motivated, make them put down a
18 deposit, give them lots of behavior therapy, and use
19 a liberal criteria, and my rates are up, not because
20 my drug is any better, but my rate is up.

21 So then, part of me would say, well,
22 what's important, as was talked about earlier, is
23 relationship to placebo, so what's important is odds
24 ratio. Okay. So, let's quit everything else, from
25 now on approval is based on odds ratios. That's a

1 very interesting idea, but we need some data to test
2 it out. Do odds ratios -- you know, we could ask
3 the question, do odds ratios stay the same across
4 time? Is the odds ratio in one month the same as
5 the odds ratio at 12 months? If that's the case,
6 I'll have to follow people for 12 months, I know the
7 answer at one month. Okay, lots of very intriguing
8 questions here that I hope the committee will push
9 my field to really look at by a scientific
10 conference.

11 So, in summary, I had three
12 recommendations. The first was to not make any
13 decisions today about labeling for two reasons. One
14 is, you are not going to have the full benefit of
15 information, and secondly, it's placing the cart
16 before the horse and you are going to end up with a
17 double standard criteria backed into approval
18 criteria. Secondly, that you not allow this
19 labeling decision to divert you from pushing the
20 field towards reexamining approval criteria, and,
21 thirdly, that you consider having a conference or a
22 small workgroup or something in which the DAAC asks
23 other organizations to help it out with this
24 decision.

25 Thank you.

1 CHAIR STRAIN: Thank you, Doctor Hughes.
2 Are there questions for Doctor Hughes?
3 Doctor Young.
4 DOCTOR YOUNG: I'm going to ask this
5 because I think it may come up again, and as you
6 said it I realized I couldn't give a simple
7 definition of it. Could you teach me what an odds
8 ratio is?
9 DOCTOR HUGHES: An odds ratio, there's
10 two ratios, one is called relative risk, one is
11 called the odds ratio, and these are measures of the
12 difference between placebo and active, because when
13 we talk about a doubling sometimes it's not clear
14 even to clinicians whether we are talking about an
15 odds ratio or relative risk. Okay?
16 But, to me, my hypothesis is, is that
17 how you choose the subjects, how much behavior
18 therapy you give them, and your definition sets the
19 base rate, and then all drugs work on a
20 multiplicative fashion on that base rate.
21 Now, Doctor Andorn talked about
22 effectiveness. Okay. We are in a funny situation,
23 because the way I design a trial to get the highest
24 quit rates is the way I design the trial to get the
25 least generalizable in the least real world. Okay?

1 Now, if my hypothesis is true, that odds
2 ratios are the same, okay, and you are going by odds
3 ratio, and let's say I'm a pharmaceutical company,
4 then running a trial in a very generalizable way I
5 will get an odds ratio exactly the same if I run the
6 trial with lots of behavior therapy and everything.
7 So, it might actually be an incentive to
8 pharmaceutical companies to run their trials in a
9 very generalizable way, whereas, if you make them
10 have an absolute quit rate they are going to run
11 their trials in a very non-generalizable way to get
12 the high quit rates. Okay?

13 But, again, all this is my hypothesis,
14 so we need some data to compare it with.

15 DOCTOR YOUNG: Tell me what's in the
16 numerator and what's in the denominator on odds
17 ratio?

18 DOCTOR HUGHES: An odds ratio, think of
19 a 2x2 table.

20 DOCTOR YOUNG: Okay.

21 DOCTOR HUGHES: Okay, with yes/no,
22 active and placebo. Okay? The odds ratio is the
23 cross product of those two, so take the diagonals,
24 multiply them together and over the diagonals of the
25 other. Okay? And, it's an odds, okay, so it's the

1 probability of one thing given another thing.

2 It seems to be a little bit -- it's
3 influenced by base rates, to some extent as well,
4 but it seems to be a more -- most statisticians
5 think it's a better, more accurate view of what's
6 happening. Okay?

7 Now, it gets very complicated here,
8 because odds ratios are not the same as relative
9 risk, so a doubling between 40 and 80 will give you
10 a different odds ratio than doubling between ten and
11 20. Okay? So, now we are into this thing about,
12 well, how do you explain that to consumers,
13 especially an OTC product, you know, I have trouble
14 explaining it to the clinicians as well. Then, at
15 ten to 20 percent, that's a ten percent difference,
16 and in a 40 to 80 percent that's a 40 percent
17 difference. They are both doublings, but one is
18 bigger than the other, and you might say, well, is
19 one better than the other, and you might say, well,
20 if you've got a population that's only ten percent
21 are quitting, that's a really tough population. So
22 bumping them to 20 percent is every bit as important
23 as taking somebody that's easy to quit at 40 percent
24 and bumping them up to 80 percent. You get into
25 these very complicated discussions very quickly.

1 Yes?

2 DOCTOR SIMPSON: You mentioned meta-
3 analysis, and I sort of had a look at the ACHPR
4 guidelines, and they did meta-analyses. Now, did
5 they address some of the issues that you looked at,
6 do you think, or -- you know, they didn't report on
7 some of the things you mentioned, and I just
8 wondered if they had addressed those in their meta-
9 analysis.

10 DOCTOR HUGHES: Well, they did exactly,
11 for example, they have coded in their data analysis
12 whether or not all the pharmacological trials got
13 behavior therapy or didn't get behavior therapy
14 along with that.

15 DOCTOR SIMPSON: Yes, that's right.

16 DOCTOR HUGHES: Okay.

17 DOCTOR SIMPSON: In a very simplistic
18 way.

19 DOCTOR HUGHES: Right, so they can go
20 back into that and they can calculate the odds ratio
21 for all the trials that people did not get behavior
22 therapy, okay, and calculate all the odds ratio for
23 all the trials that people did get behavior therapy.

24 DOCTOR SIMPSON: They actually did
25 report on that to a certain extent.

1 DOCTOR HUGHES: Right, but they didn't
2 do a formal comparison of that.

3 DOCTOR SIMPSON: No.

4 DOCTOR HUGHES: And, those trials,
5 whether you got behavior therapy or you didn't get
6 behavior therapy, let's say the trials that got
7 behavior therapy had different entrance criteria,
8 they were more stringent than the trials that didn't
9 get behavior therapy, which is possible.

10 DOCTOR SIMPSON: Probable.

11 DOCTOR HUGHES: Probable, okay. They
12 could correct for that statistically in that data
13 set so that any differences in the odds ratio were
14 differences due to behavior therapy, not differences
15 due to subject characteristics.

16 So, the point I'm trying to make is, is
17 that these meta-analyses have the ability to look
18 at, for example, point prevalence versus continuous
19 abstinence, does it matter? Is odds ratio better
20 than some other measure? Is biochemical
21 verification really necessary? For example, we had
22 a major review about three years ago that upset the
23 cart, that said maybe biochemical verification isn't
24 necessary because the same number of people lie in
25 the placebo group as lie in the active group, so

1 what do we care if they lie, because the odds ratio
2 is going to stay the same, if the rates of lying are
3 similar between the two.

4 DOCTOR SIMPSON: Just a point about the
5 odds ratio. You had some difficulty, I think,
6 explaining it, and as a statistician I also have
7 difficulty, I mean, getting people to really
8 understand what an odds ratio is and how it is
9 different from a risk ratio. I mean, you can show
10 them examples, I don't think it really registers.

11 Time and time again, even in the
12 published literature, you see the odds ratio
13 reported as a risk ratio. So, I think that that is
14 one of the really big difficulties when talking
15 about labeling and putting an odds ratio in, that
16 people really won't know what you've put there.

17 DOCTOR HUGHES: Right, but I think if I
18 was a consumer, okay, the problem with the labels,
19 with using absolute rates, is absolute rates, as I
20 mentioned, are varied by a lot of things other than
21 the drug, i.e., patients whether you give them
22 behavior therapy, that sort of thing. So that, to
23 quote absolute quit rates to me is very misleading.
24 Okay?

25 On the other hand, if we could somehow

1 convey to consumers how much the drug -- active drug
2 increases their chances of quitting that would be
3 very helpful to the consumer. Okay?

4 But, again, we haven't even gotten that
5 issue in to academicians. Academicians still may
6 have been focused, to my view, may have been focused
7 on absolute quit rates, rather than relative quit
8 rates.

9 But, I guess my concern is that if we
10 make a decision about labeling, whether it's
11 relative risk versus absolute rates, if you guys
12 make a decision on that, that is going to filter
13 down, both into the approval process and into how
14 standards are set in my field.

15 And, again, my point of view is, I would
16 rather have a wide open discussion among scientists
17 with lots of data before such an important decision
18 is made.

19 CHAIR STRAIN: Other questions?

20 Yes, Doctor D'Agostino.

21 DOCTOR D'AGOSTINO: Not to endorse the
22 notion of a conference, but I think the point of
23 odds ratio may be getting us a big far afield, I
24 think the idea of a comparative statement is the
25 mission that I think has to be revisited, that you

1 are, in fact, having different populations in these
2 studies, and you have to keep in mind the comparison
3 with the placebo group, whether it's an odds ratio,
4 relative risk, or even the absolute difference is
5 open to discussion.

6 DOCTOR HUGHES: Again, my view on this
7 is that it would be very difficult for me to make a
8 decision as to whether relative risk or odds ratio
9 is the best to convey to consumers. I think you
10 would need much more information than what you are
11 going to get today to make that decision, which of
12 those two should be used to inform consumers.

13 CHAIR STRAIN: Let me actually address a
14 question to Curtis, if I could, just a clarification
15 on that. We are not making a decision regarding
16 labeling, right? The FDA will make decisions. We
17 are simply, as a committee, eliciting information,
18 data, feedback from various people, including
19 yourself.

20 So, as far as your first point, make no
21 decisions regarding labeling, we will endorse it
22 fully, because we can't, but certainly it's well
23 heard and well understood that that is something you
24 are communicating actually to the FDA, not to our
25 committee.

1 DOCTOR HUGHES: Well then, let me change
2 it, make no advice to FDA.

3 CHAIR STRAIN: All right, very good.
4 Doctor Meyer.

5 DOCTOR MEYER: Part of my question
6 probably comes from lack of knowledge specific to
7 nicotine, but I completely agree with your notion of
8 a scientific meeting to consider some of these
9 issues.

10 I think there is probably an interaction
11 between stages of change in the pharmacological
12 effects of nicotine substitution, though I don't
13 know that, this is not my area clinically. But, I
14 would be surprised if there were not some factor in
15 how a patient feels with nicotine substitution about
16 possibilities of change, relative to how they feel
17 while they are still smoking.

18 And, we tend to think of these things as
19 almost categorical, even though we talk about it as
20 stages of change, it is more complex than to deal
21 with it.

22 The second issue is what I call the
23 Gordian knot of abstinence, and that is, abstinence
24 can be the result of a pharmacological effect, a
25 pharmacological effect plus behavioral and other

1 interventions. It also can be a function of sort of
2 a baseline compliance level, and this is an issue in
3 the alcohol. And, I would submit that the ability
4 of someone to be abstinent in the first two weeks
5 may not be as specific in some ways of
6 pharmacological effect as it is, perhaps, later
7 around issues of, you have to sort out the
8 compliance factor. You do that to some extent with
9 placebo, but maybe not.

10 The issue of craving I think again is
11 one that is extremely complex and needs to be parsed
12 out, and the last issue, which I think is important
13 for all addiction treatment, is that to some extent
14 our measures of effect and the ways in which we
15 characterize patients need to be tailored to the
16 kind of pharmacotherapy, that the models that you
17 use for nicotine substitution and the criteria for
18 nicotine substitution might be different than some
19 other approach.

20 I'm reminded, you know, of a methadone
21 maintenance model, that if you use certain criteria
22 for efficacy for 30 milligrams of methadone versus
23 70 milligrams of methadone, you know, it's very
24 useful, but it may be less useful than comparing
25 methadone to maltrexone, or it is less useful, so

1 that you need to be thinking about some of these
2 things in ways that are specific to how you
3 conceptualize the pharmacotherapy, in terms of
4 what's going on in the brain and what may be going
5 on behaviorally.

6 I think that's why you need a scientific
7 meeting, the framework needs a lot of pre-meeting
8 preparation and I wouldn't want to simply have a set
9 of scholarly papers get put in a book.

10 DOCTOR HUGHES: I think -- first of all,
11 I agree with your ideas, but those are testable
12 ideas.

13 DOCTOR MEYER: Absolutely.

14 DOCTOR HUGHES: With data sets, so, for
15 example, if compliance makes it messy at the
16 beginning, then you would think that the odds ratio
17 in the first couple of weeks would be different than
18 the odds ratio later. So, it's a testable idea.

19 And, in terms of the conference, I think
20 you are exactly right, and the way we've done these
21 before is, you have a planning committee, and this
22 you could do very specifically, you could have the
23 planning committee and you could identify the nine
24 meta-analyses. And, you could sit down, okay, here
25 are five or six questions that we want asked of the

1 data set, and now that we have SR&T you can put it
2 on our list serve, and you could say, does anybody
3 have data on this. And, if you have a data set that
4 you think would be interesting for this, send it to
5 the planning committee. Okay.

6 Then the planning committee gets 12
7 responses from people that have data sets, talks to
8 them and says, oh, yeah, these five data sets really
9 will answer the questions. Now, we're going to have
10 a meeting in two months, can you prepare a paper
11 with your data set to answer these six questions?
12 And, of course, some of these you can't answer with
13 data, and you might want to just say, okay, I want a
14 subcommittee of five clinicians to meet before the
15 meeting, banter around these ideas about these
16 things, and bring a report to the meeting and then
17 we will discuss the decision of that subcommittee.

18 So, there's lots of different ways.

19 CHAIR STRAIN: I don't want to cut off
20 discussion, but at the same time we have several
21 speakers that we'll need to get through. Are there
22 any other questions that the committee -- yes,
23 Curtis, Doctor Wright.

24 DOCTOR WRIGHT: I would just have a
25 comment, and I would think that if the Society for

1 Research on Nicotine and Tobacco would wish to hold
2 such a meeting, that would be lovely. There are
3 limits on the extent to which agency staff and
4 personnel and advisory committee members may
5 participate in their official capacity in events
6 held by other institutions, and we would seek the
7 guidance of our advisory committee staff on the
8 extent to which we could or could not properly
9 participate. But, the more people we get looking at
10 this issue the better it is that we are going to
11 make reasonable decisions.

12 I would also repeat, A, we are not
13 changing the approval standards; B, the committee is
14 not making decisions about what will go into
15 labeling today.

16 DOCTOR HUGHES: My only comment is, if
17 we had that meeting and it changed nothing about
18 FDA, it would still be useful for my field.

19 CHAIR STRAIN: Thank you, Doctor Hughes.
20 Our next speaker is Doctor David Sachs.

21 DOCTOR SACHS: Get out my timer here,
22 Doctor Strain.

23 CHAIR STRAIN: I have mine, too.

24 DOCTOR SACHS: I'm sure you do. My
25 colleague, Doctor Andorn, says she has one too, so I

1 better get going.

2 Doctor Strain, Doctor Andorn, Doctor
3 Winchell, Doctor Wright and many other colleagues
4 within this room, I'm delighted to be here today to
5 deal with some of the issues that have been
6 discussed.

7 First, my identification, I'm the
8 Director of the Palo Alto Center for Pulmonary
9 Disease Prevention, a small, independent, non-profit
10 medical research organization based in Palo Alto.
11 I'm also Clinical Associate Professor in the
12 Division of Pulmonary and Critical Care Medicine at
13 the Stanford University School of Medicine.

14 As many of you know, I have been active
15 as a researcher in the field of tobacco dependency
16 management and treatment since 1975, 22 years. I
17 don't know where the time is going, but it does go
18 fast. I have been privileged to have been an
19 investigator for most of the medications now on the
20 market that treat tobacco dependence, either
21 prescription or over-the-counter. In addition, as
22 many of you know, I've had independent research
23 grants, the Palo Alto Center has, since 1987, from
24 the NIH and from the National Institute on Drug
25 Abuse in this field of tobacco dependency treatment.

1 I served as a regular review committee
2 member of the National Institute on Drug Abuse Study
3 Section on Clinical and Behavioral Pharmacology
4 Study Section from 1983 to 1993. I've served as an
5 ad hoc and special review committee member for the
6 NIH and from NIDA from 1983, and that continues to
7 the present time.

8 I split my time approximately 75 percent
9 in the conduct of research activities, almost
10 exclusively in the field of tobacco dependency, most
11 of that research is in clinical treatment trials,
12 although some of it is more basic science, and also
13 included in that 75 percent time is the design of
14 trials and scientific writing that I try to do.

15 The other 25 percent of my time I spend
16 in the private practice of pulmonary medicine, using
17 an almost vanishing means of payment, fee for
18 service. I do not belong to any managed care
19 organizations, and I never will. I'll leave the
20 practice of medicine before I do.

21 Now, most of the comments I'm going to
22 make today, although I view myself predominantly as
23 a researcher, I'm really putting on my hat as a
24 clinician, because I think that the label as it sits
25 today is extraordinarily confusing, incomprehensible

1 and does not convey an adequate message to the
2 front-line clinician practicing in the field. The
3 message the front-line clinician gets, and I hear
4 this time, and time, and time again, whether I'm
5 giving general medical residency rounds at Stanford,
6 or whether I'm giving grand rounds at Cornell
7 University, or whether I'm giving a new medical
8 staff conference at the John Muir Hospital in Walnut
9 Creek, is that these medications are simply not
10 effective, and we know that's not true.

11 That results directly, in my view, from
12 in part some of the complexities that exist in the
13 label, and I think this really needs to be changed.

14 Now, source of funds for my
15 participation here today, though, as you know I have
16 consulting relationships with virtually every
17 company in the world that makes tobacco dependency
18 treatment medications or devices, not all, but
19 almost all, I am here today at my own time and at my
20 own personal expense. None of the companies that I
21 have or currently consult with were even aware that
22 I would be making this presentation until this
23 meeting agenda was sent out.

24 I decided to make the decision to come
25 here after talking with Doctor Andorn, because I

1 thought that this first of what I understand from
2 Doctor Winchell will be a series of meetings, and I
3 applaud the agency for wanting to do this, is simply
4 extremely important for the practicing physician out
5 in the field, the front-line, primary care
6 internists, family physicians, psychiatrists,
7 OB/GYNs and pediatricians, because of the fact that
8 they perceive tobacco dependency treatment
9 medications as ineffective, and I think this kind of
10 a meeting is a good start at beginning to change
11 those perceptions.

12 Now, what will I present today in the
13 remaining 15 minutes. First, I want to say that I
14 do agree with, essentially, all of the
15 recommendations that Doctor Andorn put up, except
16 for the one that was from, I guess, the two
17 dissenters, which recommended there not be any
18 changes to the label, that I do not agree with. I
19 think that there needs to be thoughtful
20 consideration given to appropriate changes in the
21 label that are clinically meaningful and would offer
22 useful information to the clinician, and I think
23 that the question as posed today for the committee
24 is an eminently appropriate one that the committee
25 should appropriately consider today.

1 So, in looking at what one might
2 consider for other efficacy definitions in the label
3 for tobacco dependency treatment, and note I am
4 continually using the term tobacco dependency
5 treatment, because tobacco dependency is the disease
6 that I treat. Tobacco dependency is the primary
7 pulmonary pathogen of our era. Microbacterium
8 tuberculosis was for the first half of the century,
9 and now the tobacco cigarette is. That's the
10 disease.

11 Smoking cessation is a process, it's a
12 treatment modality, but it is not the underlying
13 disease that are treating.

14 And, because I am a clinician, I'm going
15 to go back to the old grand rounds model, and I'm
16 going to present a case, case example that's drawn
17 from my private practice, because a case does not
18 the world represent necessarily I will then conclude
19 with some data from one of the many large clinical
20 trials that I have helped design, and this is, in
21 fact, the data, Doctor Winchell, you are right, it
22 was in this very room on December 12th-13th last
23 year, this is some of the data from the Glaxo-
24 Wellcome 403 trial.

25 Now, a word of disclaimer, nobody at

1 Glaxo-Wellcome knew I was going to include these
2 data, but it comes straight out of the briefing
3 booklet. The slides are my own design, they didn't
4 do them. They may not like my design, but the data
5 are data that you have already seen.

6 Then, I will conclude with my
7 recommendations, and one thing I want to say,
8 because I am going to be recommending a change that
9 some of you may think represents, and does
10 represent, a change from many of my published works,
11 in which I had for years stated that the only valid
12 outcome measure for tobacco dependency treatment is
13 one year continuous, objectively validated smoking
14 cessation abstinence.

15 Now, that is still, in my view, a
16 critically important benchmark, but not necessarily
17 one that should be used for approval of a
18 medication, because the agency has rightly and
19 appropriately over the years consistently made a
20 distinction between that which is necessary to
21 achieve immediate cessation versus that which is
22 necessary for long-term maintenance, relapse,
23 prevention.

24 Clinically, as we all know, those are
25 two totally different animals, and I would certainly

1 not want to put the burden on a company to have to
2 meet a one, or two, or a three-year outcome standard
3 before their drug could get approved, that would be
4 devastating to our field, because effective new
5 agents would be delayed from market for years, and
6 years and years.

7 But, what I am going to say is that I
8 think that using point prevalence definitions have
9 an appropriate role to play, and I say this because
10 there's been a confluence, as I've observed data
11 coming in to me, both from my own research trials,
12 which I'll show at the end from the Glaxo-Wellcome
13 403 data, as well as many, many, many, many patients
14 that I've treated, and I've wrestled, how do I
15 convey from a data standpoint the kind of patient
16 I'm going to present to you when I'm giving a noon
17 general staff conference, that these are the kind of
18 results you can expect if you treat this patient as
19 if he or she has a chronic medical disease that is
20 fundamentally no different than asthma. The only
21 major difference being the locus of where the cell
22 receptor and intercellular biochemical abnormalities
23 are.

24 So, with that, let me lead into and
25 present this case. This gentleman, when I first saw

1 him in 1990, was a 69-year old, White, married male,
2 retired psychologist and mathematics professor. He
3 came to me and was referred to me by his primary
4 physician because of severe and worsening shortness
5 of breath, intermittent and worsening paroxysmal
6 cough, productive of about three tablespoons of
7 thick green sputum daily, worsening wheezing, and he
8 was concerned that tobacco dependence was causing or
9 aggravating these symptoms.

10 His history of present illness was
11 relevant because of these pulmonary symptoms, and
12 they'd been worsening for two or three years prior
13 to his visit with me. His sputum had been
14 occasionally blood streaked, but he had never had
15 any severe hemoptysis. He'd had an increasing
16 number of bouts of acute infectious bronchitis over
17 the previous two to three years. When I first saw
18 him, he thought he was averaging two to four bouts,
19 two to four bouts of severe acute bronchitis every
20 year.

21 His smoking history was relevant. When
22 I first saw him he was taking somewhere between six
23 and 15 or so Benson & Hedges Light 100 cigarettes
24 per day, more typically, though, over the 55 years
25 of his smoking career he had smoked two packs per

1 day. He had made 16 previous quit attempts before
2 seeing me, including cold turkey times eight,
3 gradual tapering times four, the American Heart
4 Association group counseling program once, a
5 separate group counseling program once, prescription
6 use of clonidine tablets once, and two prescription
7 uses of nicotine polacrilex, obviously, he relapsed.

8 When I asked him the major reason he had
9 for wanting to stop smoking, he said, in his own
10 unique, curmudgeonly style, I don't want to stop
11 smoking, I want to smoke two or three cigarettes a
12 day, just like my mother had done all of her life.
13 Okay?

14 So, he is somewhere in the pre-
15 contemplative/contemplative stage, right? He's not
16 ready to stop smoking. Physical exam was
17 essentially unremarkable, except let me point out a
18 couple of things. His oxygen saturation on room air
19 was low, 95 percent, lower limit of normal is 98
20 percent. Carbon monoxide wasn't all that high, only
21 14 parts per million, profile at mood state total
22 mood disorder score was on the high side, 69, at
23 that time in 1990 I was not regularly measuring the
24 Becta pressure inventory, which I do now. The --
25 tolerance questionnaire was seven points, indicating

1 he was highly nicotine dependent.

2 On my physical exam, I found an
3 aesthetic White male, breathing with pursed lips,
4 which means he's got bad obstructive lung disease,
5 right then and there. This was moreover reinforced
6 by the fact that as I watched him unbutton his shirt
7 he experienced severe and acute shortness of breath.

8 When I examined his chest, basically all
9 these things say he had bad obstructive lung
10 disease. These are in your handouts that I gave
11 you, so if you want to follow along and scribble any
12 notes you can. His chest Xray showed hyperinflated
13 lung fields with low flat diaphragms, yet another
14 route of evidence that shows this man had
15 significant chronic obstructive pulmonary disease.

16 His pulmonary function studies likewise
17 showed that, and showed physiologically a moderately
18 severe obstructive lung defect, with severe
19 hyperinflation and marked impairment in gas
20 transport, and gas transport is, of course, what the
21 lungs are all about.

22 So, my impressions were, I had a
23 moderately severe obstructive lung disease, male,
24 with documented hypoxemia, shortness of breath at
25 rest, it was severe, severe dyspnea on exertion and

1 wheezing. He also, as you may have noticed, had
2 mild hypochloremia, and he had tobacco dependence,
3 certainly enough criteria for that diagnosis, highly
4 nicotine dependent by the FDQ, average nicotine
5 dependent by the serum cotinine that just --, he had
6 no current or past history of depression, he had an
7 anxiety state clinically and by the POMS, and he
8 would be what I put in the pre-contemplative or
9 contemplative stage.

10 His tobacco dependence, however, is the
11 causative pathogen for all of his pulmonary
12 diagnoses that I showed in the preceding slide.

13 So, my plans at this stage, since he was
14 really only in the pre-contemplative, contemplative
15 phase at best, somewhere in there, was to provide
16 medical information to him and realistic options,
17 that he was not likely to be a chipper like his mom.

18 Also, because of his clear-cut anxiety
19 state I instituted buspirone, not bupropion,
20 buspirone, AKA buspirone used for anti-anxiety
21 treatment, and the patient has to sit down seeing
22 what he can do on his own, continuing the use of
23 nicotine polacrilex which he was using when I first
24 saw him.

25 Well, what his clinical course like? It

1 was an interesting one, and I continue to follow him
2 to this day. So, here is the day I first saw him,
3 he's using about that much nicotine polacrilex, no
4 buspirone, and he was, in fact, smoking about ten to
5 15 cigarettes per day. The first estimate was taken
6 from his history, which was low, O₂ saturation 95
7 percent.

8 He temporized a bit, and I saw him again
9 in January of 1991. He was on the buspirone that I
10 had prescribed. He had stopped the Nicorette and he
11 was now up to a pack a day, and he had sort of
12 started to come to the conclusion that maybe he
13 really should stop smoking.

14 He came in in February again, and in
15 March of '91, not using any Nicorette in this time
16 period. The smoking is going up, and at this point
17 he decided he really should stop smoking, but he
18 correctly identified a number of fundamental
19 psychological problems that he thought needed to be
20 addressed, and so I referred him to a psychologist
21 and subsequently to a psychiatrist, who he also sees
22 to this day.

23 I didn't see him again then until
24 September 23, 1991, and I saw him because he
25 developed yet another bout of severe acute

1 bronchitis, really felt lousy, and he thought he had
2 proved to himself that he could not be a chipper
3 like his mother, and he also knew that his lung
4 health was deteriorating badly. Consequently, he
5 did want to stop smoking completely. In fact, he
6 stopped cold turkey on his own two days before, on
7 the 21st.

8 I advised him to start nicotine
9 polacrilex by prescription, of course, in those
10 days, one piece per hour while awake. He, in fact,
11 used this amount, continued that, and at the day I
12 saw him here had been smoking that amount up until
13 two days prior.

14 Note his O₂ saturation has dropped yet
15 again, and remember, the oxygen saturation scale is
16 a logarithmic scale at that point, so each point
17 drop in that range represents a severe, marked
18 dramatic decrease in actual ccs of oxygen carried in
19 every 100 ccs of blood to body tissues.

20 I saw him on a weekly interval from late
21 September to here, and he really wasn't doing very
22 well. He cut down on his smoking, but he was having
23 intermittent lapses, but never more than one to ten
24 cigarettes per week. So, at this point, courtesy of
25 the good efforts of Karl Olav Fagerstrom at

1 Pharmacia, who enabled me to gain access to four
2 milligram nicotine polacrilex on an open label
3 research protocol approved by my IRB, I had him stop
4 the two milligram dose, switched him to the four
5 milligram dose, continued him on the buspirone and
6 away we went.

7 Now, you'll notice that I left out the
8 visits, I saw him every two to four weeks in this
9 time interval here, and he really started doing well
10 on the four milligram dose. He noticed a major
11 difference, and he commented that he was basically
12 able to stay off cigarettes most times, except when
13 his brother came over or at other holiday times when
14 stress was really bad.

15 By December 27th, he was off cigarettes
16 completely, he stopped completely, and he stayed
17 that way for somewhat over a month. Then, he went
18 back to his intermittent chipping again until May
19 20th, and he has not smoked since May 20, 1992.
20 Since that time, his pulmonary physiologic status is
21 clearly improved. He's now five year cigarettes
22 free. He stopped the buspirone January 25th of
23 1996, a year and a half or so again.

24 When I last saw him he was still using
25 15 to 20 pieces of this medication daily.

1 So, what's the payoff here? All these
2 visits, all this medication, all this money spent,
3 well, his pulmonary status has continued to improve
4 during this five-year period, both symptomatically
5 and physiologically. His oxygen saturation is now
6 consistently running near normal at 96 to 97
7 percent. He has had only one bout of acute
8 bronchitis in five years, and that was three years
9 ago, June 24, 1994. He has had no hospitalizations
10 in the last five years.

11 But, more importantly, last but not
12 least, this patient is alive, and not only alive,
13 but alive with vigor. He is very active in Palo
14 Alto city politics, in cultural events, and social
15 activities. He cooks all the meals at home,
16 maintains his home, and is able to effectively care
17 for his partially disabled wife. Without effective
18 tobacco dependency treatment medications, and
19 effective tobacco dependency treatment clinically,
20 enabling control and stabilization of his chronic
21 disease, and by that I mean tobacco dependence, this
22 man would have, over the last seven years, had
23 progressive pulmonary deterioration. In fact, based
24 on my clinical experience with people like this, he
25 would have been dead now, but he's not.

1 So, what are the clinical conclusions
2 and implications from this kind of a case? Number
3 one, by any of the criteria for success in any of
4 the tobacco dependency treatment trials that I have
5 either designed or taken part in, this man would
6 have been classified as a treatment failure. Not
7 only did it take him eight months to stop having
8 intermittent lapses, but one year before that to
9 even move out of the contemplation phase.

10 I want to emphasize, and some of you may
11 say, oh, but Dave Sachs always gets great results.
12 No, I really don't, I just simply practice good
13 clinical medicine, and this case is really not at
14 all unique in my clinical practice today. Frankly,
15 it's rather representative of the many patients I
16 now am seeing. I could have presented many others
17 to illustrate the following points.

18 Number one, tobacco dependency is a
19 chronic medical disease, fundamentally no different
20 than any other chronic medical disease, such as
21 asthma, diabetes or angina. Tobacco dependence is
22 not an acute self-limited medical disease such as
23 pneumococcal pneumonia, rather tobacco dependence is
24 a chronic disease and, therefore, treatment must be
25 conceived as a long-term process, not a simple,

1 short-term fix.

2 Now, I will not present the bupropion
3 data because I'm running at 21 minutes, you've seen
4 that. The data support, I think, the
5 appropriateness of point prevalence abstinence.
6 I'll now move directly to my summary overhead.

7 First, I would recommend a change in all
8 prescription tobacco dependency medication labels,
9 but first I would urge retaining the current four-
10 week objectively validated continuous non-smoking
11 outcome benchmark as a data table, because I think
12 it is a useful benchmark. But, four weeks of
13 treatment does not necessarily mean that's what the
14 patient should be getting. This is simply a
15 regulatory benchmark and an appropriate one in my
16 view.

17 I would add six week to one year
18 survival curve graphs objectively validated, using
19 Kaplan-Meier type p values or life table analysis.
20 I would also recommend adding one week point
21 prevalence histograms for six weeks through one
22 year, using a statistical analytical technique that
23 I've only recently become acquainted with, which I'm
24 finding incredibly powerful, which is ANOVA with a
25 GEE type p value.

1 Now, over-the-counter medications pose a
2 different problem, but I think here, too, something
3 needs to be done. First, I think the box package
4 label, I'm not talking about the insert, I'm talking
5 the label that goes on the box, or the bottle or
6 whatever, the medication itself, must clearly and
7 concisely state, as is done for each and every other
8 OTC category except this category, when patients
9 should see a physician because the medication is not
10 doing what it is supposed to do, for example, not
11 being able to stop smoking in the first two to seven
12 days after starting the medication, or experiencing
13 nicotine withdrawal symptoms that are not readily
14 tolerated.

15 Now, if space is needed on the bottle or
16 the box to include that, then I would recommend that
17 there be substantial reduction from the box package
18 label of the exhaustive listing of the remotely
19 possible toxic effects which would warrant seeing a
20 physician, but which 99 percent never, ever
21 experience.

22 I think that because of an accident of
23 history and the, in my view, serious mistake to
24 treating clinicians of having a cookbook approach
25 for nicotine patches, there's going to have to be

1 some retroactive education of physicians and,
2 perhaps, this can be done by developing a physician
3 prescribing booklet for OTC tobacco dependency
4 treatment medications to include, so the physician
5 has this readily available, the same kind of
6 information, prescription trial data if the
7 medication was or is an RX to OTC conversion, given
8 the four-week objective we validated continuous non-
9 smoking after a benchmark.

10 And, let me just add, another point of
11 confusion on the part of the practicing clinician
12 has been the presentation only of the ranges,
13 without giving the mean and standard deviation.

14 I think it's critical that in this four-
15 week, last four-week objectively validated benchmark
16 that not only the ranges be given, but also the mean
17 and standard deviation and the p values, that
18 likewise the data can be mined and most of these
19 studies could go back to produce these if they were
20 not done at the time or original submission; that
21 similarly for the OTC trials that are done for OTC
22 registration that similar kinds of data be included
23 for the physician, so the physician has some way of
24 thinking of these data and looking at these data.

25 So, these are my summary

1 recommendations. I actually have many more, but
2 I'll save those for the next committee meeting and
3 be happy to answer any questions if you wish, Doctor
4 Strain.

5 CHAIR STRAIN: Thank you. Thank you for
6 that illuminating discussion, Doctor Sachs.

7 Let me remind the committee that we have
8 a large period of time this afternoon to discuss
9 amongst ourselves what we are talking about here
10 now, so if there are questions directly to Doctor
11 Sachs regarding what he's presented.

12 If not, hopefully Doctor Sachs will be
13 here as well for at least part of this afternoon.

14 DOCTOR SACHS: I'll be here until 3:30.
15 Thank you.

16 CHAIR STRAIN: Thank you again.

17 Next will be Doctor Maxine Stitzer.

18 DOCTOR STITZER: Good morning to
19 everybody, and can you hear me okay?

20 The Society for Research on Nicotine and
21 Tobacco was founded in 1994, and the mission of this
22 society is to promote expanded research and
23 increased understanding of nicotine and tobacco
24 dependence, also to disseminate scientific
25 information, and to help ensure that the science is

1 considered and included when policy is developed.

2 As President Elect of this society, I am
3 pleased to be here this morning to present the
4 response of the SRNT to these interesting and
5 important questions that have been raised by the
6 Drug Abuse Advisory Committee about how product
7 labeling for smoking cessation products might be
8 improved.

9 Before getting into the -- and, as
10 you'll see, the society took the task very seriously
11 and very literally, and we did come up with
12 responses to each and every question, but the first
13 point I would like to make, which has already been
14 made by Doctor Hughes, is that we thought that these
15 issues, because they have implications for the
16 conduct of science, for the education of the public,
17 and for the future of product development probably
18 require more extensive discussion than what would be
19 possible today, so we are offering to sponsor or co-
20 sponsor somehow with the FDA a meeting that could
21 provide a forum for more extensive discussion about
22 the interrelationships among outcome measures and
23 their implications for policy. Such a meeting could
24 also consider whether there is or is not currently
25 scientific information supporting any new

1 indications for smoking cessation products at this
2 time.

3 Now, the method of compiling and
4 formulating this response from the SRNT was a
5 consensus survey of the Executive Committee members.
6 These consist of individuals with expertise ranging
7 from clinical pharmacology of nicotine, through to
8 smoking cessation clinical trials outcomes. I think
9 I've heard this called the "BOGG set" method, that's
10 a bunch of guys and gals sitting around talking, the
11 method for compiling the response.

12 So, with that, I'd like to get into the
13 actual consensus opinion that was formulated by the
14 SRNT Executive Committee.

15 The first question raised is, should
16 point prevalence abstinence rates be reported, and
17 the consensus here was, probably yes. Now, first I
18 want to point out, though, oh, and by the way, we
19 did prepare a text, a written text response that you
20 should all have in your packet now, so I'm really
21 going to be just reiterating what's in there. I
22 want to point out that the current reporting method,
23 the weeks three to six continuous abstinence, is
24 actually quite a good one. Recent research has
25 indicated that smokers who are able to abstain early

1 in treatment have a much better prognosis for long-
2 term success than smokers who smoke at all during
3 the early treatment weeks.

4 Now, it is the case that that research
5 targeted weeks one and two post cessation, but it's
6 certainly very likely that weeks three to six
7 continuous abstinence would continue to reflect that
8 important relationship. So, the existing method is
9 good.

10 Now, what point prevalence is, it's the
11 percent of patients who meet a definition of
12 abstinence at a particular point in time, and
13 usually what that definition is, is a self report of
14 not having smoked during the previous week combined
15 with biochemical validation, using either carbon
16 monoxide or cotin. It's clear that point prevalence
17 and continuous abstinence rates would be highly
18 correlated, because many of the same individuals
19 would be counted in both measures. However, the
20 point prevalence does provide a somewhat more
21 liberal picture because certain individuals who have
22 smoked a little bit, but are currently abstinent,
23 would be included in that point prevalence.

24 Now, the point prevalence then doesn't
25 provide anything unique beyond what's already

1 reported, and if we were just talking about short-
2 term outcomes it might not be necessary or
3 interesting to report point prevalence, but it turns
4 out that point prevalence is the most convenient and
5 most readily verified measure of abstinence at
6 longer-term time points. So, the decision on
7 whether to incorporate point prevalence is very much
8 intertwined with question number two, which is, is
9 it useful to report long-term outcomes, so this is
10 really a more important question.

11 And, here the consensus of the SRNT
12 opinion was affirmative, that we did think it would
13 be useful to report longer-term outcomes in
14 labeling. And, there were several reasons for this.

15 First of all, it is the case that, I
16 believe all of the currently available smoking
17 cessation products continue to have clinical
18 efficacy at longer-term time points, such as six
19 months and one year, that is, they produce
20 significantly better cessation rates than placebo.
21 And, it's important for clinicians to understand
22 this in formulating recommendations to their
23 patients for smoking cessation strategies, so this
24 is an education point.

25 Another point that speaks to the

1 advantage of long term is that we may have new
2 products coming along with different mechanisms of
3 action that actually do change the shape of relapse
4 curves, and that are able to promote relapse
5 prevention and to enhance long-term outcomes.

6 In order to accommodate that eventuality
7 it would be very important to have long-term
8 outcomes reported and to have them reported
9 uniformly across products. Long-term outcomes
10 provide a reality check, both for patients and for
11 clinicians. It gives them some information about
12 what they can expect for long-term cessation rates.

13 And, in this regard it's also important
14 that clinicians understand the high rates of relapse
15 that are prevalent for smoking cessation. And, in
16 this regard, also the need for additional relapse
17 prevention interventions, such as behavioral
18 counseling, and this kind of information about the
19 important role of behavioral counseling for relapse
20 prevention should also be included in labeling.

21 So, overall, for these educational
22 reasons the SRNT came to an affirmation conclusion
23 that it would be useful to report long-term
24 outcomes.

25 The key point here is that whatever

1 long-term outcomes are reported have got to be
2 uniform across time points and across products, and
3 probably the point prevalence measure would be the
4 most convenient one to utilize in that fashion.
5 But, the uniformity is a key point because we have
6 to have fair comparisons across products.

7 A sort of ancillary issue that arose in
8 discussing the long-term outcome inclusion in
9 labeling is whether more than one measure should be
10 reported, in other words should continuous
11 abstinence be retained and point prevalence added or
12 should one or the other be selected, and there
13 really wasn't a recommendation on that except to
14 note that the key issue here would be clarity of
15 reporting and providing the information that's
16 needed for the target audience to understand the
17 implications and to interpret the various measures
18 that are reported.

19 Moving on then to the third question,
20 should the percent who quit for a single day be
21 reported, and here the consensus of opinion was
22 negative, that this would not be useful. There is a
23 very intriguing recent paper that's been published
24 by Westman and colleagues, which shows that the
25 ability to quit on the very first day after

1 cessation, essentially, on the quit day, is a good
2 predictor of later success, and this suggests that
3 day one quit success might, in fact, be a useful
4 rapid screen for the efficacy of products. But, if
5 you look at that data more closely you can note that
6 the day one quit success is much better at
7 predicting failure than it is at predicting success,
8 and, in fact, only about 30 percent of the people
9 who quit on day one remained abstinent for long
10 term, so that such a measure would most certainly
11 over-estimate the efficacy of a product. So, that
12 was why we came to the conclusion that this should
13 not be reported.

14 The fourth question raised had to do
15 with secondary outcome measures and which of these
16 might be useful, and there were two particular
17 outcome measures considered. The first one is
18 withdrawal symptoms, and here the consensus of
19 opinion that it would be useful to report withdrawal
20 symptoms, were on solid scientific grounds in
21 reporting withdrawal symptoms, the tobacco
22 withdrawal syndrome has been very carefully
23 delineated and characterized and it is included in
24 the official diagnostic criteria, psychiatric
25 diagnostic criteria. There's some useful functions

1 that this reporting could serve. First of all, it
2 clarifies the clinical expectations, both for the
3 clinician and for the patient, that is, that they
4 should experience some withdrawal relief. And, if
5 this expectation is not met this might inform the
6 clinician of the need for altered or intensified
7 treatment.

8 The danger here or the caveat is that
9 it's important for clinicians and the public to
10 realize that symptom relief is not the same as
11 cessation success, so that people who have relief of
12 symptoms may still relapse, so this distinction has
13 to be made.

14 The second outcome measure that was
15 consider is smoking reduction, would it be useful to
16 report smoking reduction, and here the consensus
17 opinion was negative. We didn't think that at this
18 time there was sufficient rationale supporting
19 smoking reduction as a measure to report in
20 labeling, and there were several reasons for this.
21 Well, on the positive side, smoking reduction is
22 certainly a legitimate outcome measure, it's
23 objective, it can be ascertained and reported and
24 it's objective, and certainly if treatment models
25 begin shifting more toward a harm reduction approach

1 that it would be an extremely useful and important
2 measure to report.

3 Also on the positive side, a smoking
4 reduction measure could demonstrate very large
5 behavior changes that might be -- you know, that
6 fall short of total abstinence, but that might be
7 very encouraging for smokers to realize that a big
8 change in their behavior is possible when they
9 embark on a cessation attempt.

10 On the negative side, though, there's
11 still this nagging fear that the reporting of a
12 smoking cessation measure would be construed as a
13 legitimate substitute for cessation and might deter
14 cessation efforts. I think also important is that
15 the health implications of smoking reduction need to
16 be better clarified. We need more information about
17 the health risk reduction that's associated with
18 different amounts and durations of smoking
19 reduction, and finally, there's a concern that any
20 smoking reductions that are noted proximal to a quit
21 attempt might be temporary and that the behavior
22 would just then drift back to baseline levels at a
23 later time.

24 So, overall on balance, it didn't seem
25 that there was sufficient rationale to report

1 smoking reduction.

2 In considering the responses and having
3 the discussion about these very interesting
4 questions, we did come up with two additional points
5 that we thought was essential to bring up today for
6 the committee to consider, and these are
7 unanticipated outcomes of labeling changes.

8 The first potential unanticipated
9 outcome is that changes in labeling might result in
10 exhortably in regulatory changes, either in efficacy
11 criteria or in indications. It's not that the
12 society is opposed necessarily to such changes, but
13 simply that they are much more dramatic and have
14 much more far-reaching consequences than changes in
15 labeling per se, and so they would require much more
16 discussion than what is possible today.

17 The second point is that changes in
18 labeling could lead to misleading advertising claims
19 by sponsors, and, for example, if withdrawal
20 suppression is reported in labeling and advertised
21 in the media, this might be construed as a claim for
22 efficacy independent of smoking cessation data. So,
23 the link between labeling and advertising needs to
24 be carefully specified and closely monitored, is our
25 point there.

1 So, in closing, I again want to applaud
2 the DAAC for raising these interesting issues. I
3 hope that the SRNT response will be useful in the
4 deliberations, and again reiterate that we think it
5 would be important and useful to have a meeting
6 where the interrelationships among outcome measures
7 can be more fully discussed, as well as their
8 implications for policy.

9 So, thank you very much.

10 CHAIR STRAIN: Thank you, Doctor
11 Stitzer.

12 Questions for Doctor Stitzer from the
13 committee? Doctor Simpson.

14 DOCTOR SIMPSON: I just really want to
15 clarify a point. When you talked about point
16 prevalence rates being reported, you meant in a
17 repeated measures sort of way, did you?

18 DOCTOR STITZER: Yes, I did, yes,
19 definitely, probably at one, three, six and possibly
20 12 months, and I think Doctor Sachs mentioned the
21 idea of using -- actually showing a relapse curve,
22 which would be a nice way to do it.

23 CHAIR STRAIN: Doctor de Wit?

24 DOCTOR de WIT: I have two questions.
25 One is, are there data in existence about the

1 relationship between severity of withdrawal
2 symptomatology and success at quitting?

3 DOCTOR STITZER: There are, and that
4 would certainly be something that could be
5 productively discussed at this meeting that we keep
6 talking about. Initially, when that relationship
7 was examined, there was no tie, there was no link,
8 there was no correlation, and it looks like
9 withdrawal severity really had nothing to do with
10 smoking cessation success. But, more recently, some
11 better analyses have been applied to the problem,
12 and it has been demonstrated by a couple of
13 investigators that the -- particularly the craving,
14 early measures of craving, do predict later relapse.
15 They do predict relapse versus success.

16 So, now the understanding, my
17 understanding is that, yes, there is a link.

18 DOCTOR de WIT: It sounds like the
19 position has changed, it's not really clear-cut.

20 DOCTOR STITZER: Well, right, I think it
21 would have -- yes, I think that's probably right,
22 but at first it really looked like there was no tie
23 and now it does look like there is, because a couple
24 of good studies have demonstrated a relationship.

25 DOCTOR de WIT: And, I have another

1 unrelated question. When you talk about long-term
2 outcome, over a year, do you always mean that the
3 product is only used for a short period of time, or
4 do you mean that it's used intermittently over the
5 whole year?

6 DOCTOR STITZER: Well, that's a very
7 important point, and right now our model is short-
8 term treatment that's expected to carry forward for
9 a whole year. So, that's what I mean when I talk
10 about it now.

11 But, I think one of the issues is that
12 we may move toward models of longer-term treatment,
13 such as the one lung health study which kept people
14 in treatment for several years, and, particularly,
15 if things move in that direction it would be
16 important to have long-term outcomes reported for
17 comparative purposes across models and across
18 products.

19 CHAIR STRAIN: Doctor Meyer.

20 DOCTOR MEYER: Maxine, both you and John
21 have recommended a scientific conference, but John's
22 presentation focused on meta analysis, large
23 datasets, et cetera. I'm somewhat less sympathetic
24 to that. I'm more sympathetic to some of the points
25 that you raised here that are really methodological,

1 and that require focused discussion.

2 I wonder if your society would be able
3 to come up with much more of a focused agenda for a
4 conference and suggestion -- much more specific
5 recommendations than we've seen.

6 The danger, I think, is, okay, let's
7 have a meeting and that will solve things. It
8 doesn't solve things. And your group has given a
9 lot of thought to these issues, and I think a much
10 more focused, one-page description of the kinds of
11 questions that would need to be addressed, the
12 proper format, et cetera, I think would be very
13 helpful.

14 DOCTOR STITZER: Good, we'll get to work
15 on it.

16 CHAIR STRAIN: Doctor Wright.

17 DOCTOR WRIGHT: Yes. I was very
18 impressed some years ago when we were doing a
19 coronary -- actually, you were doing a coronary risk
20 intervention study, and we found that 50 percent of
21 the people offered free treatment by an enthusiastic
22 and attractive research system, didn't make it
23 across the parking lot to somehow enroll for the
24 program.

25 And, I was a later discouraged when the

1 janitor at the Occupational Medicine Clinic where I
2 was doing one of my rotations asked me if I could
3 keep my patients from discarding the prescriptions
4 for Nicorette gum in the grounds that he was trying
5 to keep clean.

6 One of the realities of intervention
7 with people who are in the pre-contemplative, or who
8 are even in the contemplate state, is that they say
9 yes, they smile, they take the prescription, sign up
10 for the product or whatever, and they leave out the
11 door of the clinic and they have no intention
12 whatsoever, or at least a weak resolve to actually
13 use the product.

14 One of the metrics that we are
15 interested in is especially when you move into a
16 less medically intense environment, or you are
17 discussing minimal intervention medical models, is
18 how do you measure how many people ever quit at all,
19 ever? What would you recommend for a metric?

20 DOCTOR STITZER: So, you are talking
21 about collection epidemiology type of data, right,
22 from larger groups?

23 DOCTOR WRIGHT: No. When you go into
24 clinical intervention studies, you are not -- many
25 of those studies do not have the luxury of taking a

1 highly selected, highly motivated compliance screen
2 subsuit.

3 DOCTOR STITZER: Right.

4 DOCTOR WRIGHT: They are just patients.

5 DOCTOR STITZER: Right.

6 DOCTOR WRIGHT: And, you say, would you
7 like to quit smoking, and they say yes, and then you
8 give them a baseline exam, you enroll them in
9 treatment, you give them their first two-week
10 supply, you send them out the door, you bring them
11 back in a week. Some fraction of those people are
12 simply dead freight at that point, they aren't
13 taking the medicine and they aren't doing things.

14 The questions about quit for a day, quit
15 for a week, point prevalence, one of the metrics
16 that we are interested in is how many people made a
17 genuine attempt to quit.

18 DOCTOR STITZER: Well, quit for a day
19 has been used in that fashion, it's been used that
20 way for studies of self quitters, who are
21 accumulated through some kind of advertising in the
22 community, and it has some utility in that regard,
23 but what you find often is that those -- many don't
24 even quit for a day or they will quit for a day and
25 then go right back.

1 You are pretty much relying on self
2 report there, invalidated, it's better, of course,
3 if you can bring people in and actually validated
4 the quit.

5 DOCTOR WRIGHT: Thank you.

6 DOCTOR STITZER: Okay.

7 CHAIR STRAIN: Other questions?

8 Yes, Doctor Khuri.

9 DOCTOR KHURI: I thank you for your
10 excellent, really thoughtful and helpful
11 presentation, answers to questions raised before and
12 will be continued to be asked, and I'm glad you are
13 meeting before the CPPD and will really develop the
14 answers there.

15 But, I realize that your society, which
16 I also commend, is for research and research
17 parameters as described, but there was an odd non-
18 mention of any behavioral or support methods thrown
19 into this soup.

20 DOCTOR STITZER: Well, actually it was
21 mentioned, it probably just went by you, but this --

22 DOCTOR KHURI: But, not emphasized
23 certainly, the effect on outcome measures.

24 DOCTOR STITZER: Right. For that, I
25 would go back to the AHCPR guideline, which did a

1 lovely job of showing that there is a dose effect
2 for behavioral therapy in smoking cessation, the
3 more behavioral therapy that is delivered, the
4 higher the absolute smoking cessation rates, and
5 this would be both at long and short term.

6 So, that is a very important
7 relationship. It was nicely documented in the AHCPR
8 guideline, and I did mention that it would be
9 important to include this kind of information in
10 product labeling for the benefit of clinicians, so
11 that they understand that behavior therapy does work
12 as a relapse prevention tool.

13 DOCTOR KHURI: That was my point, I feel
14 it's crucial.

15 DOCTOR STITZER: Yes, I did mention it,
16 but it was kind of buried in there.

17 DOCTOR KHURI: Thank you.

18 DOCTOR STITZER: Thank you for bringing
19 it out.

20 CHAIR STRAIN: Thank you, Doctor
21 Stitzer.

22 We'll now hear from Doctor Jack
23 Henningfield.

24 DOCTOR HENNINGFIELD: Good morning, it's
25 nice to be here. I have some slides. I feel like

1 I'm back at home in Minnesota, the official slide
2 labeling system is duct tape. When I left Minnesota
3 20 years ago, my Dad gave me a roll of duct tape. I
4 guess it showed up here.

5 I'm presently Associate Professor part-
6 time at Johns Hopkins Medical School. I'm part-time
7 at Penny Associates, I'm Vice President of Research
8 and Public Health Policy. I have consulted in the
9 past for, I think, all of the companies that have
10 currently marketed smoking cessation aids. Until
11 last year, I was Chief of Clinical Pharmacology at
12 NIDA's Intramural Program, the Addiction Research
13 Center. I left in part to be able to foster a
14 greater mutual, reciprocal relationship between
15 basic research and public health application. And
16 so, the issues that I'm bringing to you are more the
17 public health perspective, which is often left out
18 of the equation.

19 John Hughes mentioned earlier that the
20 impact of decisions made here or at subsequent
21 sessions have a broad impact on the field, they can
22 have a broad impact on public health, and so I would
23 urge you to consider the public health climate.

24 I also am in agreement that we should
25 move very cautiously in this area. I think a

1 conference makes a lot of sense. I don't think a
2 conference, and Doctor Meyer, I think, alluded to
3 this, is the simple answer. I don't think we are
4 going to have a bunch of people come up with a
5 perfect consensus, but at least it will provide more
6 data that are not possible to provide in this short
7 session today.

8 Having said this, I think that John
9 Hughes might consider that I'm going to proceed in
10 some ways to put the cart before the horse. On the
11 other hand, you've got to know where the horse is
12 going, too, you've got to know something about the
13 road, and let me tell you a little bit about the
14 public health road.

15 These are smoking trends over this part
16 of the century, and over the last 20 years or so
17 that I've been involved in this area we are very
18 pleased to see a general decline in smoking rates.
19 The last couple of years they have leveled off, and
20 show some possible sign of increasing, and this is
21 really discouraging.

22 The other thing to keep in mind is that
23 the risk of premature death is roughly 50 percent,
24 roughly half of the people that don't quit
25 prematurely die and often add great suffering and

1 expense to society.

2 There is a dose response relationship
3 between exposure level, and this has opened the door
4 toward the possibility that we might help people by
5 reducing their exposure, but there are empirical
6 questions to resolve in public health as to how we
7 go about this.

8 The other thing to note is that what is
9 called Marlboro Friday, that's when Marlboro dropped
10 its price, contributed, we believe, to a leveling
11 off of the smoking prevalence. So, there are
12 factors beyond our control that have an impact on
13 the public health.

14 The other thing is that, if prevention
15 were perfect and nobody started smoking tomorrow,
16 that between ten and 20 million current smoking
17 Americans will prematurely die, and that a lot of
18 these deaths could be avoided, a lot of the
19 suffering could be avoided, productive years could
20 be added to their lives if we can find ways to help
21 them. So, there are enormous public health
22 implications of the decisions.

23 Probably most discouraging is what's
24 happening with youth. This is the pipeline to adult
25 smoking, and this has been going up at all grade

1 levels and the most recent data that CDC released a
2 couple of weeks ago, or within the last few weeks,
3 is that we now have the fifth year in a row, five
4 years in a row of young people increasing. So, what
5 we decide has implications for today's smokers, and
6 tomorrow's smokers, and has implications for
7 treatment development for young people. We have to
8 be very careful that we don't set up new barriers to
9 developing treatments.

10 Not only will these kids need treatment
11 when they become adults, about half of them try to
12 quit and fail while they are young people. We don't
13 have anything for them, so we have to be careful
14 about setting up new barriers and new road blocks to
15 companies and organizations in their ability to
16 develop pharmaceutical and behavioral methods of
17 intervention.

18 Now, another thing to keep in mind is
19 what's happening with respect to the Food and Drug
20 Administration. The FDA conclusion, for those of
21 you that are not familiar with this, is that
22 cigarettes and smokeless tobacco products are drugs,
23 and that the nicotine is a drug, that the products
24 are nicotine-delivery devices. Now, this has broad
25 implications, and it allows FDA to treat these

1 products with extraordinary leeway compared to
2 drugs.

3 Often times we refer to patch, and gum,
4 and nasal spray and things as devices, technically,
5 they are drugs, and that has enormous implications
6 for the regulatory approach, and it also means that
7 no matter what we do in the drug area, in the
8 tobacco area, the reality is that for some time to
9 come the tobacco industry will have an enormous
10 advantage, whether it's what they call their
11 products, how they market them, how they change them
12 to make them more palatable. And, again, part of
13 the message is, we have to be careful that we don't
14 inadvertently raise barriers to appropriate and
15 needed drug development.

16 The other thing to keep in mind is, I
17 think the FDA has it right, the primary objective is
18 reduce death and disease caused by tobacco products,
19 it's not anti-tobacco per se, it's not even pro
20 cessation, it's reduce the death and disease. And,
21 if you accept that as your premise, there are a lot
22 of ways to get there, and this is a discovery that I
23 think we've had in other areas in substance abuse,
24 such as heroin dependence, where we've recognized
25 that there are many ways to reduce death and disease

1 that compliment absolute cessation efforts.

2 The present treatment goal, absolute
3 abstinence participation claim, the four to six
4 weeks from the start of treatment, now often times
5 in the literature you see one year verified
6 abstinence referred to as the gold standard. I've
7 referred to this sometimes as the golden wish, it's
8 what we wish would happen.

9 If we set something like this as a
10 standard or as a criterion for efficacy, we throw
11 most of our medications out the window, present and
12 future, and not just in the area of nicotine. The
13 idea that we would consider some of these kinds of
14 criteria, for example, for buprinorphine, for heroin
15 dependence is not even an issue.

16 On the other hand, I'm in agreement that
17 from a public health perspective, and a scientific
18 perspective, it's important to collect the long-term
19 data, and this gives us some perspective on what
20 processes are going on, what behavioral and
21 pharmacological innovations might be useful to
22 promote longer-term cessation, but that's different
23 from setting an efficacy criteria.

24 Looking at things like relief of
25 withdrawal and craving, right now if you look at the

1 labeling these appear to be, I think, what would
2 meet the criteria for secondary kinds of claims. I
3 think that it is worth evaluating these and other
4 kinds of secondary claims, but, again, I concur with
5 Doctor Stitzer and Hughes that these are really
6 complex issues. For example, urges and cravings may
7 or may not be considered part of the withdrawal
8 syndrome that you are providing relief of. In the
9 workplace environment, a lot of people have to
10 abstain from tobacco, that are unable or unwilling
11 to completely give up smoking.

12 Maybe what's most important in the
13 workplace situation is cognitive, maintenance of
14 cognitive importance, and maybe cravings aren't so
15 important. The point is, even the withdrawal kind
16 of indication is a complicated indication, and by
17 opening the door to withdrawal relief we should not
18 be lowering the standards.

19 Now, if we accept the fact that the goal
20 of therapy or the goal of cessation therapy is not
21 always to treat nicotine dependence, but to reduce
22 death and disease, then cessation therapies are just
23 one means to the end, and I think it's worth keeping
24 separate our concepts of the means versus the end,
25 the elimination of nicotine dependence is one means

1 to reduce death and disease, it's not necessarily
2 the only. Well, what are some alternate and/or
3 complimentary strategies?

4 George Woody, Frank Votchy, myself,
5 pilot drug staff, contributed in 1992 to the
6 development of guidelines for tobacco and other
7 medication development, and I provided this material
8 to the committee.

9 I think what was interesting about this
10 is a couple of things. First, it looked at tobacco
11 as an instance of drug dependence, and did not
12 forget about that context. And, when we are looking
13 at tobacco we shouldn't look at it completely in
14 isolation, because there have been lessons learned
15 with the other drug dependence disorders. There are
16 some similarities that are important to keep in
17 mind.

18 On the other hand, in these guidelines,
19 and I say guidelines for tobacco medication
20 evaluation, that's just one section. There were
21 guidelines for medications for the development and
22 evaluation of drugs for the treatment of
23 psychoactive substance use disorders in general, and
24 included opiates, cocaine, marijuana and so forth.

25 And, if you go through that, you can see

1 that even in this attempt there's a lot of work to
2 think about what might be appropriate standards and
3 criteria that I think we can learn from.

4 Now, how do we get there? Where do we
5 get indications? First, besides the stork, first we
6 need a regulatory and public health flexibility. We
7 need to recognize changing climate, the changing
8 dataset. The National Cancer Institute just
9 released an enormous monograph documenting the
10 relationship between amount of tobacco exposure and
11 the risk of death and disease.

12 Now, the empirical question is, can we
13 enable people to achieve low exposure, that's an
14 empirical question. The public health aspect is to
15 recognize that there could be benefit.

16 Similarly, with respect to clinical
17 need, by opening the window and expanding the
18 envelope to potential indications and applications,
19 that's not to say we should be opening to just
20 anything that a medication might do, but what things
21 might have some medical value, some public health
22 value.

23 In the AHCPH guideline, for example, on
24 the issue of weight control, this is kind of an
25 interesting case where it pointed out that nicotine

1 gum might be preferred for some patients that are
2 concerned about weight gain, even though that
3 doesn't necessarily mean your outcome is better if
4 you control you weight.

5 Finally, data, and here we have to be
6 very careful that we don't provide some kind of
7 blanket opening of the window that goes beyond the
8 requirement for rigorous data. I think any change
9 we've made needs to be founded on companies then
10 submitting scientific data to support those
11 applications.

12 Let me give you two examples. We've
13 been dealing with nicotine replacement therapy,
14 which is not just a drug, it's the systematic
15 application of nicotine-delivering medications to
16 establish and sustain tobacco abstinence. It
17 includes behavioral approaches. I think one of the
18 benefits of the OTC conversion was that it forced
19 the manufacturers to provide more detailed
20 behavioral kinds of support systems for patients. I
21 think we need to do more of that.

22 Another kind of example, to coin my
23 friend, Saul Shiffman's phrase, exposure reduction
24 therapy. This is the premise for that, you could
25 systematically apply nicotine-delivering medications

1 and behavioral and medical principles to achieve
2 sustained reduction and exposure. Is it possible?
3 Well, this is where you need science. Is it
4 beneficial? Potentially, it's beneficial, but you
5 need, again, to consider the public health context
6 and then base decisions, not on what has been done
7 in the past, what seems possible, what may or may
8 not be counterproductive, but on empirical data.

9 Okay, the future. I think a couple of
10 things to keep in mind. One is that on our present
11 course, ten to 20 million American cigarette smokers
12 will prematurely die. We can reduce a lot of the
13 suffering. We can offer treatments, but we have a
14 long way to go in developing treatments, making
15 treatments more friendly to consumers. Labeling is
16 part of that, and it's an important part.
17 Unfortunately, labeling changes can just as easily
18 serve as barriers as it can serve as aids.

19 We need to expand, obviously, our
20 tobacco control and prevention efforts, and consider
21 how labeling changes fit into that mix. There are
22 things that are off the radar screen, like the so-
23 called herbal type medications, which can make
24 wildly extravagant claims as far as I can see,
25 without requiring any data at all. A number of

1 years ago, I made some supportive comments about a
2 company's product that was being developed. They
3 incorporated that into a commercial. It made claims
4 that the product could reduce exposure up to 90
5 percent, and quite extraordinarily cessation
6 success. They never conducted a clinical trial.
7 They had some preliminary data at Hopkins of Maxine
8 Stitzer, and it was that study that I was commenting
9 on.

10 I complained to the NIH General Counsel,
11 I think it was about a year later that the FTC took
12 some action. Meanwhile, the public, I think, was
13 not well served, I think it was confused. So, we
14 need to set standards. We have to keep in mind that
15 there are a lot of other things going on out there.

16 We have to permit and reinforce
17 innovation by pharmaceutical companies and
18 behavioral treatment developers to provide new ways
19 for tobacco dependent people to reduce their risk of
20 death and disease. Again, this is not a plea for
21 trivial applications or lowered standards, it's a
22 suggestion that a willingness to consider claims
23 that are complimentary to the existing cessation
24 claim would be considered on the basis of their
25 scientific and public health merit.

1 Finally, I would urge that we guard the
2 current cessation claim and criteria, and the high,
3 but achievable, standards, and we now know that even
4 though this four-week period of the first six weeks
5 seems somewhat arbitrary, it has worked very well.
6 Also, it has been achievable, and by achieving that
7 we know that that often translates to long-term
8 success, or at least the foundation upon which you
9 can build creative behavioral and pharmacological
10 modifications to sustain long-term success.

11 Finally, I refer back to John Hughes'
12 and Maxine Stitzer's plea to evaluate more data. We
13 need to include public health kinds of implications,
14 and trends, and data and needs in the mix, and we
15 also have to consider the enormous implications that
16 any changes can have on the health of our nation and
17 the world.

18 Thank you.

19 CHAIR STRAIN: Questions for Doctor
20 Henningfield?

21 Thank you, Doctor Henningfield.

22 Any questions from the committee?

23 If not, I entertain, it's almost 12:30,
24 considering that we might take a break at this
25 point. We're sort of in the natural spot, and

1 reconvene at 1:30, if that would be all right with
2 the remaining three open public hearing speakers,
3 take a lunch break? Would that be all right? Nods.
4 Is there a conflict? Does anybody need to, from
5 McNeil, Pharmacia or SmithKline, do we have all
6 three here? We are getting okays.

7 Okay. Then, in that case, why don't we
8 reconvene here at 1:30 sharp. You are getting five
9 extra minutes for lunch, so you've got to be back at
10 1:30.

11 Thank you.

12 (Whereupon, the meeting was recessed at
13 12:24 p.m., to reconvene at 1:30 p.m., this same
14 day.)

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

2 1:34 p.m.

3 CHAIR STRAIN: Shall we get started?

4 Shall we get started? If the committee could take
5 its seats, please? We will pick up with the open
6 public hearing and we will first be hearing from Dr.
7 Barbara Korberly from McNeil Consumer Products.

8 DR. KORBERLY: Thank you, Dr. Strain.

9 Good afternoon Dr. Wright, Dr. Winchell, members of
10 the FDA and FDA Drug Abuse Advisory Committee. My
11 name is Barbara Korberly. I am from the Medical
12 Department at McNeil Consumer Products Company, and
13 I am pleased to be with you today to respond to the
14 FDA request for a reevaluation of the labeling of
15 smoking cessation products.

16 McNeil Consumer Products is committed to
17 help battle cigarette addiction in the United
18 States. Our current smoking cessation products
19 include the OTC Nicotrol patch, the prescription
20 Nicotrol nasal spray, and the recently approved
21 Nicotrol inhaler. In response to the FDA request,
22 McNeil Consumer Products Company has submitted
23 proposed labeling recommendations to the Agency.

24 These recommendations are based on data
25 from three sources. Namely, the published

1 literature, a recent analysis from our large
2 clinical trial conducted in support of the Rx to OTC
3 switch of the Nicotrol patch, which will be referred
4 to as McNeil Study 94400, and a result of a market
5 research survey of patch study participants.

6 The proposed labeling recommendations
7 submitted are directed to both the practitioner and
8 the consumer. These recommendations are focused in
9 four specific areas. First, smoking behavior during
10 the initial 14 days of nicotine replacement therapy
11 and how it can be a predictor for short and long-
12 term success.

13 Secondly, the risk of adverse
14 experiences while smoking and concomitantly using
15 OTC or prescription nicotine replacement products,
16 which is commonly misconceived to increase the risk
17 of heart attacks, when in fact it has been
18 demonstrated that no increased risk exists.

19 Third, the prevention of relapse after
20 successfully stopping smoking, which is a key issue
21 for quitters.

22 And finally, reduction in tobacco
23 consumption using NRT, which may take patients a
24 step closer to ultimate or complete success. Our
25 summary will include comments on other secondary

1 criteria and possible next steps.

2 Now one of the most disturbing obstacles
3 that we face today is the lack of understanding of
4 the behavioral and pharmacological approaches to
5 smoking cessation on the part of health care
6 providers and consumers. Providers are often
7 reluctant to intervene, yet the Agency for Health
8 Care Policy and Research guidelines recommend that
9 counseling, even as brief as 3 minutes is effective.
10 In addition, these guidelines recommend that every
11 smoker should be given nicotine replacement therapy.

12 While we address certain safety
13 misconceptions in this presentation, it is key to
14 acknowledge that the benefits of using NRT could be
15 potentially lifesaving if the subjects stop smoking.
16 Both patients and prescribers should be fully
17 informed as to the risk/benefit profile of nicotine
18 when used as a smoking cessation aid. I personally
19 have heard many consumers and surprisingly many
20 physicians incorrectly say that nicotine is
21 carcinogenic.

22 Therefore, in order to broaden the
23 understanding of consumers, especially with regard
24 to the safety of nicotine replacement products to
25 help them quit, we would like to make the following

1 recommendation to be added to the consumer label.
2 Nicotrol works by replacing some of the nicotine you
3 receive by smoking cigarettes. However, it does not
4 contain the tars and toxins found in cigarettes.

5 Now we would like to present some
6 potential labeling recommendations based on our
7 clinical research experience with patch users. The
8 first area for discussion is smoking behavior during
9 the first 14 days of the smoking cessation attempt.
10 As some of you may recall, McNeil conducted a
11 randomized open-label multi-center OTC trial of
12 nearly 4,000 smokers to evaluate the safety and
13 efficacy of the Nicotrol patch. These data were
14 presented at the April 1996 joint meeting of this
15 committee and FDA's Non-Prescription Drugs Advisory
16 Committee.

17 In this trial, efficacy was determined
18 by self-reported abstinence of smoking status at all
19 time points, an expired carbon monoxide of less than
20 10 at 6 weeks and 6 months. When we assessed the
21 cumulative percentage success rate at 6 weeks, 3
22 months, 6 months, and 12 months with the Nicotrol
23 patch, we considered three success criteria. These
24 three criteria were 1) complete abstinence for at
25 least one month from the end of week 2 through the

1 end of week 6, the primary FDA criterion; 2)
2 complete abstinence at all visits; and 3) abstinence
3 at all visits with allowed lapses.

4 In a development design and analysis of
5 this trial, we attempted to utilize and evaluate all
6 information regarding smoking behavior during the
7 initial 14 days of NRT and its relevance to short
8 and long-term success rates. Now as you would
9 expect, the most stringent criterion, abstinence at
10 all times from day one, yielded lower quit rates at
11 all time points, with the 6-week and the 12-month
12 success rate shown on this slide. Now in contrast,
13 the more lenient criterion, abstinence with allowed
14 lapses, yielded higher quit rates at all time
15 points, with the 6-week and the 12-month success
16 rate shown here.

17 It is important to observe that this
18 group of smokers who lapsed throughout the study
19 showed a greater relapse rate at the 12-month time
20 point, 56 percent, when compared to those not
21 smoking any cigarettes from day 1, 42.4 percent. In
22 addition, a previously mentioned study by Westman
23 suggested that abstinence on day 1 of treatment was
24 a predictor of long-term success.

25 Now based on these data and in order to

1 potentially optimize an individual's chance for
2 success, we make the following label recommendations
3 for the practitioner and consumer. For the
4 practitioner, encourage all patients not to smoke at
5 all from the first day of therapy. Patients should
6 be informed that this will significantly increase
7 their chances of long-term success. For the
8 consumer, to increase their chances of long-term
9 success, stop smoking completely the first day of
10 therapy.

11 Now beyond the first day, another
12 critical point for practitioners to realize is that
13 if an individual has not stopped smoking completely
14 or significantly reduced their cigarette consumption
15 by day 14 of NRT, the likelihood of success during
16 this quit attempt is minimal. Published data from
17 the Mayo Clinic demonstrate that individuals who do
18 not achieve abstinence after 2 weeks should be
19 carefully evaluated and offered other treatment
20 options.

21 Of 240 smokers enrolled in this nicotine
22 patch trial, there was a significant relation
23 between smoking status at the end of week 2 and
24 smoking status at one year. Of the 78 subjects not
25 smoking at the end of the second week, 46.2 percent

1 were not smoking at one-year follow-up. In
2 contrast, of the 162 subjects that were smoking at
3 week 2, only 8.6 were not smoking at one year.

4 An additional randomized double-blind
5 placebo controlled study demonstrated that
6 abstinence during week 2 was highly predictive of
7 both short and long-term abstinence. In this study,
8 of the 35 patients smoking in week 2, 97.1 percent
9 were smoking 6 months later.

10 The importance of quitting during the
11 first two weeks and its relevance in determining
12 what will happen in future weeks was confirmed in
13 the large McNeil trial based on 1,920 smokers who
14 provided daily diary data for the first 14 days. As
15 you can see on this slide, for subjects not smoking
16 during week 2, the odds ratio for success at the end
17 of treatment was 11.6 relative to subjects smoking
18 during week 2. For smoking abstinence at day 1,
19 during week 1, and during week 2, the odds ratios
20 were 1.7, 2.1, and 1.9 respectively for long-term
21 success, not smoking at 6 months. These data
22 confirm that abstinence during the initial 14 days
23 of NRT will double the likelihood of remaining
24 smoke-free in the future.

25 These data demonstrate how critical the

1 first 14 days are in the quitting process and that
2 abstinence during this period can be a predictor of
3 short and long-term success.

4 For the practitioner, we would make the
5 following recommendation to be added to the label.
6 If a patient is abstinent at 14 days, congratulate
7 success and encourage complete therapy. If a
8 smoking relapse has occurred, remind the patient
9 that a relapse is a learning experience and elicit
10 recommitment to total abstinence. Consider
11 prescribing alternative nicotine replacement
12 medication or other treatments.

13 For the consumer label, we would
14 recommend the following. If you have not stopped
15 smoking completely or significantly reduced your
16 smoking by day 14, you may want to try again in the
17 near future or talk to your doctor about alternative
18 forms of nicotine medication or other treatments.

19 Of interest, in a recent market
20 telephone survey, prior patch users were asked if it
21 would be helpful to have the following information
22 on the package label. If you stop smoking sometime
23 during the first 14-day patch usage period, your
24 chances of quitting over the next 6 months are
25 greatly improved. 85 percent indicated that it

1 would be helpful to convey this message on the
2 package label.

3 The second topic for labeling
4 recommendations considers a general misunderstanding
5 of adverse experiences while using nicotine
6 replacement therapy. A possible contributing factor
7 that makes health practitioners reluctant to
8 prescribe or use NRT is the misunderstanding of its
9 risks, especially for subjects who concurrently
10 smoke. In addition, consumer research demonstrates
11 that there is an unfounded fear of starting therapy
12 with the patch and then slipping, that is, smoking a
13 cigarette and dying of a heart attack.

14 Now in the real world, despite this
15 concern, it is well recognized that a significant
16 number of smokers will continue to smoke while using
17 NRT. In fact, this is consistent with data from our
18 market research survey of patch users who were
19 discontinued after 2 weeks of therapy. These
20 patients reported smoking 8 out of the 13.5 days
21 that they wore the patch. Yet, when we asked how
22 much of a risk of serious side effects do you think
23 there is if you smoke while wearing a nicotine
24 patch, 67 percent reported that they thought there
25 was a moderate to large risk.

1 So knowing that consumers slip on the
2 patch, even though they think there is a significant
3 risk for side effects, we decided to look back at
4 the subjects in Study 94400 who smoked at sometime
5 while using the patch during the first 2 weeks of
6 treatment. The percent of subjects reporting
7 adverse experiences in the first 2 weeks of patch
8 treatment was greater for subjects not smoking while
9 wearing the patch compared to those subjects
10 reported smoking while wearing the patch, 26 percent
11 versus 20 percent. Of particular note, there was no
12 difference in serious cardiac adverse events. As
13 discussed previously at the FDA advisory meeting in
14 April of 1996, there was a substantial body of data
15 presented that there is no increased risk of
16 cardiovascular events while smoking and using the
17 patch.

18 In order to share these results and to
19 provide additional safety information to health
20 practitioners, we recommend adding the following to
21 the label. In a large clinical study, there was no
22 increase in serious adverse events in subjects who
23 smoked while wearing the patch compared to those
24 subjects who were completely abstinent. Smokers
25 should be encouraged to stop smoking completely when

1 initiating nicotine replacement therapy to increase
2 their chances of quitting, but they do not
3 significantly increase the risk of adverse events if
4 they lapse and smoke while on NRT.

5 In a consumer version, it is important
6 to emphasize the recommendation of not smoking while
7 wearing the patch in order to increase their chance
8 for success and decrease any risk of side effects.
9 Therefore, the consumer version of this label
10 recommendation does not address the low risk of
11 serious effects, but this certainly is an area for
12 committee discussion. The consumer version would be
13 similar to the current label with a minor change.
14 Smoking while wearing a patch may reduce your
15 chances of quitting completely and may cause
16 symptoms of nicotine overdose. Therefore, it is not
17 recommended to smoke, chew tobacco, use snuff,
18 nicotine gum, or other nicotine containing products
19 while attempting to stop smoking completely.

20 The third recommendation relates to
21 relapse prevention with NRT. It is important to
22 evaluate how it could be used by quitters and
23 potential quitters who are concerned about relapse.
24 In Study 94400, 1,920 patients reported written
25 daily diary data which included the number of

1 cigarettes smoked on any day. Of these subjects,
2 87.7 percent were able to abstain from smoking for
3 at least one day. In fact, if you look at this
4 slide, you will see that over half of the subjects
5 were able to abstain from smoking for at least 7
6 consecutive days, and a third of the subjects for at
7 least 12 consecutive days.

8 These data suggest that with assistance,
9 smokers can abstain for one or more days. These
10 important data support the potential role of
11 nicotine replacement therapy in relapse prevention
12 when patients may be faced with stressful situations
13 which may cause them to return to smoking. As
14 relapse prevention is a key to long-term smoking
15 cessation, these products may be beneficial in
16 helping a successful quitter stay smoke-free.

17 In accordance with these data, we make
18 the following practitioner recommendation. Clinical
19 studies have demonstrated that the majority of
20 subjects were able to abstain from cigarette smoking
21 for one or more consecutive days whether or not they
22 successfully stopped smoking. Occasional use of
23 this product by patients who have quit may assist
24 them in the prevention of relapse, especially when
25 they are faced with social or situational triggers.

1 And the following consumer
2 recommendation is made. After successfully quitting
3 smoking and to prevent relapse, even for just one
4 day, you may want to begin using this product again
5 if you have nicotine cravings or the urge to smoke.

6 The final area for consideration is
7 reduction of tobacco use with NRT. While a
8 significant number of smokers fail to stop smoking
9 completely with NRT, these subjects significantly
10 reduce the number of cigarettes smoked per day over
11 the first 14 days. In our market research survey of
12 patch users, subjects significantly reduced their
13 consumption from a mean of 27.4 cigarettes per day
14 to a mean of 4.2 cigarettes per day by day 14. In
15 study 94400, the vast majority of subjects who did
16 meet our primary efficacy criterion did reduce their
17 cigarette consumption by at least 90 percent over
18 the first 14 days of this study. By study design,
19 many of these subjects were considered treatment
20 failures by day 14 and released from the study.

21 Of interest, they were subjectively very
22 satisfied with their reduction in smoking and this
23 may have significant implications with respect to
24 long-term health consequences. When visiting the
25 study sites, I can tell you that I personally spoke

1 to numerous consumers who enrolled and were smoking
2 three or four packs a day. Although they were able
3 to reduce to only 3 to 4 cigarettes a day by day 14,
4 they were thrilled with their progress. Many of
5 them literally begged the study staff to allow them
6 to remain in the study because they were so pleased
7 with their measure of success, even if they hadn't
8 stopped completely by two weeks. They often said,
9 what will I tell my family? They are so thrilled
10 with my progress. I used to smoke so much and now I
11 smoke so little. What can I do?

12 While it is unknown whether limited
13 reduction in tobacco consumption places the patient
14 a step closer to ultimate or complete success, we
15 should not disregard the potential benefits of
16 cigarette reduction.

17 Based on these data, we recommend the
18 following label addition to the practitioner.
19 Nicotine replacement therapy may significantly
20 reduce the number of cigarettes smoked on a daily
21 basis and may decrease the risk of tobacco-related
22 diseases for the smoker and for those exposed to
23 passive smoke. Patients who are able to reduce
24 cigarette use with nicotine replacement therapy
25 should be encouraged to continue their efforts to

1 quit completely. This may require dosage adjustment
2 or use of alternate nicotine replacement therapies.

3 Because we do not want to de-emphasize
4 the goal of stopping smoking completely, no consumer
5 recommendation is made at this time.

6 Now this completes our labeling
7 recommendations. We would like to comment briefly,
8 though, on the use of other efficacy criteria in
9 smoking cessation studies. We would exercise
10 caution in the use of point prevalence data to
11 convey quit rates for any smoking cessation therapy.
12 If FDA elects to permit point prevalence rates, it
13 is important that they be conveyed in a manner that
14 fully discloses how they were derived. In addition,
15 they should be used only as adjunctive measures to
16 the well-established FDA 28-day efficacy criterion.
17 This will restrict the potential for misuse of these
18 measures in overstating product efficacy.

19 In summary, we have presented label
20 recommendations for the practitioner and consumer to
21 help both groups battle cigarette addiction more
22 effectively. Data supporting labeling revisions
23 have been presented in 4 areas, namely the first 14
24 days of therapy, the safety of NRT in the event that
25 a slip occurs, the potential use in relapse

1 prevention, and the potential in reducing cigarette
2 consumption.

3 These suggestions are in support of the
4 FDA's mission to reevaluate the labeling of smoking
5 cessation products. Although smoking in the United
6 States has decreased, there is a need for increased
7 intervention by health professionals as well as
8 increased and better defined use of nicotine
9 replacement therapy by both health practitioners and
10 consumers through expanded labeling. Together,
11 these will contribute to an increase in successful
12 quit attempts and long-term quitters. Thank you.

13 CHAIR STRAIN: Thank you, Dr. Korberly.
14 Are there questions from the committee? Yes, Dr. de
15 Wit?

16 DR. DE WIT: I have a question about
17 your use of nicotine replacement products in relapse
18 prevention. Has anyone actually done a clinical
19 trial where they recommended when a lapse has
20 occurred to use the product even though they haven't
21 been using it for some period of time? Is there any
22 actual data to base that recommendation on?

23 DR. KORBERLY: I am not currently aware
24 of one and you are correct. The primary objective
25 of this study that we did was an OTC trial for

1 switch and the primary objective was not relapse
2 prevention. But we just provide that information.
3 These are the data that we collected to show how the
4 people used the product. In addition, I can give
5 you information anecdotally that at the 6-week
6 juncture, when I was at the sites and we saw people
7 coming in who were successful and it was their last
8 visit and they had stopped and when you would look
9 at their diary, they hadn't used the patch for the
10 last couple of days or even sometimes the last week.
11 And upon questioning, they would say, well, I just
12 wanted to save a couple just in case.

13 DR. DE WIT: I think it certainly has
14 potential, but I think before we recommended that as
15 a way to use the nicotine replacement products, we
16 would like to have some systematic data indicating
17 that effect.

18 CHAIR STRAIN: Dr. Simpson?

19 DR. SIMPSON: I just was looking at the
20 BK-15. The recommendation, I think, is based on
21 this. From what was said earlier, I got the
22 impression that in fact if someone quit smoking on
23 day one, it is not a particularly good predictor.
24 However, when you compare the odds ratios at the end
25 of treatment, it looks like if they have quit by the

1 end of week 2 that that looks pretty good. But then
2 if you go to the 6-months, those odds ratios don't
3 differ at all significantly, do they?

4 DR. KORBERLY: No. They seem to be
5 quite similar at 6 months.

6 DR. SIMPSON: So if day one is not a
7 good predictor, how is week 2 a good predictor?

8 DR. KORBERLY: Week 2 seems to be -- in
9 our study data here, it was a very good predictor of
10 abstinence at the end of treatment period. But you
11 are correct in stating that at 6 months, there
12 doesn't seem to be a difference and they all
13 essentially double the likelihood. In addition, I
14 guess what we have tried to say, at least in our
15 first two labeling recommendation sections, is that
16 there is something important and I think a lot of
17 the speakers talked to it this morning. There is
18 probably something important going on in the first
19 couple of weeks of therapy. It may involve the
20 first day, the first week, and the first two weeks,
21 but there clearly is something going on in the first
22 14 days that help us determine what happens in the
23 future and/or would help us recommend that the
24 patient talk to their doctor about alternative
25 medications.

1 DR. SIMPSON: I am sort of new to this
2 language. When you are talking day one or week 2,
3 are you talking basically week 3, day one, or are
4 you talking day one day one?

5 DR. KORBERLY: Day one is day one. Week
6 1 is 1 to 7. Week 2 is 8 to 14.

7 CHAIR STRAIN: Yes, Ms. Falkowski?

8 DR. FALKOWSKI: I was struck by the
9 difference in labeling recommendations for the
10 practitioner and for the consumer regarding adverse
11 experiences in the sense that for the practitioner
12 it says if a person were to lapse, it does not
13 significantly increase their risk of adverse events.
14 Whereas, for the consumer it says smoking while
15 wearing the patch may cause symptoms of nicotine
16 overdose. It strikes me that for most consumers, an
17 overdose is an adverse event. So that is very
18 curious to me and it strikes me as suggesting two
19 different things or at least being misleading to the
20 consumer. Could you comment on that?

21 DR. KORBERLY: Well, what I think we
22 would like to point out here is that in the adverse
23 experience for the practitioner, what we really
24 wanted to do was demonstrate that in this study, we
25 saw no -- there were more subjects who wore the

1 patch and didn't slip reporting adverse events than
2 subjects who were slipping. And the reason we did
3 not put that into the consumer recommendation is
4 that we didn't want to, I guess I would say,
5 encourage consumers that it is okay to slip. We
6 don't want to encourage them that it is okay and
7 nothing will happen to you. We want to tell them
8 that they won't die of a fatal heart attack, but we
9 would like to suggest that they don't smoke while
10 they wear the patch because we think that has other
11 implications in long-term success.

12 DR. FALKOWSKI: Right. And I think that
13 could be done without implying that harm will come
14 to them in the sense that it is as currently stated.

15 DR. KORBERLY: Yes. The issue with
16 regard to symptoms of nicotine overdose is very
17 similar to the language, you are correct, which is
18 on the label now.

19 DR. MEYER: I think that is particularly
20 important given what we heard earlier this morning
21 that patients will buy the PDR and if they hear
22 advice that is totally contrary to what is being
23 given to their practitioner, it will be a terrible
24 precedent.

25 DR. KORBERLY: Well, we will modify the

1 consumer one.

2 CHAIR STRAIN: Dr. Lloyd?

3 DR. LLOYD: A question that I had I
4 think is reflected on BK-30. It is just a
5 curiosity. I don't think that it is a flaw of any
6 kind, but just a curiosity in the reduction of
7 cigarette use. Did you in any way select out
8 anybody who had used other forms of tobacco?

9 DR. KORBERLY: No. These were all
10 cigarette smokers.

11 DR. LLOYD: So when the question was
12 asked about their reduction in cigarette smoking,
13 did you ask the question, had you used a pipe or a
14 cigar?

15 DR. KORBERLY: Well, let me be more
16 specific. These were actually patients who were in
17 a clinical patch trial who were dropped at day 14.
18 Therefore, they were excluded from using other types
19 of tobacco to even get into the trial. So they
20 wouldn't have used it.

21 DR. LLOYD: Okay.

22 CHAIR STRAIN: Other questions? If not?
23 Thank you. Our next speaker is Dr. Karl Fagerstrom
24 from Pharmacia and Upjohn.

25 DR. FAGERSTROM: And the pulmonary

1 department of the local hospital in Helsingborg.
2 Drs. Strain, Andorn, Winchell and Wright, ladies and
3 gentlemen, I am very pleased to be able to speak in
4 front of you. I think we are talking about a very,
5 very important subject today. That is a picture
6 that is sad. It is tragic, and I think it says it
7 all. We are here to contribute to this. We do not
8 want to see this. This is not an American kid, nor
9 is it a Swedish kid, but it is a kid that is
10 smoking.

11 I also would like to connect with this
12 by saying that what you are doing here -- and FDA is
13 certainly, I dare to say, the regulatory authority
14 in the world that is more interested in this than
15 any other -- that has ramifications also outside the
16 U.S. So please help the world to control smoking
17 and reduce harm, the morbidity and mortality.

18 I think it is very timely to review
19 labeling and the indications for these products.
20 Because I think since 1983, when I was present at
21 FDA at that time discussing the labeling for the
22 nicotine gum, there hasn't actually been a
23 substantial review of this drug. And there is,
24 despite secondly that nicotine has been so much
25 researched and the notion about nicotine has changed

1 so much over these 15 years, that today we should
2 look upon nicotine on par with other illicit
3 dependency producing drugs. So I am calling for
4 some organization here actually.

5 And thirdly, do I dare to say that
6 clearly now FDA has got the authority not over just
7 nicotine from pure medications but also over
8 nicotine delivered in tobacco vehicles, and that
9 also might call for some review and possibly
10 harmonization.

11 A few slides that will lay the basis for
12 the rest of my talk, that is, that there are four
13 things other than nicotine that are the most
14 important causes of acute cardiovascular events.
15 And certainly nicotine is not implied in respiratory
16 disorders and cancer. We have cigarettes out there
17 that contain nicotine, but they contain a lot of
18 toxins. Probably the most contaminated drug that
19 ever existed in the world. They are cheap and they
20 are extremely available. They are more available
21 than water and bread.

22 There are also treatments that contain
23 nicotine but have no toxins. These are having
24 restricted indications and their availability is
25 also very much restricted.

1 And there has been a number of
2 scientists and policy makers that have realized that
3 there is possibly an opportunity to use nicotine to
4 combat disease and death. If smokers are driven by
5 their nicotine seeking but nicotine itself is not
6 that harmful, maybe we could get more mileage out of
7 treatment. I guess that is why we have seen a trend
8 throughout the world from a few years ago. I think
9 it started with a conference at Johns Hopkins in
10 1995 called Smoking Cessation Alternative
11 Strategies. It continued with the health education
12 authority in the UK when they discovered that there
13 was no way that they were going to meet their health
14 of the nation targets by the year 2000. So what can
15 we do? Are there other routes we can pursue?

16 More recently, there was a conference,
17 Alternative Nicotine Delivery Systems Upon Reduction
18 at Public Health in Toronto, and there will be
19 another one within the UN system organized by the
20 United Nations Conference on Trade and Development
21 in September called Social and Economic Aspects of
22 Reduction of Tobacco Smoking by Use of Alternative
23 Nicotine Delivery Systems.

24 The country where I am coming from is
25 odd at least in one sense. We use a lot of fine

1 grain moist fluff that beautiful creatures like this
2 one is putting up between the upper lip and the gum.
3 It is not so common among women, but it is very
4 common among men. But before coming to that, I have
5 captivated some rough figures in trying to figure
6 out of all nicotine consumed in my country and the
7 U.S., how much is taken in by alternative nicotine
8 delivery systems, meaning non-smoking nicotine, and
9 it is approximately 35 percent in Sweden and 6
10 percent in the U.S. For men in Sweden, it is
11 probably closer to 50 percent. You can see here, we
12 are in the population roughly 19 percent daily
13 smokers, which is lower than in any other developed
14 country in the whole world. But 17 percent upon the
15 19 percent of men, they use this -- we call it snus
16 in Sweden -- this moist tobacco. So nicotine
17 dependence in Swedish men is in the order of about
18 36 percent. But the point I want to make is that if
19 we look at the WHO and P too, the statistics of risk
20 of dying in middle age, that is much lower in Sweden
21 than in any other country in the developed world
22 also, and it is really much lower. It is not just
23 the lowest. It is in another different division.

24 So I think that there is some mileage to
25 get out of this nicotine cessation and possibly

1 other cessation treatments, and I would like to
2 discuss then some possible extended uses. Extended
3 duration -- we have the American Lung Health Study
4 where there has been gum use for 5 years. We all
5 have heard anecdotes. We have heard Dr. Sachs
6 speaking. We may have friends. And we certainly
7 saw today that there seem to be a number of smokers
8 that probably cannot give up with any treatment at
9 all, not even with NRT. There is a larger group
10 that can be off smoking if they have access to some
11 other form of nicotine, particularly those with a
12 tendency for depression as has been identified as
13 benefiting from extended use. So I think this
14 becomes quite obvious.

15 Secondly, there is a number of
16 specialists and experienced doctors that are
17 combining various nicotine replacement forms
18 already. Some actually more than two also. And
19 here there are at least 3 or 4 published studies
20 that all have shown that combined use is more
21 efficacious than using a single product. And, of
22 course, it makes sense that with patch use, you lay
23 a ground level of nicotine, which is enough for some
24 and certainly not enough for a lot of heavy
25 dependent smokers, and rather than putting on a

1 number of patches, the better and more fine tuning
2 alternative is to take some other treatment or
3 medication that gives nicotine more acutely.

4 We have what I am calling here the
5 Cooper and Clayton method, and that means that in
6 this program, they give up smoking regularly. They
7 cut out a cigarette each day, so they taper
8 cigarettes down, and at the same time in parallel,
9 they taper up the use of nicotine replacement. They
10 usually use gum. So the nicotine level should be
11 constant in the consumers and subjects. And at a
12 certain time, they are only using nicotine
13 replacement, and then after some time, they taper
14 off.

15 A special case of using smoking and NRT
16 at the same time could also lead to familiarize with
17 the NRT product a few days or a week before target
18 quit date. Because these products are not easy to
19 use and to get used to it and to get used to the
20 side effects and the does, et cetera -- and again,
21 there is actually some evidence there that it
22 certainly decreases the untoward effects of the
23 products and also may increase the success rates
24 thereof.

25 There are many -- or actually the

1 majority fail. I don't think that all who fail
2 would be candidates and would like to keep on using
3 a nicotine replacement medication, but I think those
4 who would like to do so to keep their smoking down
5 until they feel recharged again and would like to
6 make a new attempt should also be allowed to use
7 that harm reduction strategy.

8 Then we come to exposure reduction,
9 reduced smoking harm reduction -- there are many
10 names on this. Many do want to give up smoking, but
11 all do not. And all who say they would like to give
12 up do not in reality actually make an attempt. So
13 if I could distinguish the population that wants to
14 give up and wants to do it maybe abruptly to those
15 who are not willing nor interested or they cannot.
16 Why not expose them to an exposure reduction model?
17 In my thinking, we do have some evidence from two
18 studies that the motivation to give up altogether
19 seemed to increase if they enrolled in an exposure
20 reduction program. All of these have the end goal
21 of complete cessation.

22 Now we come to this temporary or forced
23 abstinence situation that we -- I am saying
24 fortunately -- have in this country more than on the
25 other side of the ocean, but I hope it will come to

1 us as well. I guess that is good for many smokers
2 that they have to be without cigarettes. However,
3 there are problems with it, of course. Hospitals
4 are a problem where a patients sneak into toilets.
5 They may endanger things. In the industry, I guess
6 there are frictions created. I guess there are
7 decreased performances. I could even envision that
8 there might be an increase of certain accidents. I
9 must say that I am quite happy when I am flying that
10 there is not an enforced smoking ban in the cockpit.
11 So I think there is also some room for looking into
12 using nicotine to control nicotine withdrawal
13 syndrome, which has the diagnostic entity of 292.
14 And again, who knows if they could use it to get by
15 easier, maybe they would see that there is something
16 that works and why don't I give up altogether.

17 Then to determining efficacy. Okay.
18 Let's discuss this a little bit. In the 1980's,
19 when 6 weeks was suggested to be enough for
20 determining efficacy, I was surprised. I thought it
21 was too short a time. I sent papers to journals. I
22 reviewed papers. And then we were going up to
23 longer and longer time intervals. Certainly 6
24 months -- that is what we have today -- or one year.
25 But over the years, I must say that I have changed

1 my mind a lot. If we look at at least two types of
2 criteria here -- this is from the Baker's placebo
3 controlled smoking cessation trial under the
4 European Respiratory Society with some 3,500
5 smokers. And if we use the FDA criterion, at 8
6 weeks 32 percent were abstinent. If we use lapses
7 allowed, 43 percent. That seems to be clearly
8 better than 32 percent, but at one year there isn't
9 much of a difference. And if we go and stay a
10 little longer with the six inhaler studies which
11 have recently been reviewed by FDA and we have the
12 continues complete abstinence from week 2 to week 6,
13 31.5 percent are abstinent, but 48 percent if lapses
14 are allowed. So as a consumer, I certainly buy this
15 treatment and I think I can put up a lot more money
16 also than for that treatment. But, if we go to one
17 year, the difference is 14 and 16.5. There isn't
18 much difference at one year.

19 So actually I think this stringent short
20 criterion predicts long-term abstinence very well,
21 and I think it does predict better than the more
22 loosely set up criterion. If we had point
23 prevalence here -- it is not included in this
24 picture -- we would have even higher abstinence
25 rates there, but it is not so predictive. And in my

1 scientific terminology, I think a more lenient
2 criterion introduces more variance into the figures.
3 That means it would be more difficult to assert a
4 difference between an active and a placebo group.

5 So Pharmacia & Upjohn is not in favor of
6 changing this seemingly stringent criterion. It has
7 served its purpose for efficacy testing, we think,
8 very well. Acknowledging that it is difficult to
9 compare across studies, I think with this very
10 stringent criterion, we have some ability also to
11 compare across time, across treatment populations,
12 and treatments, and that will also be lost with new
13 criterion.

14 The problem is where they are
15 communicating to the public. When the hypnotist has
16 80 percent success rate, that is the problem. And
17 we could discuss that, but my time doesn't allow for
18 that. So I am ending up with three conclusions.
19 First, that all of the labeling changes to be made
20 for the interest of public health. There is no
21 valid reason to change, i.e. lower, the criterion
22 for determining abrupt cessation efficacy for those
23 smokers attempting that, but other ways of reaching
24 abstinence should not be discouraged. And third,
25 new tobacco smoking products should at least be as

1 restricted in terms of availability and indications
2 as FDA approved treatments. Thank you.

3 CHAIR STRAIN: Thank you, Dr.
4 Fagerstrom. Are there questions from the committee?
5 Yes, Dr. Simpson?

6 DR. SIMPSON: Can we just have that
7 slide back up again? Do you have like figures for
8 the placebo group for these six studies?

9 DR. FAGERSTROM: I don't have them in my
10 mind and I don't have them in paper either, but I
11 could say that -- you mean -- I have a rough figure
12 that at one year, I think the placebo for the FDA
13 criterion had something like 9 percent.

14 DR. SIMPSON: And what was the
15 abstinence at 6 weeks just roughly? Can you
16 remember?

17 DR. FAGERSTROM: This is for the
18 placebo?

19 DR. SIMPSON: Yes.

20 DR. FAGERSTROM: We have a guess of 20
21 here. I would probably say or a little less.

22 DR. SIMPSON: Okay. Thank you. I just
23 wanted --

24 DR. FAGERSTROM: These could be easily
25 brought to you if you are really interested.

1 DR. SIMPSON: I was just interested in
2 sort of the comparison of the one year to the 6
3 weeks in both groups. That is what I was trying to
4 get from you, and also with the lapses also if you
5 had it -- but if you don't.

6 CHAIR STRAIN: Other questions? If not?
7 Thank you, Dr. Fagerstrom. Next we will be hearing
8 from SmithKline Beecham, Dr. George Quesnells and
9 Dr. Saul Schiffman.

10 MR. QUESNELLS: Good afternoon. My name
11 is George Quesnells. I am not a physician. I am a
12 vice president of medical marketing and sales for
13 SmithKline Beecham Consumer Health Care, the U.S.
14 distributor for Nicorette and NicoDerm CQ patch.

15 I have been personally involved with
16 developing cessation communication to smokers and
17 health care professionals since the first nicotine
18 replacement product, Nicorette, became available by
19 prescription in 1984. I appreciate the opportunity
20 to address the committee on the issues raised in the
21 Agency's letter dated April 21, 1997. I am speaking
22 because many of the questions asked in the letter
23 directly relate to how smoking cessation products
24 are marketed.

25 Please realize that although the

1 questions refer specifically to professional
2 labeling, any changes in professional labeling can
3 make their way into consumer communication,
4 especially in print advertising, where the rules of
5 directed consumer advertising can be satisfied by
6 running the prescribing information for the product.

7 In addition, both current OTC products
8 and Rx products have the same primary indication,
9 smoking cessation. Both OTC and Rx products are
10 promoted and advertised to both health care
11 professionals and consumers. Any changes made to
12 the Rx labeling will have an impact on these OTC
13 products.

14 My remarks will, therefore, apply to
15 both professional and consumer communication.
16 Specifically, the Agency's letter proposed the
17 following questions. How would your presentation of
18 your scientific results and your promotional
19 material have differed had you been able to make
20 more liberal claims in labeling? And secondly, how
21 would reporting your data as point prevalence have
22 modified your labeling claims?

23 I can tell you that SmithKline Beecham
24 would not have promoted our products any
25 differently, even if more liberal claims had been

1 permitted by the Agency. In fact, we believe it
2 would be detrimental to the category, and more
3 importantly to the public health, to allow more
4 lenient standards for approval and promotion of
5 smoking cessation products. Our reasoning is
6 supported by years of marketing research and
7 experience with both medical professionals and
8 consumers.

9 Rather than seeking the most favorable
10 standard, promotion of smoking cessation products
11 must walk a fine line to manage the expectations of
12 the smoker who is attempting to quit. Let me
13 briefly explain what this means. On the one hand,
14 the product has to offer some realistic hope to the
15 smoker or the smoker could become discouraged and
16 not make a quit attempt at all. On the other hand,
17 the product must not over-promise. Over-promising
18 leads the consumer to the impression that a product
19 is a magic bullet and ignores the complex
20 interaction of physical addiction and habituation
21 that makes smoking such a difficult addiction to
22 break. Over-promise leads to a fad phenomenon where
23 sales peak quickly as smokers who are desperate to
24 quit seek what appears to be an easy solution.
25 Sales then fall equally as fast when smokers realize

1 that there is no magic bullet.

2 From the beginning, SmithKline Beecham
3 has worked diligently to walk this line in our
4 promotion and advertising for Nicorette and NicoDerm
5 CQ. We do not promise a fast and easy solution, but
6 we do offer specific help with the complex challenge
7 of quitting smoking. The standard for approval of
8 smoking cessation products -- 28-day continuous
9 abstinence at 6 weeks -- and the labeling that has
10 resulted from this standard allow ample room for
11 companies to market their products in a responsible
12 way.

13 In fact, experience indicates that
14 lowering the standards for approval and/or promotion
15 could actually result in more discouraged smokers
16 and fewer successful quitters. I can cite two
17 examples. The first is from the OTC marketplace.
18 Please recall that the type of advertising that was
19 common for OTC products that were available before
20 1993. These products with active ingredients of
21 either lobeline sulfate or silver acetate were
22 removed from the market in 1993 because the FDA
23 could not find sufficient evidence that they were
24 effective. The advertising for these products made
25 such claims as "once you've tried our program, you

1 will never want to smoke again", and "you are
2 guaranteed to stop smoking without withdrawal and
3 without gaining weight", and the terrifically
4 understated "some people call it a miracle." Such
5 extravagant claims cause the sales of these products
6 to follow a typical fad sales curve. For example,
7 Cigarest, a lobeline sulfate product, was introduced
8 in 1986 with claims such as "just one week and you
9 will be a nonsmoker", and "no weight gain, no
10 withdrawal." Sales more than tripled by 1988 from
11 12 million to 38 million but plunged to under 7
12 million by 1992 as smokers realized that the product
13 could not deliver on its claims. This experience
14 damaged the credibility of the entire smoking
15 cessation product category and quite likely had an
16 impact on many smokers confidence that they could
17 quit successfully.

18 Now, without benefit of an approved new
19 drug application but presumably under the guise of
20 the Dietary Supplement Health Education Act,
21 Cigarest tablets are again being advertised on TV
22 and sold as homeopathic medicine with the same
23 outlandish and unsubstantiated claims. The
24 distributor also plans to introduce a Cigarest anti-
25 smoking gum this summer through the home shopping

1 network. This should be of concern to all involved
2 in the smoking cessation effort.

3 My second example comes from the
4 prescription side. The launch of the Rx patches in
5 1992 was accompanied by an unprecedented level of
6 direct to consumer advertising. This advertising,
7 while not over-promising in terms of effectiveness,
8 did not manage expectations well. The result was a
9 rush of consumers to their physicians. Sales peaked
10 within three months at 1.3 million total
11 prescriptions per month and then fell three months
12 later to 500,000 prescriptions per month, and
13 finally settled at less than 25 percent of this
14 initial surge when the market stabilized. Again,
15 this experience caused smokers and clinicians to
16 lose confidence in themselves and in the products
17 available to help them.

18 In contrast, the current OTC smoking
19 cessation market has remained very stable since its
20 inception last year. We estimate that over 4
21 million people have made a quit attempt using a
22 nicotine patch or Nicorette gum in the 14 months
23 since they were made widely available. We know from
24 our clinical trials that these 4 million people
25 doubled their chance of quitting smoking for good

1 compared to what would have happened if they tried
2 cold turkey. This is good news for them and for the
3 public health.

4 For almost 20 years, the well
5 established standard of 28-day continuous abstinence
6 at 6 weeks has insured that products approved for
7 smoking cessation have passed close scientific
8 scrutiny. As a marketer, I have the range I need
9 within the current labeling to market my products
10 aggressively and yet with an eye toward
11 appropriately managing the expectations of the
12 smoking public. Allowing different end points such
13 as point prevalence will only create a situation
14 where some manufacturing might seek to use whatever
15 cut of the data shows their product in the best
16 light. It is then only a short step to
17 inappropriate comparisons across studies with these
18 differing endpoints resulting in mass confusion for
19 the health care professional and the consumer alike.

20 There are many legitimate comparisons
21 that can be made already. There are form
22 differences, differences in the lengths of therapy,
23 differences in the support programs offered, and in
24 addition, comparisons made on the basis of actual
25 head-to-head studies between two specific brands are

1 also allowed provided the studies are well designed
2 and unbiased. In short, we have what we need.

3 In the last 14 months, a great deal has
4 been accomplished through the careful management of
5 smokers' expectations. The current standards allow
6 ample room for responsible manufacturers to
7 advertise and promote their products. Relaxing the
8 standards for communication with physicians or
9 smokers would severely endanger the usefulness of
10 the previously approved effective products in
11 helping smokers quit. Therefore, I urge you to hold
12 to the current standard. Thank you for your time.

13 CHAIR STRAIN: Will Dr. Schiffman be
14 also speaking then?

15 MR. QUESNELLS: Yes.

16 CHAIR STRAIN: Is that the plan? Okay.
17 Are there any questions for Mr. Quesnells?

18 CHAIR STRAIN: Thank you. I am sorry.
19 For Mr. Quesnells from the committee? Thank you,
20 sir. Dr. Schiffman?

21 DR. SCHIFFMAN: Good afternoon. First
22 let me tell you how grateful I am to not be the one
23 who is keeping you from lunch as was originally
24 scheduled. Of course, now I am keeping you from
25 discussion, but I promise to be relatively brief.

1 I am a professor of psychology at the
2 University of Pittsburgh. I have been doing
3 research on smoking and smoking cessation for 23
4 years, since I started as a babe with Murray Jarvik,
5 who was here this morning. I currently consult for
6 SmithKline Beecham, although like many of the
7 speakers you have heard, I have consulted to just
8 about everybody. SmithKline Beecham asked me today
9 to share with you my views about the appropriate
10 assessment of efficacy and also the appropriate
11 communication of efficacy, and I think that is very
12 important.

13 Let me say briefly, because this is not
14 my major point, that I want to reinforce some of
15 what you heard about keeping a current and very high
16 standard. To put it in technical terms, it seems to
17 me that this ain't broke. It is not clear to me why
18 we would want to make changes when we have an
19 established approach to evaluation and communication
20 of efficacy. I think it is critically important to
21 have a single clear standard labeling, as we heard
22 from DDMAC, as communication, and we need clear
23 communication and not confusion. I will come back
24 to that issue.

25 One of the major points I want to make

1 is that even within a current standard like 28-day
2 abstinence at 6 weeks, there are some potential uses
3 of such data that would be misleading, and I want to
4 take you through some of that. These are data from
5 a meta analysis by Chris Cilangi of almost 50
6 nicotine replacement studies, and he broke the data
7 out according to the intensity of behavioral
8 intervention. Now these are the quit rates for
9 people on the active nicotine replacement that
10 includes both gum and patch. And one would be
11 tempted from these data to assume, if one was doing
12 a quit rate comparison -- you see, our communication
13 has to be clear and focused -- that this set of
14 treatments were more effective than those sets of
15 treatments in terms of nicotine replacement. But as
16 we have already heard, that conclusion would, in
17 fact, be misleading. Because if we look at the
18 placebo groups in those same studies, you can see
19 that under the high intensity, high behavioral
20 intervention that the placebo group is also doing
21 better. So the differences between these two are in
22 fact not attributable to the effect of the
23 medication, but to the adjunctive behavior therapy.
24 In fact, if we then compute an odds ratio, which you
25 have heard so much about this morning, what you can

1 see is that in fact the efficacy specifically of the
2 medication is about the same in both contexts.

3 So it seems critically important not to
4 allow comparisons of absolute quit rates because
5 they are almost always misleading. This is also not
6 just an academic exercise for meta analysts. As you
7 know, we now have a very complex world in which we
8 have both OTC and prescription products available to
9 help smokers. And let me show you next some data on
10 the same product now, NicoDerm patch, from the Rx
11 pivotal trials presented to FDA and from the OTC
12 trials presented to FDA. Again, the point is that
13 there are pretty big differences in the overall quit
14 rates. What you have to remember is that in this
15 study, these were extremely highly selected
16 patients. The trials and the treatments were
17 intensive and run by probably the world's best
18 smoking cessation experts. This was an OTC
19 simulation trial with no support other than what
20 comes in the box, not even with the Committed
21 Quitters Program that is now available in the
22 marketplace. And indeed, again you see the same
23 pattern where if you look at the placebo group, the
24 picture changes quite a bit. And if we go straight
25 to the odds ratios, you will see again that the

1 initial comparison of quit rates was really quite
2 deceptive and misleading in terms of the efficacy of
3 the medication, per se. Again, this is important
4 because we now have a world in which there are both
5 Rx and OTC products, and comparisons are going to be
6 mighty tempting for practitioners, for sales people,
7 and so on.

8 So it is important to remember that quit
9 rates are hugely effected by selection of patients,
10 by provision of other forms of treatment. They do
11 not clearly express pharmacological effects. And I
12 think we need then to go to some sort of
13 comparative. But as you heard this morning, that is
14 not easy. This next slide, I was actually not
15 planning to show, but John Hughes's dilemma
16 explaining odds ratios convinced me into it. This
17 actually shows the relationship between risk ratios
18 or relative risk, what most patients and
19 practitioners think of when they hear a ratio, and
20 odds ratios, which are statistically more
21 manageable. And what you can see is that the
22 relationship between them is not simple, and that in
23 fact it depends on what I call the base percentage.
24 That is, if your placebo group, if you will, have a
25 relatively modest quit rate, then odds ratios and

1 risk ratios will track pretty closely. But as you
2 get to more higher base percentages -- read
3 intensive treatment and prescription pivotals --
4 then there is a huge divergence between odds ratios
5 and risk ratios.

6 So I think even the matter -- if we
7 could agree statistically on what is an appropriate
8 expression of this relationship -- the matter of how
9 we communicate it to smokers and to practitioners is
10 not at all simple.

11 I think it is very important to realize
12 -- I hear us talking about professional
13 communication and communication to consumers as
14 though they were really different beasts. I have to
15 tell you from my experience of doing more dozens of
16 CME talks than I care to remember that the gap isn't
17 as large as we think. I mean we had trouble here
18 this morning -- most practitioners don't understand
19 ratios. They don't understand point prevalence.
20 And I think we have to be very careful to
21 distinguish communication to other experts in
22 smoking cessation and drug abuse treatment from
23 labeling, which is essentially communication to
24 civilians, if you will, whether they be
25 practitioners or smokers.

1 There are, though, areas where I think
2 we might expand communication about the benefits of
3 these medications, and you have heard this from
4 other speakers already. Relief of craving and
5 withdrawal is an important clinical benefit. I
6 agree with what others have said that it is
7 certainly not a perfect predictor of cessation.
8 However, it is beneficial even if it is not a
9 predictor. I mean, the analogy I give to patients
10 sometimes when they are going on medication is, you
11 know, your dentist can pull your tooth and it might
12 be equally successful one way or the other, but most
13 patients prefer novocaine. So even if craving and
14 withdrawal were not predictors of outcome, and again
15 they are, it seems to me that there is a significant
16 clinical benefit to a medication that reduces
17 craving and withdrawal.

18 This becomes important because as we get
19 more diverse medications, medications may well
20 differ on this parameter. We already have different
21 forms and different kinetics for nicotine
22 medications, and we have now compounds other than
23 nicotine that have been approved for smoking
24 cessation. So it is at least plausible that there
25 are going to be differences in symptomatic relief

1 that are independent of differences in cessation.
2 So I think it is appropriate to allow claims or even
3 indications for relief of craving and withdrawal,
4 but I think it is very important that that be done
5 with appropriate evidence. Again, it is very
6 important to have a clear standard and to maintain a
7 level playing field.

8 In summary then, it is very important
9 that we maintain high and consistent standards.
10 This is not a time to be relaxing the standard. I
11 think it is essential that promotion of absolute
12 quit rates be discouraged because of how misleading
13 it can be, both to consumers and to providers, while
14 we may allow claims for relief of craving. I come
15 back, however, to the issue of communication, and I
16 think someone said earlier that the customer -- the
17 presenter for DDMAC pointed out that the customer
18 for labeling is the provider in the Rx world and the
19 customer is the smoker in the OTC world. Neither
20 customer is going to be well served by a confusing
21 communication in which there are multiple standards
22 in which they have to figure out what a 7-day point
23 prevalence is when they just simply want to quit and
24 want to know what works.

25 Similarly, I think that getting into

1 issues of communicating 12-month abstinence rates
2 again creates a huge potential for confusion. I
3 think we also have to reexamine some of our
4 premises, that is, we have medications, as several
5 speakers have pointed out, that are approved at most
6 for use for 12 weeks, but then we want the outcome
7 to be what happens a year later. That is simply
8 unrealistic. Most of the variance after that time
9 is not going to be attributable to the drug. The
10 drug will have established initial abstinence.

11 So we need to keep standards high, to
12 have them based on data, and to be sure that we
13 distinguish the complicated scientific regulatory
14 communication that we engage in from the
15 communication to providers and smokers which needs
16 to be crystal clear. Thank you.

17 CHAIR STRAIN: Thank you, Dr. Schiffman.
18 Questions from the committee? Yes, Dr. Simpson?

19 DR. SIMPSON: Dr. Quesnells -- I am
20 sorry for my pronunciation. He made a comment -- he
21 said that we want the smokers to know that they have
22 doubled their chance at quitting by using. Now, if
23 you look at the labeling for the NicoDerm and the
24 Nicorette, I -- you know, looking at the information
25 there, I just can't see that information there.

1 DR. SCHIFFMAN: Only because it is not
2 there.

3 DR. SIMPSON: And in fact, there is no
4 indication that what he said was true. I mean, if
5 you look at --

6 DR. SCHIFFMAN: On the label, you mean?

7 DR. SIMPSON: On the labeling.

8 DR. SCHIFFMAN: No, that is true.

9 Again, the labeling doesn't reflect that. I think
10 what -- I can't speak for him, but I suspect that
11 what Mr. Quesnells was referring to was that if you
12 look at the literature as a whole, and in fact FDA
13 staff have done a particularly good job of graphing
14 this, that across a variety of studies it looks as
15 though there is a doubling of quit rates. But that
16 is not now currently in the labeling.

17 DR. SIMPSON: In fact, it looks a lot
18 worse than that from the labeling.

19 MR. QUESNELLS: If I could answer that?

20 DR. SCHIFFMAN: Why don't you speak for
21 yourself?

22 MR. QUESNELLS: Yes, okay. The clinical
23 trials do demonstrate basically a doubling of the
24 success rate. Our advertising never talks about
25 that. What consumers -- it is not in our labeling.

1 What consumers want to know is that there is a
2 chance that they can quit and there is something
3 that will help them. But they also know full well
4 that it is their job to quit smoking and what a
5 smoking cessation product does is help them. So
6 that is how we talk to consumers. We don't get into
7 quoting individual quit rates because frankly it
8 confuses consumers and tends to discourage them from
9 making an attempt.

10 CHAIR STRAIN: Dr. de Wit?

11 DR. DE WIT: I have a question about the
12 use of craving in the product information. I notice
13 in a couple of the labeling -- samples of labeling,
14 they have craving listed on a chart or on a graph
15 but they deleted the measure on the Y axis, which to
16 me makes it meaningless. And I wonder if there is
17 any effort in the community to kind of standardize
18 the measure of craving, both in terms of a
19 questionnaire method or in terms of the time period
20 that they are asking the patients over, whether it
21 is right now or over the last day or over the last
22 week. There are so many questions about the use of
23 craving as a measure that we can't really recommend
24 it now as an outcome.

25 DR. SCHIFFMAN: First of all, I am

1 inclined to agree that we need standards if it is to
2 become an indication or an FDA reviewed claim.
3 There has certainly been a lot of literature
4 published on craving, as you know, since then, and
5 so some items tend to be reused. But there is by no
6 means at this point a consensus we could just pick
7 up from the field. In fact, some colleagues and I
8 are writing a paper on the measurement of craving
9 and part of what we are saying is that both on the
10 one hand that we need standards but also that to
11 some extent you need to do the assessment of craving
12 differently depending on the context in which you
13 are studying it. So laboratory studies and field
14 studies, for example, may not lend themselves to the
15 same approach.

16 That doesn't mean, however, that it
17 wouldn't be possible to develop standards that would
18 be common across. I am not sure labeling the axis
19 is the critical thing. I suspect that consumers get
20 the picture with the picture, but I think there does
21 need to be a standard way of assessing it so that
22 products can be compared equitably.

23 DR. DE WIT: I guess I think there are a
24 lot of ways to present the picture, especially that
25 kind of picture with no Y axis to put points on.

1 DR. SCHIFFMAN: Yes.

2 CHAIR STRAIN: Yes, Dr. D'Agostino?

3 DR. D'AGOSTINO: I'd like to just go
4 back a moment to the idea of the 50 percent
5 increase. There is a fair amount of reviewing of
6 the literature that has been done and has appeared
7 before this committee and the nonprescription
8 committee of the clinical trials, and they do come
9 out to that 50 percent when you are doing drug
10 versus placebo. And I think we are talking here
11 about professional labeling. I think that those
12 type of measures personally should be in our
13 consideration. I think the individual rates that
14 now are given introduce an awful lot of variability
15 because they are dealing with individual centers. I
16 don't know what your committee is going to say about
17 it, but they are dealing with individual centers and
18 you don't see the sort of summary number that is
19 really involved in a lot of these clinical trials by
20 looking at those individual rates in the centers. I
21 think it is useful to have that, but I think that
22 some sort of summary numbers in the professional
23 label that is showing that it is 5 percent with
24 placebo and 10 percent with the drug are very useful
25 and maybe a confidence interval around whatever is

1 considered the appropriate measure, be it a
2 difference in percentages or an odds ratio. That is
3 up for discussion. But something that summarizes
4 with some sort of variability I think would be very
5 useful.

6 CHAIR STRAIN: Other questions for Dr.
7 Schiffman or Mr. Quesnells?

8 DR. SCHIFFMAN: Thank you.

9 CHAIR STRAIN: Thank you. I will now
10 give a summary. I am going to review the written
11 responses received by the working group. But before
12 I do that, actually I think it might be useful --
13 and it perhaps ironic that we have reached almost
14 3:00 in the afternoon before we have looked at this.
15 I am going to review the questions, actually, that
16 were sent out and were posted for people to respond
17 to.

18 There were essentially either five or
19 six questions that were sent out, depending upon who
20 was receiving them. The first question -- and this
21 is exactly how they read or virtually exactly. For
22 the indication smoking cessation with the standard
23 of success in clinical trials defined as quit for a
24 month, number 1, what other things do you think
25 should be included in labeling that would be helpful

1 to the practitioner? So a general question. Number
2 2, how would your presentation of your scientific
3 results and promotional material have differed had
4 you been able to make more liberal claims fully
5 supported by your data in labeling? This was a
6 question that was only included in those letters
7 sent out to sponsors. So, for example, a question
8 that went out to NIDA or a letter that went out to
9 NIDA did not include, obviously, this question.
10 Number 3, are there significant secondary outcomes
11 that you would like to see reported such as
12 reduction in tobacco use, quit rates that include
13 subjects who abstained for a month but not weeks 2
14 through 6, et cetera? So this was a more specific
15 question. Number 4, are point prevalence quit rates
16 informative? How would reporting your data as point
17 prevalence have modified your labeling claims?
18 Number 5, would it be useful to present information
19 regarding the fraction of patients who were able to
20 quit at all, even for a day? And number 6, is
21 presentation of long-term data for a short-term
22 treatment useful?

23 I think it is useful to see these
24 questions again in part because the responses --
25 many people responded -- and many as you have heard

1 this morning have responded, but they haven't always
2 responded to the questions directly. Some have to
3 varying degrees.

4 I am going to briefly and rather quickly
5 run through and try to summarize for the committee
6 what I know you have all read and thought about. So
7 just to remind you and reorient you in the materials
8 that you have received. We received materials of
9 various forms from the American Cancer Society, Elan
10 -- is that the correct pronunciation -- Elan
11 Pharmaceutical, Glaxo Wellcome, John Hughes, McNeil,
12 Novartis, NIH, Dr. Thomas Glynn in particular,
13 Pharmacia & Upjohn, SmithKline Beecham, and SRNT.
14 And of course we have also heard from some of these
15 in the open public form today.

16 Let me briefly remind you what they
17 said. The American Cancer Society sent us a letter
18 that included their standards for evaluation of
19 group smoking cessation programs. This is not
20 really pertinent to our discussion. It is an
21 interesting letter. It is a set of standards that
22 they have developed for group smoking cessation
23 programs that cover these five topics. I don't
24 think we are going to really spend much time looking
25 at this although it is useful information and we

1 appreciate their response. And I would be willing
2 to go back to these at any point if anybody wants to
3 flesh them out further.

4 I am going through these alphabetically.
5 NIH through Dr. Thomas Glynn, the Chief of
6 Prevention and Control for the Research Branch sent
7 a letter that I think is very interesting,
8 especially because of the last point, as we will get
9 to in a moment. First he said, quit for one month
10 is too liberal. He recommended quitting for 6
11 months as a standard measure. Secondly, it might be
12 useful to include reduction in tobacco use.
13 Thirdly, he thought information on change status pre
14 and post-use of product would be interesting to know
15 about in the label. Fourth, he thought point
16 prevalence rates were useful but the key is
17 continuous abstinence rates. Fifth, information on
18 patients able to quit even for one day would be
19 useful interestingly. Sixth, more guidance about
20 what is meant by comprehensive behavioral program.
21 And then after all that, he suggested that we make
22 the labels more succinct. I think that is a well-
23 taken point here has we consider adding more to
24 labels that we do need to keep it something that is
25 within reason.

1 SmithKline Beecham -- they have
2 presented here today, so let me just acknowledge
3 that they also sent some very nice materials
4 including a letter making points regarding the
5 complexity of smoking cessation, that we need to
6 consider the target audiences for primary and
7 secondary efficacy information, and regarding
8 scientific standards -- I have quoted them here --
9 the basis for initial approval of smoking cessation
10 must remain the 28-day continuance abstinence
11 measure versus placebo. So they came through quite
12 clearly on that.

13 Next, John Hughes sent us a letter. We
14 heard from Dr. Hughes this morning. He made
15 essentially two points in his letter, that we need a
16 reasoned reconsideration of the scientific validity
17 and critical appropriateness of approval criteria
18 and claims definition, and he again, as we have
19 heard from a couple of different sources,
20 recommended a meeting of some sort -- a work group
21 or a small symposium -- with leading scientific
22 experts that could inform on the scientific validity
23 of various outcome measures and claims definitions.

24 Next I am going to talk about the
25 Society for Research on Nicotine and Tobacco. SRNT

1 sent a letter which I think the committee just
2 received today actually. It is a very nice letter,
3 I think, and I am going to go through it again even
4 despite Dr. Stitzer's presentation, to just talk on
5 a couple of points again from it. They made the
6 points that they again wanted to co-sponsor a
7 meeting on labeling and they responded to four
8 questions. So somehow they didn't get to all of the
9 questions, but the ones that they did, I think they
10 did very nicely.

11 First of all, they asked are point
12 prevalence quit rates informative? They pointed out
13 that this is a somewhat more liberal picture of
14 success. That they probably are not providing new
15 or unique information but would give another
16 perspective to one-month abstinence information. It
17 is a more encouraging outcome picture, which could
18 have a positive impact on motivation to engage in
19 the cessation effort. And they specifically said
20 that they should be used at several time points,
21 such as 1, 3, 6, and 12 months.

22 Should long-term outcomes be reported?
23 They pointed out that this provides a realistic but
24 discouraging perspective. Most products continue to
25 have better success rates versus placebo, even at

1 long-term time points. They pointed out new
2 medications could influence the course of long-term
3 treatment. It can be discouraging and dampen
4 motivation to engage in a cessation effort. And
5 overall, they thought "advantages outweigh the
6 disadvantages." They questioned how should long-
7 term outcome data be presented. And they made the
8 point that there could be a danger of confusing the
9 target audience if too much information is provided
10 here, which again is a good point.

11 The third question, would it be useful
12 to report the fraction of smokers who are able to
13 quit for even a single day? They thought it wasn't.

14 And regarding secondary outcome
15 measures, they wanted to include possibly withdrawal
16 symptoms and smoking reduction should not be
17 included in the label they thought.

18 Finally -- well, no, let's skip that.

19 Elan Pharmaceutical sent us a letter
20 addressing the six questions specifically. They
21 included points that quitting smoking isn't easy.
22 Light smokers find it easier to quit than heavier
23 ones. Some may need more than six weeks with a
24 patch before they quit. They would emphasize point
25 prevalence data if they had been given the

1 opportunity to do so. Regarding secondary outcomes,
2 reduction in number of cigarettes smoked per day
3 would have been included if they had had the chance.
4 And subjects who managed to quit for a month, even
5 if not the week 3 through 6, would have been
6 included.

7 They go into some discussion about the
8 higher percentages for point prevalence quit rates
9 versus the 2 to 6 week definition and reporting such
10 on the label might provide a greater incentive to
11 persevere with the smoking cessation program. And
12 they actually were in favor of including shorter
13 quit rates sort of in a qualified yes if this would
14 serve as an incentive to encourage patients to try
15 again or to try another smoking cessation program.
16 Finally, regarding long-term data, they thought
17 long-term data may help maintain support for someone
18 who has quit.

19 McNeil we have heard from today. They
20 sent a document with a series of recommended label
21 statements. Five are geared towards the consumer
22 and five to the practitioner based upon data from
23 their study 94400 as we have heard about. We have
24 heard about these and I have tried to generalize
25 what those changes were that they recommended. They

1 are in our materials that we have and they
2 essentially emphasize a variety of points regarding
3 early cessation efforts, for example.

4 Glaxo Wellcome, who we have not heard
5 from here today but they sent a letter stating
6 succinctly, "We believe that the 28-day continuous
7 abstinence endpoint is an appropriate and proven
8 endpoint to support approval of a smoking cessation
9 product." And there you have got it.

10 Novartis sent a letter containing the
11 following points. That information about the degree
12 of relief from nicotine withdrawal should be
13 included. They recommended requiring continuous
14 quit rates but could consider continuous rate
15 survival curves rather than summaries in a table.
16 And also could include point prevalence quit rates
17 at key time points. They thought it would be
18 helpful to include guidance on appropriate measures
19 of patient support, use of printed material, and
20 follow-up, and make clinicians aware of relapse
21 prevention and intervention. Those were the two
22 points that they had to make in their letter.

23 We have heard from Pharmacia & Upjohn
24 today. They sent a document containing the
25 following points. Regarding criteria for

1 establishing efficacy, the didn't think the
2 criterion of 4 weeks should be lowered. Regarding
3 broader use of smoking cessation products, they
4 wanted to extend the duration of use. They talked
5 about using them to reduce smoking as an interim
6 stage towards cessation and using products for
7 relief of withdrawal symptoms. In addition, they
8 thought other things to include in the label might
9 be extended duration of use of products, a point
10 they made earlier, and combined use of different
11 products. Repeated quit attempts should be
12 encouraged. Gradual reduction, reduced smoking
13 until smoker is prepared or motivated to make a quit
14 attempt, and relief of withdrawal symptoms.
15 Regarding how this might change promotional material
16 if more liberal claims were allowed, scientific
17 results presented to support different uses of
18 products as noted in the previous responses and
19 continued focus on complete cessation of smoking as
20 the primary goal. They didn't really address in
21 their letter secondary outcomes that they would like
22 to be able to report. Regarding point prevalence,
23 Pharmacia said point prevalence would probably not
24 be of any valuable. And useful to present
25 information regarding the fraction of patients who

1 were able to quit at all -- this may be an advantage
2 to quitting for short times, but it is not clear.
3 And they thought long term outcome is really the
4 definitive outcome from a public health perspective.

5 That is all of the written responses I
6 want to review. Let me try to quickly -- perhaps no
7 quicker than what I have already done, summarize
8 this. I tried to get a sense of with respect to
9 those questions then, where do we stand? And for
10 the first two questions, there is no real easy
11 summary based on these written responses.

12 Starting with the third question, are
13 there significant secondary outcomes that you would
14 like to see reported? Regarding reduction in
15 tobacco use, three supported this -- Elan,
16 NIH/Glynn, the letter from Dr. Glynn, and Pharmacia
17 & Upjohn. SRNT did not support this idea in their
18 response. Regarding quit rates that include
19 subjects who have abstained for a month but not
20 weeks 2 through 6, the only response in writing
21 actually that directly addressed this was Elan, who
22 supported this idea. Regarding the secondary
23 outcome, information on reduction of withdrawal
24 symptoms, three responses directly addressed this --
25 Novartis, Pharmacia & Upjohn, and SRNT -- and all

1 three liked this idea.

2 Regarding point prevalence quit rates
3 being informative, four responded yes -- Elan,
4 Novartis, NIH, and SRNT. One said no, that was
5 Pharmacia & Upjohn.

6 The fifth question, would it be useful
7 to present information regarding the fraction of
8 patients who were able to quit at all, even for a
9 day? This was evenly split. Elan and Glynn thought
10 yes. Pharmacia & Upjohn and SRNT said no.

11 And finally, is presentation of long-
12 term data for short-term treatment useful? Three
13 said yes -- Elan, Pharmacia & Upjohn and SRNT. No
14 one said no. So there you have a quick review of
15 the written materials we have received from other
16 agencies or other sponsors to complement the
17 materials received from academicians that we heard
18 about from Anne Andorn earlier this morning.

19 At this point, I am wondering if perhaps
20 we should take a 10-minute break before we move into
21 a general discussion by the committee. If that is
22 all right, why don't we plan a meeting at 3:15 or
23 3:20 -- 3:20. Thank you.

24 (Whereupon, at 3:06 p.m. off the record
25 until 3:27 p.m.)

1 CHAIR STRAIN: If everybody could take
2 their seats for the committee. It has been
3 suggested that we blink the lights. We are not sure
4 how to blink the lights. So if everybody would just
5 shut their eyes for a moment and then open them.
6 Dr. Wright?

7 DR. WRIGHT: I would like to answer one
8 of the questions that was brought up by one of the
9 speakers.

10 CHAIR STRAIN: Before you start, could I
11 just -- let me apologize that I didn't include
12 McNeil's responses in my summary. I overlooked
13 that. I apologize to McNeil and their team for that
14 oversight. Dr. Wright?

15 DR. WRIGHT: Okay. Possibly as a way to
16 kick off the discussion during this part of the
17 session, I would like to address one of the
18 questions that was brought up by one of the open
19 public speakers who asked what was broke. And I
20 think I can answer a little bit of that.

21 First of all, I am very pleased -- if
22 you live long enough, you see stuff come back again.
23 When we first come up with the they ought to quit
24 for about a month standard, it was hotly disputed by
25 some as arbitrary and capricious and a whimsical

1 standard that the agency had pulled out of somewhere
2 and that it wasn't based on science. Now I find
3 that after approval of their products, companies are
4 now defending this as the tradition of our
5 forefathers, which has taught me a lot about human
6 behavior, and I am very grateful for that.

7 We are having, at the review level, some
8 difficulties, however. The first is that all we are
9 seeing in smoking cessation therapy are single-dose
10 parallel group, 6-week to 3-month nicotine
11 replacement therapy studies with rare exceptions.
12 And the original intention of setting up the
13 standard was not to mandate a duration of treatment
14 and not to suggest that one dose fits all and not to
15 suggest that combination therapy was imprudent or
16 improper, and we need to find a way to allow
17 research that shows how to effectively use these
18 medicines get into labeling or that research won't
19 get done. If you can't put it in your label, there
20 is no earthly reason why a pharmaceutical firm that
21 has their wits about them, and most of them have
22 their wits very much about them, would do that.

23 At the agency level, we need to suppress
24 misleading anecdotal idiosyncratic findings in
25 labeling, but I am uncomfortable that sometimes our

1 establishment of standards acts to actually suppress
2 information that both the practitioner and the
3 public feel very strongly that they have the right
4 to know. And I am very uncomfortable when someone
5 suggests, well should we allow that in the labeling?
6 It doesn't meet our usual standard. I have trouble
7 deciding on what basis we would withhold that
8 information from the public.

9 The issue is one of overt paternalism.
10 There is a question as to how much of this treatment
11 is provided by a truly learned intermediary, a
12 physician acting as a learned intermediary, and how
13 much of it is coming, as people have said, from
14 patients walking into the office and saying I need
15 this drug. Certainly, we are seeing more and more
16 800 numbers and infomercial types of things
17 suggesting a new day is dawning, call 1-800-whatever
18 and ask about something new.

19 I think your responsibility as the
20 committee is to act as an agent for the public. It
21 is clearly improper if the agency asks for
22 information it doesn't need. If we can get good
23 solid predictable questions asked and answered about
24 efficacy, not effectiveness, in 6 weeks, then what
25 justification do we have for asking for 3 months or

1 6 months or a year's worth of studies. On the other
2 hand, if there are questions that physicians need
3 answered, as reflected in the survey that the
4 subcommittee did and which is very interesting and
5 for which we are very grateful, then we should ask
6 more in those areas. You may not be able to answer
7 those questions today, but you do need to wrestle
8 with the question of are we unduly restricting the
9 information that is available to the practitioner
10 and to the patient, and I would focus in that
11 direction, not what is essentially a stalking horse
12 of are we going to liberalize the approval criteria,
13 because I assure you we are not.

14 So the question is information
15 transmittal. Are there things that are not in there
16 that we should get to the practitioner and the
17 patient?

18 CHAIR STRAIN: Thank you, Dr. Wright.

19 DR. YOUNG: Dr. Strain, may I ask Dr.
20 Wright a question? Curtis, I need another
21 definition. Can you distinguish for me the
22 difference between effectiveness and efficacy?

23 DR. WRIGHT: Sure. It is -- but it is a
24 long answer. I will try to make it as brief as
25 possible. There are two questions that you can ask.

1 One is can you show that this treatment works better
2 than a comparator in patients in a clinical trials
3 setting. That is efficacy. You are using outcome
4 measures that are generally recognized as being able
5 to tell the difference between an effective and an
6 ineffective medication. An example of that that is
7 easy to comprehend is you give this drug and it
8 lowers blood pressure in these patients by this
9 much. The placebo didn't.

10 Effectiveness is a much broader concept
11 that has to do with the actual utility of the drug
12 in clinical practice or in settings that are so
13 close as to be indistinguishable from clinical
14 practice. Therefore, a trial that studied
15 volunteers who were in their mid-40's who were of
16 relatively high SES, who were highly motivated to
17 quit in a good behavioral program who got NRT would
18 give you a quit rate and a placebo quit rate and
19 some kind of odds ratio or likelihood of success.
20 Whereas, a study done in K-Mart looking at people
21 who got Nicorette prescriptions might give you a
22 very different kind of answer. One is an efficacy
23 study and the other is an effectiveness study.
24 Effectiveness studies always include analyses of the
25 context, the patient population, the prognosis, and

1 incorporate some information about the health care
2 delivery system as well. For a better discussion of
3 that, I would direct you to Dr. Lin Cheng's very
4 articulate discussion of this in the last few
5 approval packages for OTC switches.

6 So efficacy is can you make it work in a
7 model system that we accept as relevant and
8 sensitive. Effectiveness is what is the actual
9 impact in terms of health outcome for the
10 population.

11 DR. ANDORN: If I could make a comment,
12 I think that is the issue facing us with this
13 question about the label. It is very clear to
14 everybody who has sat on any of the committees in
15 looking at the sponsor data that these are
16 efficacious drugs. But as Dr. Sachs said, both
17 patients and clinicians perceive them as ineffective
18 when prescribed the way that they think they
19 understand the label to read they should do.

20 CHAIR STRAIN: Dr. de Wit?

21 DR. DE WIT: I am a little bit confused
22 about how much flexibility the sponsors have in the
23 treatment program. Curtis, you suggested that there
24 hasn't been very much creativity in the design of
25 the treatment programs. That everybody is stuck

1 with this kind of set -- is it 2 weeks of treatment
2 essentially, short-term treatment -- and that there
3 is a need for more creative treatment methodologies.
4 And I am not clear how much that is set by FDA rules
5 or to what extent the industry or the sponsors could
6 be more flexible in their designs and then make
7 claims based on those. Is there anything you can
8 say to that, Dr. Wright?

9 DR. WRIGHT: There is a bit of a self-
10 fulfilling prophecy. If we make a standard that
11 says success is continuous abstinence for a month
12 and then we say, but you can have a week or maybe
13 two weeks at the front end as a run-in. Then you've
14 got a 6-week study, and that tends -- and financial
15 pressures and the pressures of getting the studies
16 actually done and analyzed and reported -- tends to
17 push toward relatively short-term treatment
18 durations, although that has varied a little bit.
19 But we have not seen many trials, if any, where the
20 relapsers have been reintervened.

21 DR. DE WIT: And it would be okay for
22 the initial treatment to be extended to a 4-week
23 period? The protocol would still be acceptable to
24 FDA?

25 DR. WRIGHT: The initial treatments are

1 usually always 4 to 6 weeks at least.

2 DR. DE WIT: Well, I meant -- it is
3 usually two weeks with a drug and then four weeks --

4 DR. WRIGHT: Celia, you take it.

5 DR. WINCHELL: I think the shortest on
6 the high dose has been 4 weeks. The longest has
7 been 12 weeks. And then the tapering periods range
8 from 4 weeks to 12 weeks. So we have had studies
9 where the treatment and taper phases were as short
10 as 8 weeks or as long as 24 weeks. And all of them
11 make a determination of efficacy at a month.

12 DR. DE WIT: I see. Okay. So we
13 haven't really heard in today's presentations
14 distinctions between the durations of the drug
15 treatments and we don't know whether that is an
16 important factor?

17 CHAIR STRAIN: Dr. Meyer?

18 DR. MEYER: I think this is --
19 unfortunately, I didn't hear the first part of what
20 Curtis was saying, but we category briefly outside
21 because it is basically an efficacy versus an
22 effectiveness issue. And in that regard, it is not
23 unlike what you face in other areas of
24 pharmacotherapy including for example antidepressant
25 treatment and the issue of long-term, for how long,

1 et cetera. The trials run for 12 weeks, but in
2 practice the treatment can run considerably longer.

3 Drug companies are investing in post-
4 marketing studies to clarify some of these issues,
5 and that doesn't change the labeling, but it can in
6 fact change the way clinicians practice. And I
7 think that is one piece of information that is
8 gathered in the context of effectiveness. One thing
9 I heard today that I think would amplify on the
10 efficacy issue is the issue of withdrawal symptoms,
11 and one would expect that withdrawal symptoms should
12 get better with nicotine replacement. It is not
13 clear whether that data was collected, and that
14 would seem to be pharmacologically an effective
15 measure.

16 But beyond that, I think there are
17 really three points that I think are intriguing in
18 the context of the clinical environment. One is the
19 issue of post-marketing studies. The second is the
20 issue of what managed care will pay for, and I
21 thought Dr. Sachs' presentation was interesting at
22 the outset. In the context of your patient, managed
23 care wouldn't have paid for you to see him once a
24 month, and yet once a month was critical and in fact
25 the relative frequency in fact was very important in

1 retaining him in treatment. And they probably
2 wouldn't have supported his continuing on nicotine
3 replacement at this juncture, even though it was
4 keeping him smoke-free. I think that is a terribly
5 important issue and it falls between the cracks. No
6 one, in fact, can force this issue.

7 It raises an interesting point in terms
8 of over-the-counter. Because over-the-counter gets
9 managed care off the hook. Over-the-counter means
10 you go into the drug store and it is your business
11 whether you buy it or not. I think that is a
12 particularly interesting issue that the relative
13 gradient against this treatment being covered under
14 managed care now is much greater because it is
15 available in various forms over-the-counter. They
16 are not going to pay for the kinds of additional
17 intervention that are essential for long-term
18 effectiveness. I think it is an interesting series
19 of dilemmas that we have. And it is not clear to me
20 that a drug company would want to do the post-
21 marketing studies in this area since essentially,
22 particularly in the nicotine replacement, there are
23 enough products out there that are in fact going to
24 be simply handled over-the-counter.

25 DR. ANDORN: I think one of the points

1 of changing the label, and particularly as Curtis
2 said, if the label says a statement that here is the
3 point prevalence data for six months and the
4 literature supports you need to treat for at least
5 six months, then the post-marketing studies will
6 become pre-marketing studies and it will change the
7 way a sponsor approaches new products and
8 essentially will have to change the existing post-
9 marketing studies being done now. There is that
10 positive aspect of changing the label.

11 DR. MEYER: I think the cat is out of
12 the bag now. It is hard to put it back in.

13 CHAIR STRAIN: I would like to bring up
14 something that John Hughes mentioned earlier, which
15 I have been struggling with over the course of this
16 time. And that is that I think we have -- I have
17 tried to think of an analogy. We have a situation
18 right now with this question -- with this dilemma
19 that we are grappling with where we are not dealing
20 with an isolated system where any change
21 contemplated has repercussions in other systems.
22 And it seems to me that there are three systems that
23 we have to consider or three communities. There is
24 the scientific community, there is the practitioner
25 community, and there is the patient community. And

1 we are tending to probably focus on the practitioner
2 community because the label is generally addressed
3 to the practitioner community, but any change made
4 has repercussions in those other communities.
5 Obviously in the patient community through the
6 practice and also in the patient community through
7 the probability that the changes will trickle over
8 to the OTC usage and then also trickles over to the
9 scientific community because what we do impacts upon
10 what people like John Hughes plan to do in terms of
11 how they design their studies. If we decide that
12 looking at rates of changing your hair color while
13 you are on these products are important, then they
14 will do studies that include that as an outcome
15 measure.

16 So it seems to me that while we want to
17 focus in and hone in on just one thing, it is very
18 difficult to do that. I know, Celia, when we have
19 had discussions about this as a work group, we have
20 wanted to keep it very loculated and simple, but I
21 don't think it can be and that is a dilemma.

22 It seems to me that the answer to the
23 question is quite clear that as an advisory
24 committee, I think we do want to consider including
25 other secondary outcome measures such as withdrawal,

1 as Dr. Meyer mentioned. That seems entirely
2 reasonable and good and probable, and that other
3 possibilities certainly could exist. The direction
4 to go with those other possibilities I think perhaps
5 goes back to the idea of looking at data more
6 systemically and making a determination of that.
7 Yes, Dr. Simpson? Hopefully, that will get some
8 discussion going. Dr. Simpson?

9 DR. SIMPSON: Actually, I was going to
10 follow up on something that Dr. Meyer said.

11 CHAIR STRAIN: Okay. Please do.

12 DR. SIMPSON: I am sorry. One of the
13 points that Dr. Meyer made was that in a lot of
14 other pharmacologic drugs, the study design is such
15 that the patients may be studied for four weeks, but
16 it is well known that a lot of these treatments are
17 long-term treatments. This is, I guess, where the
18 analogy gets a little hazy because as far as I
19 understand it, these -- for example, like a patch,
20 they are given the patch for four weeks or up to 12
21 weeks, and then it is stopped. And then the long-
22 term follow-up that is reported is on the people
23 without the patch. They are no longer having a
24 treatment. So that is where the analogy to other
25 studies or other psychopharm drugs gets a bit weak.

1 And it also then becomes a bit difficult
2 to even justify giving any long-term results if, in
3 fact, you are looking at them using the patch long-
4 term. Because if the study is only done for four
5 weeks, that doesn't bear any resemblance to what you
6 are looking for in a long-term result. Is that
7 right?

8 CHAIR STRAIN: It is partly right. And
9 this -- again, Celia, you may want to pitch in here.
10 I think part of the dilemma has been that different
11 studies have done different things. So that you are
12 looking -- you have to look at what particular study
13 -- how long the active pharmacologic treatment
14 intervention has occurred and then what your follow-
15 up period is after that. But I would agree that
16 making analogies to things like antidepressant
17 treatment can be problematic at times. Yes, Dr.
18 D'Agostino?

19 DR. D'AGOSTINO: I think the notion of
20 the long-term follow-up and the relapse is actually
21 quite important. I realize it is no longer the drug
22 effect. I think from the public health point of
23 view, and I think it is appropriate in the
24 professional labeling, to have a sense of how many
25 of these individuals are going to go back to smoking

1 with weight reduction and so forth. I think that is
2 useful information. So it is a question of what the
3 drug is doing and it is also a question of what are
4 the expectations and the realities of people who
5 took the drug. It is not like -- I don't think the
6 analogy that you are making that it is a steady drug
7 therapy really probably is appropriate here. We
8 know the drug stops, but they can take it again.
9 But they may or may not take it. The point is that
10 they have stopped. There have been successes in
11 this 4-week period or the 6-week period. What can
12 we anticipate 6 months down the road or 12 months
13 down the road? I think that is very important
14 information and I think the companies should be
15 asked to look at that information.

16 CHAIR STRAIN: Dr. Simpson?

17 DR. SIMPSON: You know, I agree with you
18 that the information could be useful, but I guess
19 this is where I am not quite clear. If the
20 clinicians are tending not to restrict the patients
21 to four weeks, but the information that they studies
22 give are where the treatment is restricted for four
23 weeks, then how useful is it? Because if, for
24 example, they are allowed to use the patch or
25 whatever they are using for the full year, then

1 maybe they won't relapse at all.

2 DR. D'AGOSTINO: They can do post -- I
3 mean, in addition you can do post-marketing studies.
4 I mean, that is back to this efficacy. That doesn't
5 say you should exclude the follow-up in the clinical
6 trial, but you can switch also to where you can
7 additionally get epi studies or post-marketing
8 studies to get at that information.

9 CHAIR STRAIN: Dr. Falkowski?

10 DR. FALKOWSKI: When we look at outcomes
11 from other treatments of other addictive disorders
12 like chronic alcoholism or drug abuse, we typically
13 do look at 6-month outcomes and we look at one year
14 outcomes in spite of the limitations of looking at
15 that. In spite of the fact that some clients come
16 in who have all these things going for them, who
17 because of these other things they have going in
18 their lives are going to have a better prognosis
19 than clients who are more impaired on multiple
20 levels. So I think there is a danger in our
21 discussion here of thinking that we are going to
22 create a special case for nicotine addiction in the
23 sense that aren't we also going to hold this as our
24 new addictive disorder of the decade here to the
25 same sort of standards and criteria of evaluation

1 that we do other addictive disorders? And that does
2 mean that even if the treatment period is only 2
3 weeks or 6 weeks or 8 weeks, that still there is
4 inherent value in knowing what the outcome is 6
5 months down the road and a year down the road.

6 I would also like to throw out for our
7 consideration that especially in the treatment of
8 very late stage chronic alcoholics, there is a
9 movement in the field now to look at well maybe if
10 this person has reduced his use that that is some
11 sort of success. That that is not a treatment
12 failure simply because this person is not abstinent.
13 And in that sense, if these products help reduce
14 smoking, isn't there merit in including that
15 information as well? I don't understand the
16 vehemence with which people are opposed to putting
17 that on the label or the harm that would come from
18 including that information on the label to
19 physicians as well.

20 CHAIR STRAIN: Dr. Meyer?

21 DR. MEYER: One of the problems with
22 drug addiction is that it is held to standards that
23 are untenable with other chronic illnesses. I just
24 recently reviewed the NIAAA project match study,
25 which actually had a very good set of treatment

1 outcomes for three different treatments, but the
2 bizarre thing to me was that they were looking at
3 39-month outcome comparing one treatment of 8 visits
4 with another treatment of 8 visits with a treatment
5 of 4 visits. And they were trying to look at a
6 treatment match 39 months later, which is sort of --
7 it makes the man looking under the lamp post for the
8 keys that he lost up the block look very logical,
9 because it doesn't make sense.

10 I think the issue is really outside of
11 the FDA's territory. I think this is -- it is a
12 real world issue. I think the American Heart
13 Association, the American Cancer Society, and the
14 American Lung Association have really a
15 responsibility to define the clinical realities of
16 smoking cessation. I think it is important for the
17 scientific community or the research community to
18 begin to think about the nicotine substitution in
19 different ways. If it is a method on analogy, then
20 look at it and study it as a method on analogy
21 rather than simple as -- I mean, the prospects and
22 the limitation of short-term substitution seem to be
23 reasonably well known. It is not a bad outcome, but
24 it certainly isn't enough to deal with the public
25 health consequences. And the public health

1 consequences are of such significance that you want
2 to essentially produce smoking cessation. It
3 doesn't seem to me that that is the way that they
4 have gone about this in the context of these very
5 short-term trials. They have established efficacy,
6 but in terms of long-term effectiveness, there
7 really is a need to develop models that will be more
8 effective for more people.

9 There are treatment guidelines that
10 actually John Hughes helped to prepare for the
11 American Psychiatric Association under nicotine
12 dependence. It has been a while since I read them
13 and I can't recall whether he deals with examples
14 like David Sachs's case where he was quite
15 comfortable going back and forth with repeated
16 episodes of substitution. I just think we know
17 enough about the long-term issues related to short-
18 term treatments that we really need to look at the
19 real world clinical significance. Again, I don't
20 think it is an FDA issue. This is not a licensable
21 drug like methadone in terms of the fact that you
22 want to have FDA control it. But I do think there
23 is a lot more information that could be gathered
24 around real world treatment and the advocacy by
25 these organizations is going to be critical if

1 managed care is going to pay for it.

2 DR. ANDORN: There is one other point I
3 would like to make about managed care. Where I
4 live, managed care did not pay for the patch anyway
5 prior to OTC and doesn't pay for the interventive
6 treatments. But I do think that the concept that
7 what the FDA does does influence public health and
8 not just in the States but worldwide, and maybe the
9 label of these products is a way to do that by
10 including the longer term treatments and by
11 requesting longer term treatment and then it kind of
12 elevates it to the level of chronic illness and will
13 help the managed care partners look at it a bit
14 differently, and maybe we need to use the label for
15 that purpose too.

16 CHAIR STRAIN: Dr. Young?

17 DR. YOUNG: That is similar to the point
18 I was going to make. Because I think one issue in
19 talking about outcome is talking about looking at
20 longer term outcomes of the current short-term
21 treatment. But then as I was listening to the
22 speakers talk about evidence that extended use of
23 the product or periodic reintroduction of the
24 product might be the more productive way to use the
25 product, I went back and quickly started reading the

1 labeling stuff we have in the book about how long
2 you were recommending to use the product. And some
3 of the things that I found quickly said essentially
4 something akin to the product hasn't been used for
5 longer than 3 months. I don't remember if the word
6 recommended was there. But it seems to me that
7 especially using the useful analogy of substance
8 abuse disorders as being chronic relapsing disorders
9 is a primary characteristic. We ought to think
10 about whether or not the labeling discussion should
11 open the possibility of adding descriptions of
12 extended treatment -- the outcomes of extended
13 treatment periods to the labeling if such
14 information is available in the clinical assessment
15 of the product. And also opening the possibility of
16 descriptions of the effects of reintroducing the
17 nicotine replacement therapies in various ways after
18 the initial treatment episode and then what is the
19 outcome of that type of reintroduction. So it seems
20 to me that it is not only outcome -- longer term
21 outcome of the current short-term treatment, but
22 should there be some way in which labeling could
23 reflect the fact that this is a product that the
24 patient may need to stay on for a longer period of
25 time or may need to be reintroduced to in a variety

1 of ways. And I would also, as someone who does not
2 do clinical work, comment that one of the issues for
3 OTC I think that came up in some of those
4 discussions was the fact that once you move a
5 product out of the prescription arena, then you get
6 into an issue that patients can't pay for it.

7 CHAIR STRAIN: Dr. Wright?

8 DR. WRIGHT: I need to get the committee
9 to say some things again clearly so I can hear them.
10 It has only been relatively recently that we have
11 achieved unanimity in this committee that tobacco
12 addiction is a real clinical entity. That it is not
13 a behavior. It is not something that people are
14 doing because they have nothing else to do with
15 their hands. It is a nicotine addiction. We are
16 close to getting agreement that this is a life-
17 threatening illness. That this is every bit as
18 serious for those who have it as AIDS or cancer.
19 And I am hearing you say today that the model of
20 intervention/cure that has been abandoned for other
21 areas of addiction medicine should be abandoned here
22 as well.

23 DR. MEYER: Unfortunately, it hasn't
24 been abandoned in other areas of addiction medicine
25 and should be.

1 DR. WRIGHT: That the notion that
2 somehow we are going to put somebody through a
3 program or pay for a counseling session or treat
4 them once and they are going to walk out and they
5 are never going to have that problem again is naive
6 and is not supported by the clinical realities and
7 that it is an improper approach to this kind of
8 disease. That people relapse. Relapse is expected.
9 It is a part of the illness and it is as silly to
10 say that a smoker is going to walk out and smoke no
11 more as it is to say that a diabetic is going to go
12 out of the hospital, get treated once, and never
13 need medical care again. There are, in fact, adult
14 onset diabetics who have very smooth clinical
15 courses after a brief intervention, but they are
16 rare unfortunately. So I just need to be reassured
17 by the committee that you view this as a chronic,
18 relapsing, life-threatening illness that requires in
19 most cases or certainly many cases long-term medical
20 management.

21 CHAIR STRAIN: Is there anyone on the
22 committee who would want to take issue with that?
23 It has our stamp of approval.

24 DR. KHURI: And we so move.

25 CHAIR STRAIN: We so -- yes. And we

1 will move it again and again and again. Dr. Khuri?

2 DR. KHURI: Dr. Wright has more
3 eloquently than I made one of my principle points.
4 We have come a long way baby since our days in
5 medical school when we were taught that alcoholism
6 was weak moral character and opiate addiction was
7 criminal behavior and that was it. Certainly, if we
8 evaluated -- I hate to use the methadone analogy too
9 much, because it is an imperfect analogy. But if we
10 evaluated the efficaceousness of methadone at 3, 6,
11 or 9 months, we wouldn't have methadone maintenance
12 probably. But at the same time, we have a dilemma
13 here, I think. We are told to be succinct. At the
14 same time, we want to emphasize, as Dr. Wright also
15 said, information transmittal -- and to the
16 consumer. I feel rather strongly about that. I
17 object to having one set of directions for the
18 physician and one for the consumer. We are way
19 beyond that and we would be laughing stocks with
20 PDR's piled up at Barnes & Noble -- the business of
21 overdose. We have come away, I hope, from fear
22 tactics. We need to transmit true information. And
23 yet at the same time, we have this whole opposing
24 force. I appreciated your remarks of managed care
25 and access to care and nobody going to doctors

1 anyway to get their advice and people making their
2 decisions in the pharmacy reading the labels or
3 looking at the ads in whatever magazine -- Glamour
4 or whatever. It is important that we get the right
5 information out there and be honest about this
6 disease. At least the ads for Revia are very
7 different from the ads for Trexam. The same thing -
8 - now Trexam. But Revia is, as you know, one step
9 at a time diminish your drinking days, as you
10 pointed out. And I think that all of our
11 information should underline the chronic relapsing
12 nature of this disease and the fact that you don't
13 give up at 4 weeks or 6 or 8 or 10. And the
14 information that we do impart should be designed to
15 moralize the patient, not defeat them. I have a lot
16 of relatives who have said, oh, those smoking
17 cessation things don't work when I sort of timidly
18 suggest they try them. And these are supposedly
19 well-informed people. But we need to counter that
20 image in all of our information and in our labeling,
21 getting back to what we are supposed to be talking
22 about labeling.

23 CHAIR STRAIN: Dr. Lloyd?

24 DR. LLOYD: I am taken by the direction
25 that we need to be more succinct and more concise

1 and I would like to share an anecdotal, non-
2 scientific observation. And I would like to preface
3 that by excluding the practitioners in the room.
4 This comes from my experience as a pharmaceutical
5 sales representative, and almost without exception
6 the practitioners, when they were offered a package
7 insert or suggested that the full disclosure was in
8 the package insert, the response that I got as a
9 drug representative was, I don't have time for those
10 things. They are too busy. There is just too much
11 in there and too much I don't really care about. So
12 just summarize it for me and tell me what I need to
13 know. So maybe we are on the wrong track here and
14 have been for some time because my observations go
15 back 20 years. Maybe it is time to consider a
16 different direction completely and totally.

17 CHAIR STRAIN: Dr. Khuri?

18 DR. KHURI: I think, again, the ogre
19 Medussa of managed care raises its head. If the
20 physicians didn't have time before, they certainly
21 have less time now. And I think the consumers, very
22 often, are those who are more receptive and want to
23 know what their doctor gave them, if indeed the
24 doctor did give it or recommend it. They say
25 mentioning it is terribly important even. Not

1 necessarily joining a group or formal relapse
2 prevention effort. I think that it is very
3 important to have it out there available for the
4 interested consumer, and I think increasingly the
5 consumer has more time and is more interested than
6 the physician.

7 CHAIR STRAIN: Dr. Simpson?

8 DR. SIMPSON: I was -- I am afraid I am
9 going to -- I would just like to address a few
10 things that I saw in the labeling that I found
11 difficult. I have sort of harped on it a bit
12 before. I did find the way that the rates after 6
13 weeks or whatever the period -- the fact that it was
14 given in ranges was perhaps confusing. It didn't
15 clarify what, in fact -- it didn't even clarify why
16 the particular treatment was superior to the placebo
17 in some cases.

18 I hate graphs without axis. You know, I
19 would fail a student who gave me a graph without an
20 axis marked as to what it is. I think that the
21 argument that different people use different
22 instruments is a poor argument because even if they
23 use different instruments -- and I mean, people do
24 in studies. They use different depression scales
25 and they use different things, but then they say

1 which depression scale they are using and then they
2 mark the scale on the axis. So I would say let's go
3 back to marking our axis in the labeling.

4 And I would say especially if we are
5 going to put some more secondary measures like
6 withdrawal and so on, because I am sure there are
7 several instruments out there for withdrawal also.
8 So I think that those two things -- that is my
9 feeling. I am looking at it very simplistically,
10 and those aren't making it more succinct perhaps.

11 DR. DE WIT: I have just a very small
12 thing to add to that and that is that the use of
13 standardized questionnaires would make everyone's
14 life very much easier and the data much more
15 interpretable. So if the community can agree on
16 standardized tests of whatever a craving or a
17 dependence or withdrawal symptomatology, it would
18 make this job much easier.

19 CHAIR STRAIN: Dr. Andorn?

20 DR. ANDORN: Going back one step to how
21 long and lugubrious the label is, I am sure nobody
22 wants us to attempt to rewrite any statutes or
23 manuals here. I think we are stuck with a good
24 portion of that label. But perhaps to go back to
25 our colleague who suggested a discussion section be

1 added to labels where the bottom line is reiterated
2 and then some discussion of salient features based
3 on the evidence that is given above, and then at
4 least if the clinician has time, they can read the
5 whole label. If not, maybe they can just skip to
6 the bottom line and we will have them learning from
7 the label rather than the detail man or woman, who
8 most often is not unfortunately a Pharm.D.

9 CHAIR STRAIN: Dr. Winchell?

10 DR. WINCHELL: I appreciated Dr.
11 Simpson's comments because of the things I have been
12 hearing today, there is a lot of ideas but some that
13 actually relate to the labels as they are now. I
14 heard some of the sponsors expressing some concern
15 that we would change things for future products and
16 maybe give a competitive edge to products yet to
17 come. But actually, I was thinking more about what
18 we could do with existing data and how we could
19 improve the labels that are already out there by
20 presenting the data that exists for these products
21 in perhaps a different way. So I heard some
22 specific things that I would just like people, if
23 they have something particular to say about them, to
24 comment on. One was the question of quit rate. Is
25 the range for quit rates the range for placebo and

1 range for treatment across centers? Those
2 comparisons, are those good? Should we think about
3 keeping those or replacing them with something else?
4 If we replace them, should it be a particular number
5 for the study for each treatment group or perhaps a
6 range of ratios across centers? Would they be
7 qualified by confidence intervals or by standard
8 deviations? What seems good? I don't expect
9 anybody to have a complete answer off the top of
10 their head, but maybe they could give me some
11 initial impressions of what they have thought of
12 today.

13 So that first question, how we present
14 the efficacy or the quit rates, I would like to hear
15 discussed. And then the second was presentation of
16 non-continuous abstinence, which is the best way I
17 can express this concept of how many people are
18 abstinent at various points in the study. Some
19 sponsors have this data already that can be
20 presented as these one-week quit rates, but some may
21 also have data where they could say, for example, at
22 six months how many people have quit for a month.
23 Is that of interest? Is a rolling 4-week quit rate
24 of interest? A rolling one-week quit rate or no
25 presentation of non-continuous abstinence? For the

1 reason that if we have a variety of abstinence rates
2 in a label all next to each other, one sponsor could
3 choose to promote one and another sponsor choose to
4 promote another and thereby create a great deal of
5 confusion. So those were my particular points that
6 I would like to hear discussed.

7 CHAIR STRAIN: Dr. Meyer?

8 DR. MEYER: Dr. Winchell, I think that
9 falls back into the trap of what the 6-week trial
10 predicts 6 months down the road. I think there are
11 real advantages to having the four weeks of
12 continuous abstinence because that has become a
13 standard. The issue is what additional will help to
14 inform the label. I was not convinced, in fact I am
15 less convinced now about the point prevalence issue,
16 because I really think the bottom line comes down to
17 the problem of recidivism, both during that 4-week
18 period and after. What can be done to increase the
19 ability to keep people in smoking cessation.

20 I don't know how you get data on what
21 Dr. Sachs was doing and whether this kind of thing
22 is in fact more normative than we think or than the
23 companies even know. But I think it is terribly
24 important that you find out data on experience,
25 dosage, safety, and efficacy for essentially non-

1 labeled use of this compound, which is going on now.
2 This patient of his had been on it for several years
3 -- mostly on and not off. I think that was a very
4 instructive kind of presentation. I don't know how
5 you get that information, but I think it would be
6 helpful to FDA and to the companies, and in fact
7 reassuring to the public to get information on the
8 long-term safety and dosage questions. Because it
9 is not there and it is obviously being used. So I
10 would be more interested in getting that kind of
11 information than in coming up with other ways of
12 defining abstinence after a 6-week trial long-term
13 abstinence. I don't think that is as relevant.

14 CHAIR STRAIN: Dr. Falkowski?

15 DR. FALKOWSKI: So what you are really
16 suggesting is in a sense to have some labeling that
17 helps physicians figure out how am I going to use
18 this with people like his case study clearly
19 illustrated, which hit on a lot of the points that
20 Dr. Wright was talking about in terms of the
21 chronicity and the relapse. And I think that case
22 this morning was more typical than atypical of
23 people who are trying to quit smoking.

24 DR. MEYER: And that raises a lot of
25 safety questions which we have but we don't have any

1 answers to.

2 DR. FALKOWSKI: Right. And in that
3 case, it also raises for labeling sort of uncharted
4 ground of using it as a mechanism to educate
5 physicians on how to treat -- you know what I mean?
6 I am not sure that is the place to do it.

7 DR. MEYER: I agree with you.

8 CHAIR STRAIN: Dr. Wright?

9 DR. WRIGHT: I'm going to buck the trend
10 a little bit. I realize that there has been sort of
11 a dumbing down phenomenon on the American physician
12 saying that of course they are too -- by tacitly
13 saying, of course they are too busy to read the
14 package insert. These things are every bit as
15 dangerous as a handgun. These things are every bit
16 as dangerous as a circular saw or a chain saw or an
17 automobile, and I think the committee should have
18 the expectation that if you are going to prescribe a
19 drug, you ought to have at least read the package
20 insert. And that accepting as a giveaway that
21 physicians can't understand the normal language of
22 science and can't wrap their head around such
23 concepts as they are twice as likely to succeed as
24 on placebo, I think is giving away an awful lot that
25 we shouldn't give away.

1 Lord knows, we can improve the quality
2 and clarity of the package inserts and there are a
3 number of places within the agency at very high
4 levels that are working very hard on trying to make
5 those things more penetrable. I have been
6 impressed, by and large, with the responses of the
7 companies to try to present their detailing material
8 in ways that are highly effective, and we have had
9 some notable successes in recent years within the
10 division.

11 There is one question I would like to
12 ask and that is, Ms. Yaroma, what is -- from a
13 consumer perspective, what are the people -- what is
14 the public going to think of what we put in this
15 labeling? What should we put there?

16 MS. YAROMA: Well, you know, people have
17 a lot of questions. People don't like to have
18 withdrawal symptoms. You know, they want to know
19 how to relieve their withdrawal. Is it safe to keep
20 buying these products for a year? I mean, if you
21 are not successful for a month, is it safe to buy
22 the higher dose for two months? We need to know. I
23 mean, everybody wants to know all that. How to
24 prevent relapse -- some help. Give us an 800
25 number. They have a lot of money. Drug companies

1 have a lot of money. They could put an 800 number
2 out for somebody that -- just like a 12-step program
3 works. You want to pick up a cigarette -- call an
4 800 number and get some kind of help.

5 DR. FALKOWSKI: I guess I just wanted to
6 get back to responding to what Dr. Wright had eluded
7 to and I didn't want my remarks to imply that
8 doctors and physicians can't read tables. I guess
9 more what I was getting at is for years we have had
10 physicians who say, oh, you ought to quit smoking.
11 But now we are expecting them, as the tide is really
12 turning about cigarettes in his country, to become
13 more actively involved. And I think there is a big
14 learning curve that we are all expecting them to hop
15 upon and labeling is part of that, but it is not the
16 core of it.

17 CHAIR STRAIN: I am wondering if we are
18 honing in and giving you, the FDA, specific
19 directions here and fulfilling our mission for today
20 or whether we need to look at some specific
21 questions before our time runs out for what we
22 allotted today. Are we getting near a product in
23 your minds as to what you were looking for? Have we
24 been ambiguous on some of these things?

25 I have a series of points that I have

1 drawn from this -- I am not sure if the committee
2 has necessarily -- and I would be willing to go
3 through -- let me try going through those. For the
4 record, Dr. Wright gestured yes to that
5 enthusiastically, since he was not recorded.

6 First, I think that it would be good to
7 allow secondary outcome measures to be included in
8 labels. But let me stop and just make that a
9 statement. Secondly, I think that there is a desire
10 to encourage research by sponsors and the research
11 community on a number of topics, some of which would
12 be related to secondary outcome measures, some might
13 be related to post-marketing surveys, some might be
14 explicit studies on various topics. And I can see
15 where we might want to -- or it may be helpful to
16 get explicit about what those research topics are,
17 but I didn't make the explicit list.

18 Third, it seems that it would be useful
19 to encourage extended outcomes to be reported and to
20 be considered for inclusion in labels. And then
21 there are two different types of extended outcomes
22 that need to be explicitly addressed. One is
23 outcomes post-treatment with replacement, post-
24 treatment with NRT, and the other is long-term
25 outcomes with NRT. And that again may come through

1 post-marketing surveys or it could come through
2 explicit studies.

3 And then finally that it would -- I am
4 not sure where we stand on this. Personally, I
5 think I am supportive of the idea of some -- of
6 encouraging some organization like SRNT to sponsor a
7 meeting, perhaps a meeting that members of this
8 committee are encouraged to attend, although not as
9 members of this committee, to talk about and to
10 consider what do we know and what do we need to know
11 as SRNT as an organization. What would they like to
12 see in terms of direction for new labels, new
13 labeling indications for either primary or secondary
14 outcomes, recognizing that that influences how their
15 membership might then do their research or some of
16 their research. So those are perhaps a loose set of
17 things. But, yes, Dr. Meyer?

18 DR. MEYER: I just want to reinforce
19 what Dolores Yaroma said. I think she is right on
20 target in terms of what the public needs and wants
21 to know about a consumer product like this. I think
22 it is also what physicians need to know and that
23 that kind of information should be up front. And
24 that kind of label -- I mean that kind of
25 information should be on the label. That is what

1 people care about. And it can be written in
2 English.

3 CHAIR STRAIN: But there does need to be
4 some --

5 DR. MEYER: Supplementary --

6 CHAIR STRAIN: Well, there needs to be
7 some data that drives what that is. That data may
8 exist. I think that is John Hughes's point. The
9 data may exist, and if it does exist, then let's get
10 it in there. And if it doesn't exist, then as an
11 organization, the FDA perhaps can say, hey, we would
12 encourage people to get this kind of data because we
13 would like to see it appear on the labels.

14 DR. WRIGHT: The agency is powerful, but
15 it is not omniscient and it is not omnipotent. I am
16 very grateful for that. There are some things that
17 we can do. We can ask people who enroll patients in
18 smoking cessation studies to try to find a way to
19 find them again a year later or two years later and
20 see how they are doing.

21 We can shift our attitude from viewing
22 extended use as an adverse outcome and a
23 demonstration of addiction to accept the reality
24 that there are some patients that are going to need
25 prolonged treatment with nicotine replacement

1 therapy, and approach that as something that we can
2 gather information about rather than try to prevent
3 or worse yet flag as something that is wrong with
4 the product.

5 There is a statement that Dolores made
6 that I think is very important which is that
7 withdrawal symptoms hurt and relieving that
8 suffering is a worthy goal of treatment. There has
9 been kind of a tacit willingness to ignore the
10 suffering of addicts on some principle that perhaps
11 it is good for them or at least they deserve it. So
12 there are some things that we can do in terms of how
13 we set up the information gathering from the
14 clinical trials and what kind of trials we suggest.
15 We are limited in that there are questions the
16 research community would like the answers to that it
17 is simply not proper or fair to mandate that
18 industry answer. Every dime of that industry money
19 comes out of a patient's pocket and we are very
20 sensitive to that.

21 So you've given some very definite
22 suggestions. Does the rest of the committee share
23 your perceptions?

24 CHAIR STRAIN: Shall we go through
25 points -- point by point and get a sense from the

1 committee whether there is any general agreement or
2 disagreement?

3 DR. WRIGHT: I would like to make --

4 CHAIR STRAIN: Yes, go ahead.

5 DR. WRIGHT: I would like to offer a
6 first point for discussion to determine if there is
7 agreement. It sounds like you are proposing that
8 the appropriate model for smoking cessation is that
9 it is a life-threatening chronic illness in which a
10 relapsing remitting course is to be expected and
11 there are multiple possible beneficent clinical
12 outcomes. There is more than one outcome for these
13 patients. I would like a read on that if you could.

14 DR. LLOYD: Yes.

15 DR. DE WIT: I agree with that but then
16 you would have to standardize something in your
17 outcome measure. If you are going to look at a year
18 after the treatment and then you are going to allow
19 additional treatments and you are going to allow
20 them to relapse and smoke for some period of time --
21 I mean somehow we need to come up with some kind of
22 standard, even if it is a relapsing disorder. Not
23 only that, I am not sure how we would test this with
24 a placebo control. I mean, is this something that
25 you would maintain them on a placebo and then

1 administer placebo again after they relapse?

2 DR. MEYER: No. I think what you would
3 do is you have populations now -- the drug is
4 available. It is a post-market -- I don't think you
5 would add this to the premarketing study of these
6 drugs. But in the post-marketing period, these are
7 people who failed at some point after they had this
8 initial treatment of nicotine replacement. Now you
9 know they have failed or they are likely to fail or
10 start to smoke. They go back on the medication.
11 They don't have to go back on the placebo.

12 DR. DE WIT: And then do you make a
13 distinction between those that stay on the
14 medication and don't smoke versus those that stop
15 the medication and don't smoke? I mean is one
16 outcome better than the other?

17 DR. MEYER: I think you decide that
18 those who -- you have modifiers of outcome. But you
19 don't attribute to that single episode of treatment
20 that --

21 DR. DE WIT: I am completely in
22 agreement with coming up with more flexible outcome
23 measures of some kind, but I think that it is going
24 to be a huge job to standardize these. And I think
25 that we certainly can't get it done in an hour or

1 whatever we have left. But I think the committee in
2 general is in favor of the idea or the concept of
3 doing it, but the mechanics, as you I am sure know,
4 are going to be very difficult.

5 CHAIR STRAIN: Dr. Andorn?

6 DR. ANDORN: Well, and that is where the
7 advantage of a symposium. I wouldn't necessarily
8 limit it to just SRNT. I would certainly like some
9 input from NIDA, NIAAAA, and the other societies like
10 American Cancer, American Heart, and American Lung.
11 I think we have a lot to learn from other
12 investigators. If we look, probably fewer than 100
13 viewpoints in the field were presented today and
14 there are a lot more viewpoints out there that could
15 benefit the agency as it tries to define these
16 outcome measures.

17 CHAIR STRAIN: Dr. Khuri?

18 DR. KHURI: Yes. I would include in
19 that list the American Society of Addiction
20 Medicine, ASAM. Certainly, I think, they would have
21 quite a bit to say about this formally. And I
22 certainly heartily endorse Dr. de Wit's remarks
23 about outcome measures. I think once it were done,
24 it would save a lot of time and money in all of the
25 studies and enable us to extend study, which we must

1 do over a longer period of time. But it will
2 require an initial effort certainly and consensus
3 from a variety of groups.

4 CHAIR STRAIN: Dr. Meyer?

5 DR. MEYER: I think that the concept
6 that you raised that the addiction to nicotine, if
7 it leads to smoking cessation, is a more benign
8 outcome is a major change in thinking about this
9 disorder and needs to be factored into other outcome
10 criteria. I am not sure how you would do that
11 except through careful study.

12 CHAIR STRAIN: Any other comments? Yes,
13 Dr. Winchell?

14 DR. WINCHELL: I don't want to beat a
15 dead horse, but when I sit down next year to write
16 the next label for the next NDA that comes in and
17 the sponsor hasn't had time to incorporate our new
18 ideas about what to design and what to look at --
19 when I get to the clinical trial section and I am
20 writing the results with the quit rates, I heard you
21 say put as long a follow-up as I have available.
22 Put all the quit rates that they have collected out
23 to a year if possible. Yes?

24 DR. MEYER: Yes.

25 DR. WINCHELL: And should I stick with

1 this approach of writing that there was a range
2 across centers? I hear that that is a point that we
3 should discuss in our follow-up meeting exactly how
4 to present those quit rates, whether as a range, as
5 ratio, as a number.

6 CHAIR STRAIN: Dr. de Wit?

7 DR. DE WIT: I really like having the
8 range because it gives you a clearer idea of the
9 absolute success as well as the variability across
10 studies. One thing that is not there in the range,
11 though, is how many studies that represents. So
12 that might be an interesting additional piece of
13 information.

14 DR. WINCHELL: Would it be helpful if we
15 paired the placebo rate with the treatment rates?

16 DR. DE WIT: Yes. Yes.

17 DR. WINCHELL: So that you would like to
18 see a table that showed the by center rate for
19 placebo and treatment rather than these ranges that
20 obscure the relationship or the pairing.

21 DR. DE WIT: Right.

22 DR. ANDORN: Can I make an interruption
23 as a physician user here? Keeping it simple means
24 as simple as possible, no complicated tables. Yes,
25 do compare it to placebo. Forget ranges. Nobody

1 has time to sit down and figure those out,
2 particularly in an HMO. Give the mean and give the
3 bottom line. Interpret it. Go ahead and interpret
4 it for the physician.

5 DR. WINCHELL: Well, this sounds like a
6 topic that should be added to the list for further
7 debate because I hear two equally strong arguments
8 in both directions.

9 CHAIR STRAIN: Dr. Simpson?

10 DR. SIMPSON: I think you could
11 compromise maybe and give one figure with a
12 confidence interval of some kind. So it would be an
13 abbreviated table.

14 DR. WINCHELL: Now others have said I
15 don't want to see a table. I want to see a graph.
16 I want to see a survival curve. Is the table
17 preferable to a graph? Is that a whatever floats
18 your boat kind of thing or do people feel strongly
19 about that? I just want to know how to write this
20 one page of my label.

21 DR. SIMPSON: I think that -- you know,
22 I always say a graph -- you know, a picture is
23 better than 1000 words.

24 DR. YOUNG: But only if you standardize
25 those Y axis. So that one can't stop at 20 and the

1 next one stops at 17 and the next one stops at 12.
2 Run them all up to 50.

3 DR. SIMPSON: But I was going to say
4 that survival curves, although they are supposed to
5 be self-evident, I am not sure people really
6 understand what they are unless they have been told
7 what they are. And a lot of people haven't been
8 told what they are. So if you put one in, they may
9 misinterpret it.

10 DR. WINCHELL: Then would a histogram be
11 preferable? A histogram showing the -- well, I
12 guess it is a bar graph. I mean, the placebo versus
13 treatment at each of the measured points. Because a
14 survival curve implies that we were measuring every
15 day and we weren't.

16 DR. DE WIT: That is certainly -- the
17 histogram. I would vote for the histogram.

18 DR. YOUNG: It is the quickest to get
19 the point across.

20 DR. DE WIT: But you will get debate on
21 this too.

22 DR. WINCHELL: So, it sounds like we
23 have some general ideas that even the specific way
24 we write that table needs improvement although we
25 don't know exactly in which direction. And when it

1 comes to adding in data on withdrawal or craving, I
2 heard a clear message that whatever that data is,
3 put it in there and make it explicit what it is, and
4 don't worry about the fact that one guy measured one
5 thing and one guy measured another. Just say what
6 they measured.

7 DR. MEYER: Well, no. I think that they
8 are looking systematically at the withdrawal.

9 DR. WINCHELL: Everybody uses a
10 different measurement.

11 DR. MEYER: Craving is different. I
12 mean I think that that is much more complicated.
13 But I think withdrawal symptoms are reviewed.

14 DR. DE WIT: I think you are and then
15 you have to standardize them because you are going
16 to get people selecting the withdrawal measure that
17 that product does the best on or in that particular
18 study how it does. So I think you have to have an
19 absolute set of withdrawal criteria or symptoms and
20 everybody rates them the same on those criteria.

21 CHAIR STRAIN: Dr. Simpson?

22 DR. SIMPSON: I was just going to say, I
23 think in a sense that standardization comes about
24 because people believe that a certain scale works
25 better to rate a certain thing. But I think if the

1 pharmaceutical company, before they do the trial,
2 agrees on using a certain scale, then they can't
3 bias their results as you suggest in the
4 presentation.

5 DR. DE WIT: Right. But what if
6 different companies use different scales and then
7 they happen to have not reported this one ahead of
8 time. It just opens the way to a lot of
9 misunderstanding I think.

10 I would vote against one of the
11 suggestions that came up of having a discussion
12 section in the package insert. It seems to me that
13 that opens the door for all kinds of unscientific
14 and unsubstantiated claims and we don't have room
15 for -- if we don't have room for the actual
16 empirical data, we certainly don't have room for
17 people's opinions. So I would vote against that
18 idea.

19 DR. KHURI: I second that.

20 DR. WRIGHT: It sounds like we need to
21 know if you've done enough for today. We are about
22 that time. Celia, do you have at least a starting
23 point for the next label?

24 DR. WINCHELL: I think so.

25 DR. WRIGHT: And some suggestions for

1 the next sponsor that comes in with a development
2 plan. I would strongly suggest that the concept of
3 at least one external symposia and if we can lure
4 any other professional organizations into doing a
5 symposia as well. This is a fertile topic because
6 the more I study this problem, Mr. Chairman, the
7 more I become convinced that there is a level of
8 efficacy that can be reached with patient directed
9 therapy with the OTC products or with a product that
10 is essentially handed as a script to a patient with
11 a suggestion that they use it, which is currently
12 the standard of care in all but a few centers for
13 smoking intervention. I think there is a real role
14 for the learned intermediary in this. I think it is
15 a real part of medical practice. And I think that
16 it is time to go into the second generation of
17 product development to learn how to really do this
18 job right. So we are content if you are content.

19 CHAIR STRAIN: Are we content? Are
20 there other points that the committee would like to
21 -- Dr. Young?

22 DR. YOUNG: I just wanted to make one
23 comment in response to something Dr. Wright said. I
24 wanted to reinforce your suggestion that perhaps the
25 notion of extended use of these compounds should be

1 removed from the category of adverse outcome. And
2 consideration should be given to whether or not
3 longer term use in fact ought to be the standard of
4 care required for this type of chronic relapsing
5 disorder for a great many of the patients.

6 DR. WRIGHT: Is that generally held by
7 many?

8 DR. DE WIT: Well, actually extended use
9 is one of our indicators that the product itself is
10 being abused. So somehow we would have to develop a
11 means to distinguish those. So I think that is
12 material for another meeting, but I think --

13 DR. YOUNG: But I think in terms of
14 educating the clinician and educating the consumer
15 or the two types of consumers for the product, in
16 reading through here I think there is an issue if
17 you constantly see that you have problems if in fact
18 you have used the product for longer than six weeks
19 or longer than two months. When, in fact, what I
20 heard today was at least clinical impression that
21 longer use may in fact be required for a substantial
22 portion of the people if they are going to achieve
23 the goal of cessation of smoking. I mean, the
24 cessation rates -- efficacy here is still pretty
25 lousy in terms of smoking cessation.

1 DR. WRIGHT: We have unequivocal data
2 from some trials of some products of people who
3 successfully abstained from cigarettes for an
4 extended period of time who when the product was
5 withdrawn at the end of the availability period
6 relapsed to smoking cigarettes immediately. They
7 exist.

8 CHAIR STRAIN: Yes, Dr. Khuri?

9 DR. YOUNG: They should be more
10 effectively published to the prescribing physician.

11 DR. KHURI: Following up exactly on that
12 point, lest I also be accused of dumbing down
13 doctors, I am just talking about the realities of
14 practice today. I think there is an opportunity
15 here for a tremendous educational project on the
16 part of everybody, certainly including the
17 pharmaceutical companies and those of us who have
18 some expertise in addiction medicine, that to train
19 primary care family practitioners, general doctors
20 who are becoming the majority, that using these
21 products intelligently, effectively, and with
22 support and moralizing, the patient is indeed an
23 efficient way to practice medicine and will save a
24 lot of time and trouble, morbidity, and mortality
25 down the pike. There is a tremendous, and obvious

1 to us probably in this room, lesson to be taught
2 doctors here that it is a very effective use of time
3 to study this and to read the insert and to know
4 more about it and to sell it to their patients, even
5 in the 5 or 10 minutes they have with the patient.

6 CHAIR STRAIN: Thank you. Other
7 comments? I would like to -- before we adjourn, I
8 would like to thank Dr. Andorn and her working group
9 -- so I have the pleasure of thanking myself -- and
10 Dr. Schneider, who wasn't able to be here for all
11 the work that went into the presentations that were
12 done today. And I would like to also thank those
13 who attended and presented, both the sponsors as
14 well as others from various organizations. Your
15 contributions were invaluable and greatly
16 appreciated over the course of today. I would make
17 a motion for adjournment?

18 DR. ANDORN: So moved.

19 DR. DE WIT: Second.

20 CHAIR STRAIN: Then we will be
21 adjourned. Thank you. See you tomorrow morning at
22 9:00 a.m.

23 (Whereupon, at 4:42 p.m., the meeting
24 was adjourned to reconvene at 9:00 a.m. the
25 following day.)