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UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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DRUG ABUSE ADVISORY COMMITTEE MEETING

OPEN SESSION

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MONDAY, FEBRUARY 10, 1997

The meeting took place in the Ballroom,
Holiday Inn, 2 Montgomery Village Avenue,
Gaithersburg, Maryland, at 8:30 a.m., Max A.
Schneider, M.D., CADC, Chair, presiding.

PRESENT:

MAX A. SCHNEIDER, M.D.	CADC Chair
KIMBERLY TOPPER, M.S.	Exec. Secretary
HARRIET de WIT, M.D.	Member
CAROL L. FALKOWSKI	Member
ELIZABETH KHURI, M.D.	Member
LLYN A. LLOYD, R.Ph.	Member

1 ERIC C. STRAIN, M.D. Member
2 ALICE M. YOUNG, Ph.D. Member
3 SUSAN A. COHEN Consumer Rep.
4 CURTIS WRIGHT, M.D. FDA Rep.
5 E. DOUGLAS KRAMER, M.D. FDA Reviewer
6 JOHN LONGMIRE, M.D. FDA Reviewer
7 MONTE L. SCHEINBAUM, Ph.D., M.D. FDA Rev.
8 SURESH DODDAPANENI, Ph.D. FDA Presenter
9 SPONSOR REPRESENTATIVE:
10 MICHAEL S. FEY, Ph.D. New Life Health
11 Products Corp.
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8:32 a.m.

CHAIRMAN SCHNEIDER: With your permission I will call the meeting to order. And before I go further I would like to introduce Ms. Kimberly Topper, our Executive Secretary.

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting, all financial interests reported by the committee participants, it has been determined that all interests in firms reported by the participants present no potential for an appearance of conflict of interest at this meeting with the following exceptions.

In accordance with 18 USC Section 208(b)(3), full waivers have been granted to Dr. Max Schneider, Dr. Elizabeth Khuri, and Mrs. Susan Cohen. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 at the Parklawn Building.

In the event that the discussions involved

1 any other products or firms not already on the agenda
2 for which an FDA participant has a financial interest,
3 the participants are aware of the need to exclude
4 themselves from such involvement and their exclusion
5 will be noted for the record.

6 With respect to all other participants, we
7 ask in the interest of fairness that they address any
8 current or previous financial involvement with any
9 firms whose products they may wish to comment upon.
10 Thank you.

11 CHAIRMAN SCHNEIDER: Thank you very much.
12 My name is Max Schneider and what I would like to do
13 for these two days -- this really is for the committee
14 -- is that we have a tremendous work load ahead of us.
15 We will need to introduce ourselves for each of the
16 discussion meetings because there will be some closed
17 meetings -- right now we're involved in an open
18 meeting -- so that it will be a little repetitious for
19 the committee itself.

20 Secondly, because of the schedule -- I do
21 not like to cut off debate at any time. However, we
22 do have a timeframe in which we must accomplish our
23 work, and so I'm going to ask that we move along as
24 rapidly as we can and as succinctly as we can, to do
25 these chores that have been handed us.

1 I will start the ball off by introducing
2 myself, and then why don't we go down and do it. My
3 name is Max Schneider. I'm a physician/internist/
4 gastroenterologist by training; in the addiction
5 medicine field for over 43 years, which is something
6 I don't like to remember. And I am Director of a
7 treatment program, non-profit, in Orange, California.

8 DR. STRAIN: I'm Eric Strain. I'm a
9 psychiatrist from Johns Hopkins University in Balti-
10 more.

11 MS. FALKOWSKI: I'm Carol Falkowski. I'm a
12 Drug Abuse Specialist with the State Alcohol and Drug
13 Abuse Agency in the State of Minnesota.

14 MR. LLOYD: I'm Llyn Lloyd with the Arizona
15 State Board of Pharmacy.

16 DR. de WIT: I'm Harriet de Wit at the
17 University of Chicago.

18 MS. COHEN: I'm Susan Cohen, the Consumer
19 Member.

20 DR. YOUNG: I'm Alice Young, a psychologist
21 at Wayne State University in Detroit.

22 DR. KHURI: Elizabeth Khuri, a physician at
23 Cornell, a New York hospital in Rockefeller Universi-
24 ty; 26 years in addictions and a specialty of adoles-
25 cent medicine and public health.

1 DR. LONGMIRE: Jack Longmire, Medical Review
2 Officer, FDA.

3 DR. WRIGHT: Curtis Wright, Acting Director
4 of the FDA Review Division.

5 CHAIRMAN SCHNEIDER: Dr. Wright, do you have
6 any comments you'd like to make at this time?

7 DR. WRIGHT: I think we should do the open
8 public session, and then I'd like to make some
9 comments prior to the first section on the agenda.

10 CHAIRMAN SCHNEIDER: All right, sir. Then
11 we are open and I believe that we have people from the
12 New Life Health Products, is that correct? There is
13 no open discussion. It will either be presentation
14 and the discussion by the group here.

15 DR. WRIGHT: I understand, Mr. Chairman,
16 that no one has approached the committee Executive
17 Secretary, to make comments in the open public session
18 on this day.

19 CHAIRMAN SCHNEIDER: Thank you. Would you
20 introduce yourselves, and the floor is yours.

21 DR. WRIGHT: Well, before we go into the
22 sponsor's presentation for the first session I do have
23 a comment that I would like to make.

24 CHAIRMAN SCHNEIDER: Oh, go ahead. That's
25 what I thought.

1 DR. WRIGHT: We asked this sponsor to make
2 this presentation because his product poses a dilemma.
3 One of the things that the Agency has to be especially
4 careful of is that our methods of testing do not
5 interfere with a sponsor's or an investigator's
6 ability to demonstrate efficacy for a class of
7 products that we have been worried about for some
8 time; which includes naltrexone, disulfiram, and
9 possibly this drug, silver acetate, which are aversive
10 in nature.

11 There is a regulatory and a clinical
12 dilemma. These are products that appear to have a
13 clear, pharmacological effect. They appear to do
14 something in man, and that thing which they do should
15 be therapeutic.

16 However, when you place them in a clinical
17 trial setting in addictive disorders with no mecha-
18 nisms in place to enhance compliance, they often fail
19 in clinical trials, resulting in the very difficult
20 position of having an agent that appears to work and
21 yet you have extreme difficulty demonstrating this in
22 traditional, paralleled group, controlled clinical
23 trials.

24 For this kind of product I would ask the
25 committee how we should define as a regulatory agency,

1 clinical benefit in this area since we do not regulate
2 the practice of medicine. And if there is a gray area
3 between a therapeutic effect and actual effectiveness
4 in clinical use, what shall we ask sponsors to prove
5 about their drugs in addition, in this area?

6 Because it would be a tragedy to us if we
7 kept a product off the market, not because it did not
8 work, but because our testing paradigms were unable to
9 demonstrate that it works.

10 So I would ask you to pay particular
11 attention to this presentation. Mr. Chairman.

12 CHAIRMAN SCHNEIDER: Thank you, Dr. Wright.
13 Now, New Life folks. You may introduce yourselves.

14 DR. FEY: My name is Dr. Michael Fey from
15 New Life Health Products Corporation, and with me
16 today is Mr. Rick Lufkin who's on the Advisory Board
17 of New Life Health Products Corporation.

18 MR. LUFKIN: Chairman Schneider and members
19 of the Advisory Committee. I want to give you a brief
20 introduction to this product. The first product that
21 we'll discuss is 2.5 milligram silver acetate lozenge.
22 We would like to present this product to you to make
23 you familiar with it, and also to get your ideas as to
24 how we should proceed with an aversion drug product.

25 Now, this product gives cigarettes a bad

1 taste. It is an aversion product much like antabuse.
2 Now, aversion products have difficulty showing
3 efficacy in cessation if the standard intent-to-treat
4 analysis is used. However, if you do not use intent-
5 to-treat analysis but simply do an analysis on only
6 those subjects that take the drug, it is not that
7 difficult to show efficacy.

8 That's the problem with aversion drug
9 products. The sponsor will show you data on his
10 particular product to demonstrate this.

11 Now, our specific questions for this
12 product, considering that it is an aversion drug
13 product -- these are the same questions that were sent
14 to you in your pack -- are: how should the sponsor
15 proceed with the clinical trial design; what should be
16 our basis of approval; and if approved, in the
17 Advisory Committee's opinion, what is the best
18 clinical use of this type of product?

19 DR. FEY: As mentioned before, my name is
20 Dr. Michael Fey from New Life Health Products Corpora-
21 tion. I am the developer of this product; I have been
22 involved with this for a decade, since 1987; and have
23 been working with the Food and Drug Administration
24 since about 1991.

25 And I would like to first say that the Food

1 and Drug Administration has been extremely helpful to
2 our small business in helping us design and plan the
3 types of studies that we have done, and in helping
4 guide us through the regulatory maze that we have gone
5 through.

6 We do not have a lot of expertise in this
7 area. We do not have a whole support of clinical
8 assistance. We have had to depend on the University
9 of Medicine and Dentistry of New Jersey. We do not
10 have deep pockets and large finances to support our
11 operations.

12 We are seeking help as part of the Small
13 Business Innovative Research Program which has funded
14 us, a sister agency, the National Institutes of
15 Health, and the National Heart, Lung, and Blood
16 Institute in helping bring this product before the
17 public and into the public domain.

18 So this really frames what we're looking for
19 from you today. We truly need your help with the next
20 step and to us, this is what the step looks like. I
21 would urge the Advisory Council to please read and
22 reread the cover letter that came with the packet of
23 information and published studies. It literally
24 defines in full what we're looking for out of the
25 Advisory Committee if we can get it, and that is some

1 help.

2 And we had mentioned before, this product is
3 a two-and-a-half milligram silver acetate, smoking
4 deterrent product. This product makes smoke taste
5 bitterly unpleasant at the first few puffs of a
6 cigarette, continues to get worse with each puff,
7 until smokers are forced to do this.

8 There's the look of the lozenge -- this
9 happens to be a cherry-flavored lozenge and we have
10 peppermint-flavored lozenges -- smokers will put their
11 cigarette out. That's what this product is designed
12 to do.

13 Its deterrent action lasts up to a few hours
14 and the reason that this is variable is that people
15 may eat or drink and interfere with the drug in the
16 mouth -- which is a bathing of silver ions in the
17 mouth -- and there is also some genetic variability
18 that takes place in people's availability to taste
19 this product.

20 Approximately 15 to 20 percent of the
21 smokers out there are genetically blind to the taste,
22 but for 80 to 85 percent of the people, they do get a
23 deterrent taste reaction which continues to get worse
24 with each puff of a cigarette until they are forced to
25 put their cigarette out or reminded not to smoke in

1 the first place. Therefore, this particular product
2 has applicability to help smokers cut down on the
3 amount that they smoke, to stop smoking completely,
4 and perhaps to prevent relapse.

5 This is an aversion therapy; this is not a
6 nicotine replacement therapy as with the nicotine
7 chewing gum and the nicotine patch. This is not
8 contraindicated with the chewing gum and the patch.
9 It can be used in combination, thus providing two
10 separate therapies, or two modalities to work on the
11 problem of smoking addiction and to help smokers find
12 a way to quit.

13 I got into this back in 1987 when a dear
14 cousin of mine died from smoking, and I became
15 somewhat of a zealot and tried to use my talents and
16 energies to try to help people to quit smoking, and
17 this is the path I've chosen and worked on and have
18 applied all my energies to it in the last decade for
19 what I believe in.

20 I also want to say that this is not a
21 miracle cure. I don't believe there is a miracle cure
22 for smoking. I do believe that there are ways to help
23 people to quit. People must continue to try to find
24 ways to quit smoking. Some ways will work, some
25 won't.

1 But the key message here is, if they
2 continue to try they will come upon a method that will
3 help them to quit. And we believe this is just one of
4 many methods that will allow them to quit and a new
5 alternative for the marketplace.

6 We have a couple of different products that
7 we have marketed under in the past. We'll be passing
8 around to the committee some packages. There is some
9 information in the package that I've given to you that
10 shows what the label has said for these kinds of
11 products, and these have all been in compliance with
12 the FDA recommendations in the Federal Register.

13 And these products have been sold primarily
14 to smoking cessation professionals, where we believe
15 that their use can best be directed. We believe that
16 no single product out there on its own will have as
17 much of an impact in helping smokers to quit as a
18 product that's being supported by a professional. And
19 I think smokers need that professional component or
20 need some peers beside them to help them get through
21 this very tough and difficult addiction of smoking.

22 Our problem currently and our barrier is FDA
23 approval. This product has been sold in the United
24 States and overseas, from 1988 in the U.S. until 1993.
25 We are currently in the IND process with the Food and

1 Drug Administration and we have been there since 1991.

2 And again, I do wish to reiterate that we
3 have had a very good working relationship with the
4 Food and Drug Administration, and they have been
5 extremely helpful in directing us toward the right
6 kinds of testing to do and helping us with data and
7 literature, and we are very thankful to FDA for even
8 allowing us the opportunity to be here before you
9 today to present.

10 This product was removed in the U.S.
11 marketplace by the Food and Drug Administration in
12 1993. This was part of an overall, sweeping ruling
13 that started back in the early-1980s to remove many
14 different products in the marketplace. And there are
15 hundreds of different products that were removed for
16 lack of data to support both safety and efficacy. And
17 this particular product lacked data to support
18 efficacy and as part of that process was removed.

19 At the same time, we entered into the IND
20 process -- the Investigational New Drug process -- in
21 an attempt to provide data to support efficacy.

22 I'd like to talk about FDA's current
23 definition of efficacy, and the definition involves
24 two, randomized, double-blind placebo-controlled
25 studies. And these are -- quick success is being

1 determined at zero cigarettes, 28 days.

2 We believe that the zero cigarette, 28-day
3 criteria is a bit rigorous for a product like this,
4 for an aversion therapy. This is not a nicotine-
5 replacement therapy; it does not lend itself to zero
6 cigarettes for a period of 28 days, in our opinion.

7 And we believe that this is what the
8 Advisory Committee needs to take a look at and make
9 recommendations to FDA upon. We think it would be
10 difficult for this product to meet that challenge.

11 I would like to just pretty well go over
12 what the position, I believe, of FDA is as written in
13 the Federal Register of what a smoking deterrent is.
14 This is defined -- it's listed in your package -- as
15 part of the Federal Register back in 1982.

16 And that is that, the definition of a
17 smoking deterrent is a substance that is used tempo-
18 rarily to help the individual to want to stop smoking,
19 become cigarette-free, or to break the cigarette
20 habit.

21 And I guess the key word here is "temporari-
22 ly", but let me point out, it is by no means our
23 intent to ensure that smokers just stop and that's it;
24 we want them to quit. We believe this product is a
25 way to help them along that path of quitting even

1 though it's a temporary aid.

2 The indication is a temporary aid to those
3 who want to either stop smoking cigarettes or break
4 the cigarette habit. I'd like you to keep that
5 definition in mind because we believe our product,
6 more than anything else out there, does meet that
7 criteria.

8 I'd like to first talk about the safety of
9 two-and-a-half milligrams silver acetate lozenge. A
10 1982 Advisory Panel -- I imagine just like this one --
11 the Advisory Panel concluded that six milligrams of
12 silver acetate, not two-and-a-half, was safe every
13 four hours up to six times a day, for no more than 21
14 days. Or if you multiply that all out, that comes up
15 to 756 milligrams of silver acetate, or silver salt.

16 Our product uses far less than that, less
17 than half of that, and we believe is even safer than
18 the OTC Panel's recommendation prior to this. So we
19 believe that safety has been established.

20 A product like this at six milligrams has
21 been used in Europe for quite a number of years with
22 no adverse health effects -- and that's at six
23 milligram level -- and we have experienced no adverse
24 health effects since using this product from 1988 to
25 current, among tens of thousands of smokers. Not one

1 adverse claim or health effect. So we believe this
2 product has a very good history of demonstration of
3 safety.

4 It has low systemic toxicity, and the only
5 concern about this product is argyria, which is a
6 discoloration of skin. That has not been demonstrat-
7 ed. It has been demonstrated in two cases in Europe,
8 but that was only after long-term abuse.

9 This product does not lend itself to long-
10 term abuse; it's an aversion product. If anything,
11 you want to avoid using the product because you get
12 hit over the head each time you use it. It's a
13 deterrent, a taste deterrent.

14 I'd like to talk a little bit about the
15 data. And again, we were funded under the Small
16 Business Innovative Research Program by NIH, National
17 Heart, Lung and Blood Institute.

18 And the way they worked is Phase I, Phase
19 II, Phase III, where Phase I is a small amount of
20 funding to demonstrate the idea or the concept, and
21 phase II is a larger amount of money to test that
22 concept -- in this particular case a clinical trial,
23 a larger scale clinical trial.

24 Phase III is the commercialization side
25 where the company is expected to go to the outside

1 industry and get some assistance in commercializing
2 the information that was obtained in Phases I and II.

3 Phase I was a \$50,000 grant in which we did
4 a study at the University of Medicine and Dentistry
5 and showed indications of efficacy. And Phase II was
6 what I'm going to talk about right now.

7 It was a large, rather large, 500-patient
8 study -- randomized, double-blind, placebo-controlled
9 study -- of the lozenge by Dr. Norman Hymowitz and
10 Haftan Eckholdt -- this is an M.D. instead of Ph.D. --
11 at the University of Medicine and Dentistry of New
12 Jersey.

13 And this was conducted independently of us.
14 We outlined the study, submitted it to FDA, our plans
15 to conduct this study, got comments, revised it, and
16 basically contracted with the University to indepen-
17 dently do this study. So the data that you see that
18 came out of this study -- and it's been published and
19 in your packages -- is not something that we wrote up
20 or fantasized about. It was done at the University.

21 And the results simply were: at zero
22 cigarettes, 21 days, the quit rate approached signifi-
23 cance at 17 percent for the active two-and-a-half
24 lozenge versus 11 percent for the placebo. An effect
25 almost meeting the five percent level of -- a 95

1 percent level of confidence.

2 Again, this is not a miracle-cure drug; it's
3 a drug that indicates from these kinds of studies,
4 efficacy. We're very concerned that the zero ciga-
5 rette, 28-day criteria and the intent-to-treat
6 criteria hurt us in this particular study, but even
7 through that we did find that there is some level of
8 significance approaching that of zero cigarettes in 28
9 days but not quit meeting that criteria.

10 We failed the test; we failed the zero
11 cigarette, 28-day criteria test. But we do have some
12 data to support indications of efficacy.

13 This was significant at 26 percent active
14 versus 16 percent placebo at the five percent level of
15 confidence when the data was analyzed for subjects who
16 really used the lozenge. And again, this type of
17 product does not lend itself toward use and repeat
18 use; it's an aversion product.

19 You'll use it once, twice, three times and
20 then you'll say, I'd rather avoid using the product.
21 You'll either go back to smoking or you just won't
22 smoke. It's one or the other; it's very simple. It's
23 not a kind of a product that people want to continue
24 to use, smoke, have a bad experience, and then do it
25 again and again and again.

1 But it's the kind of product that if you're
2 in a situation and you feel like you have to light up,
3 it will stop you from smoking through that situation.
4 And a number of those situations and you've either
5 helped yourself to quit or you're not going to quit
6 and you're going to try something else -- some other
7 modality.

8 Some things came out of this study that we
9 really didn't know about. But the first thing that we
10 did know about was that the rating of the lozenge was
11 most aversive and it was most aversive for those
12 people who are likely to quit. So there was a
13 relationship between the aversion and the quit, and
14 you'll see a graphic example of this in a minute.

15 This product produces an aversive effect and
16 the result is, those people who do use the product
17 will quit, and there is that relationship and that's
18 significant.

19 And another thing that came out of this
20 study we did not realize is that Black Americans
21 tended to rate the lozenge more aversive than white.
22 Highly significant. We don't know why, but this was
23 just a finding that cropped out as the data was
24 analyzed.

25 And it suggests that perhaps the lozenge may

1 be used to help Blacks who have more of an aversive
2 experience with the lozenge. So maybe we can orient
3 and point this particular drug towards a minority
4 group in this country and perhaps help them along as
5 well.

6 Further going on, on data to support to
7 efficacy, this product again, through the SBIR Phase
8 I and II trials was peer-reviewed not once, but twice,
9 by at least 15 different smoking cessation profession-
10 als each time. So our submissions were peer-reviewed,
11 again, by about 30 different professionals in the
12 smoking cessation area.

13 So we had the 50-patient study which
14 indicated efficacy, the 500-patient study which
15 indicated efficacy, we had two, large, consumer-usage
16 studies conducted by independent research firms and
17 funded by a large pharmaceutical company.

18 And it indicated that smokers do experience
19 the aversive response, they like this kind of a
20 product, they like the alternative of a non-nicotine
21 product, they like to have the ability to use this
22 product to help them to quit. So consumers would
23 accept this product.

24 We also did a label-usage study. We have
25 some packets circulating here of the stop smoking aid

1 brand, in which we asked consumers out there if they
2 could read and understand the directions. And we did
3 this two separate times. We worked with FDA on this
4 type of a study just to get a feeling for whether
5 consumers understood the product and its label
6 instructions and how to use it.

7 And indeed, very high levels of percentage.
8 And that is included in your packet as well. We found
9 that consumers understood the product, understood the
10 label, and understood how to use it.

11 We're going to show you some graphic
12 evidence in a minute which is going to basically take
13 everything I've been saying and just boil it down to
14 ten minutes' worth of smokers using this product, and
15 you'll see for yourself what the product can and can't
16 do.

17 Historical literature as well supports
18 silver salt. Silver salts have long been known to
19 interact with smoke to produce a bitter taste. So
20 there's quite a bit of history and knowledge about
21 silver salts in and of themselves.

22 And as I mentioned, there have been some
23 products in Europe that use silver acetate, and there
24 was silver acetate products in the U.S. market,
25 including our product, back in the late-'80s to early-

1 '90s. So it's not like we're dealing with a foreign
2 substance.

3 So at this point I would like to address
4 your attention -- we have about ten minutes, two
5 patients -- this was conducted at random back in 1993
6 never knowing that I'd be here today showing it to you
7 -- but I think it provides graphic and compelling
8 evidence in support of efficacy of this particular
9 product. So if we can have that video.

10 (Videotape played.)

11 You know, you never know when you're doing
12 these tests whether you're going to find somebody
13 who's a non-taster. And I was beginning to worry she
14 might have been a non-taster because it took her quite
15 a bit longer than it took the first person to experi-
16 ence that taste-deterrent effect.

17 And again, there is some variability among
18 different people and depending on whether they had a
19 cigarette just prior -- if they put the lozenge in
20 their mouth just prior to coming in there, if they had
21 just smoked, they might get an immediate reaction with
22 the residuals of the smoke in their mouth. So you
23 never know what you're going to expect.

24 We did about a dozen people like that --
25 those were just the first two off the tape -- and out

1 of the dozen or so we had two that were non-tasters.
2 And it's absolutely amazing when you sit there and
3 watch them smoke and smoke and smoke and they experi-
4 ence absolutely nothing.

5 It's just absolutely amazing to watch that,
6 knowing that with other people, one, two, three puffs,
7 four puffs, they've got to put that cigarette out and
8 they can't smoke. And they're stuck for a couple of
9 hours -- up to a couple of hours of not being able to
10 smoke, depending on whether they wash their mouth out
11 or eat or whatever.

12 So let me continue on with that.

13 CHAIRMAN SCHNEIDER: Can we have the lights,
14 please?

15 DR. FEY: Yes. Okay, this is a rather busy
16 slide; I'm not going to try to make it too busy for
17 you. But I'm getting near the wrap-up of this and I
18 want to talk about the benefit of your recommending to
19 the FDA to lower the barrier to approval of this
20 product. We believe that the smoking deterrent -- the
21 efficacy of the smoking deterrent is rather apparent
22 and graphic, as illustrated a few minutes ago in the
23 video.

24 We believe that short-term efficacy for this
25 particular product is demonstrated. Although this

1 product has applicability as an OTC product and has
2 been in the marketplace before as such, if this
3 product were to be deemed an Rx-type of a product, it
4 would permit its use by professionals to study it for
5 quite some time while they're using it, and also later
6 on as an OTC switch-type product, so it would give us
7 additional experience.

8 This type of product is applicable or
9 suitable for behavior modification. It's safe for use
10 with younger smokers, may be used in conjunction with
11 nicotine-replacement therapies to include quit rate
12 percentages, particularly when people tend to cheat.
13 And there is a known problem that people tend to
14 cheat; they tend to smoke while using the nicotine
15 patch and they get an extra dose of nicotine in their
16 body.

17 This product may be used in conjunction with
18 nicotine-replacement therapy; the combination of
19 aversive therapy, nicotine-replace therapy, to further
20 enhance quite rate success in smokers.

21 We did find anecdotal evidence of the same
22 deterrent taste reaction with marijuana, possibly with
23 other smokable drugs. We would need to study this
24 further, but this opens up a whole new realm of
25 attacking or approaching the problem of smoking other

1 drugs, providing deterrent taste effect.

2 There are other products, innovations in
3 mind, that we are not able to mention today that would
4 allow us to even improve upon the success of how we've
5 been able to use silver acetate so that we can
6 approach and attack this problem of smoking, not just
7 from cigarettes but other smokable drugs.

8 In conclusion, we believe that this is a
9 safe and effective drug to help smokers to quit. It
10 has a prior history of safety, it has apparent
11 efficacy. We question the criteria of zero cigarettes
12 in 28 days as a measure for efficacy of this product.
13 We ask why? Why draw the line at zero cigarettes, 28
14 days?

15 This product is apparently effective, at
16 least in the short-term, as a temporary aid, as a
17 smoking deterrent according to the definition provided
18 by the Food and Drug Administration, and we ask again
19 -- this product was in the marketplace before -- why
20 delay approval?

21 We ask your advice to get over the regula-
22 tory barrier right now and to help get this product
23 back in the marketplace, in the public domain where it
24 belongs and get it among professionals who can be out
25 there using this as a weapon to help smokers help

1 themselves to quit.

2 Thank you very much.

3 CHAIRMAN SCHNEIDER: Thank you very much,
4 sir. The committee is now open to either ask Dr. Fey
5 some questions -- the three questions we've been asked
6 to discuss would be -- and I'm going to repeat them --
7 how would the committee suggest that the sponsor
8 proceed with the clinical trial design?

9 Question 2 is, what should be the basis of
10 approval with this product; and if approved, how
11 should this product be used? Any comments from the
12 panel? Let me ask a question or two, if I may.

13 DR. FEY: Yes sir.

14 CHAIRMAN SCHNEIDER: Has this been used, in
15 your experience, with other forms of behavior modifi-
16 cation -- i.e., group therapy and this type of thing
17 -- and what is your stance in terms of having this
18 product be part of, rather than just standalone?

19 DR. FEY: To answer the latter question
20 first, we would prefer this product be used as part of
21 a program, because we believe that smokers will be
22 better served when they have that additional part of
23 the program. Their chances for quit rate success are
24 increased when this product is used with professional
25 support and behavior modification and professional

1 advice.

2 As to answer your first question, when we
3 sold this product we sold it to a wide range of
4 smoking cessation professionals out there and pretty
5 much left it up to them to utilize and incorporate the
6 lozenge in the program as they saw fit. We did not
7 maintain or keep data or do anything other than get
8 anecdotal feedback that the product was working for
9 them.

10 And for those customers that repeat-pur-
11 chased from us, it was obvious that whatever it was,
12 was a benefit to them, and for those who did not
13 purchase from us again, it's -- I guess it's obvious
14 that for one reason for another, they decided not to
15 use the product.

16 CHAIRMAN SCHNEIDER: Does your literature
17 and your advertising encompass the recommendation that
18 this be used in addition to?

19 DR. FEY: Absolutely. As a matter of fact,
20 the postcard that was included in your packet was part
21 of our mailing and it was directly pointed to smoking
22 cessation professionals who would incorporate this in
23 their smoking cessation program.

24 If I may for one second, just point you to
25 the particular postcard that we had used and what it

1 says on the back in here, and it suggests how they may
2 use it in their program as part of a way to help
3 smokers cut down on the amount that they smoke, until
4 they eventually wean off cigarettes, or as a way to
5 help them stop completely or to prevent relapse.

6 And again, we're looking to not put this in
7 a box. It's suggested it can only be used in this
8 manner, but to provide them with the tool and let them
9 utilize the tool in the way they see fit with their
10 different type of program that's out there. Because
11 there's many different types of programs out there to
12 help people to quit.

13 MR. LUFKIN: Let me offer another perspec-
14 tive on this. When we conducted our 500-patient
15 clinical trial at the University of Medicine and
16 Dentistry in New Jersey, the FDA encouraged us to use
17 this drug in conjunction with an intensive support
18 program. Their thought being that a smaller number of
19 patients, an intensive support program, would result
20 in more people/patients quitting and as a result, a
21 better showing of efficacy in drug versus non-drug
22 users.

23 Our clinical investigatory, Dr. Norman
24 Hymowitz, he basically declined that advice. His
25 thought was -- and frankly, we do support him -- was

1 that we were trying to mimic the actual consumer use
2 situation of someone going into a drugstore, buying
3 something and walking out the door with it and never
4 having any professional support.

5 Because out in the real world out there, not
6 everyone who wants to quit smoking is going to go
7 through the formality of a program. Some people want
8 to do it themselves, and so the way we set up this
9 trial was to basically try to replicate the situation
10 of someone going into a drugstore, buying a drug and
11 walking out the door.

12 As a result, as Dr. Wright pointed out, with
13 the intent-to-treat analysis the statistics killed us,
14 but as Dr. Hymowitz pointed out in his paper, when you
15 look at this from a user's point of view, when you
16 actually use the product, then you have a statistical-
17 ly-significant probability of quitting.

18 So what we're wrestling with is definition
19 of efficacy. On intent-to-treat we got shot; without
20 it, we seem to be effective.

21 DR. FEY: Let me also point out that even in
22 the product that we put together that's in your
23 packages, we -- and for people who came to us directly
24 for help -- we use the *National Cancer Institute Guide*
25 *For Quitting* as an accompaniment, and we essentially

1 modified that guide, the guide to quitting, with, when
2 you have an urge to light up, use a lozenge instead,
3 and that will help you to overcome this urge that you
4 have to light up and smoke.

5 MS. FALKOWSKI: Yes, I'd like to ask, did
6 you collect any data on type of cigarettes smoked,
7 whether it's menthol or non-menthol?

8 DR. FEY: Yes, Dr. Hymowitz did do this, and
9 I believe he's in the process of publishing a paper on
10 that particular issue. I don't have anything here to
11 present to you. I think that his orientation more was
12 among minorities -- particularly Blacks -- and how
13 they tend to smoke a much higher percent of menthol-
14 type cigarettes than other minorities or the majority.
15 But indeed, the one thing that did come out is that
16 Blacks found lozenge to be far more aversive than
17 whites, which was totally unexpected.

18 MS. FALKOWSKI: Which could simply be a
19 reflection of brand choice, other than anything --
20 with race. Okay.

21 DR. FEY: That's possible, right.

22 CHAIRMAN SCHNEIDER: Go ahead, Doctor.

23 DR. KHURI: Before my general comments I
24 wondered what the experience now in Europe is with
25 this. What's going on with this medicine in Europe?

1 DR. FEY: I wish I would answer that,
2 because I don't have a lot of knowledge about what's
3 going on in Europe. I've not spent a lot of time,
4 effort, and resources -- I don't have a lot -- to
5 monitor what's going on in Europe. I can only assume
6 that -- the product that they had was a chewing gum --
7 it's still being sold in Europe and used.

8 But in my mind the chewing gum was not the
9 right kind of vehicle because it's a matter of a lot
10 of silver acetate which is not being bathed in the
11 mouth and used where the drug is supposed to be used,
12 and it's swallowed down into the gut where you don't
13 want it to be. And so I have not particularly
14 followed what is happening in Europe.

15 DR. KHURI: Just also a general comment.
16 That as most of us in this room know, the addictions
17 are very tenacious behaviors and/or diseases. And
18 increasingly we accept partial success -- a decline in
19 drinking days for example, rather than total absti-
20 nence -- of course, ideally in a general program with
21 many other aspects to it.

22 But people often decide to give up their
23 addiction impulsively, and the timing is all. You get
24 them right then and there. So even a decline in the
25 number of cigarettes per day, or the number of days

1 without cigarettes -- for whatever motivation -- could
2 be extremely useful in this.

3 Another general comment. In comparing it
4 with disulfiram or naltrexone, these indeed -- well,
5 disulfiram is an aversion therapy; naltrexone is not.
6 My anesthesiologist patients who are opioid addicts do
7 not get sick, they just don't feel the effect of an
8 opioid.

9 On the other hand, I have patients that like
10 to drink through their disulfiram; they like the head,
11 for whatever peculiar reasons. So none of these are
12 fully successful I would say -- with zero success at
13 21 days is my point.

14 DR. FEY: Well, I remember --

15 DR. KHURI: I mean, zero stoppage, positive
16 success at 21 says.

17 DR. FEY: I specifically remember the words
18 of former Surgeon General Koop who basically said that
19 this is a very terrible addiction, and his advice out
20 there for smokers was, if you try to quit and fail
21 that's fine. Keep trying, don't stop.

22 Eventually you will settle upon that method,
23 that program, or that time in your life when you'll be
24 able to quit. And we believe that this particular
25 product just offers another option out there to help

1 smokers where they couldn't be helped otherwise.

2 The testimonials that we've gotten back from
3 some smokers are that they love this product and it's
4 the only thing that has helped them to quit. But I
5 would venture to say that it's a very small percentage
6 of the overall people out there who try to quit. This
7 is a modest treatment program; it's not a miracle
8 cure.

9 MR. LUFKIN: Conventional treat approaches
10 to smoking cessation using drugs have focused on
11 nicotine replacement. Our perspective is maybe a
12 little different. We're looking at the, what do you
13 do with your fingers aspect of habituation, rather
14 than nicotine replacement. And as a result, people
15 who use this we believe, this will be a tool for
16 people who are less nicotine-dependent and more
17 fidgety-dependent. And again, the perspective is to,
18 what does this do? It physically forces you to put
19 the cigarette down.

20 DR. LONGMIRE: Dr. Fey, what is your
21 experience with nicotine gum? Can the product be
22 taken with a nicotine gum, or is it the nicotine
23 itself that causes the bad taste?

24 DR. FEY: We had done a very small study
25 with a small medical practice in which they had

1 patients use nicotine chewing gum and also the
2 lozenge. And had a very small result which again, is
3 difficult to extrapolate anywhere since there's no
4 statistics or anything else.

5 And indeed, they found the combination of
6 the product very helpful, and we submitted that data
7 to the Agency. It's part of everything that indicates
8 that this lozenge has its place. Again, not a miracle
9 cure, but it has its place out there and should be
10 back in the public domain to help people.

11 CHAIRMAN SCHNEIDER: Dr. de Wit.

12 DR. de WIT: I think the efficacy data is
13 disappointing, and I think like with any aversion
14 therapy the problem is that the people are not so
15 likely to take the lozenge. I think this product has
16 a unique place in smoking cessation in relapse
17 prevention.

18 That is, once people have succeeded in
19 stopping, that they could use the lozenge when they
20 feel an urge to cigarette, and we don't have any
21 pharmacological treatments for relapse prevention, and
22 it's the major problem in smoking cessation and in
23 fact, in any substance abuse treatment.

24 So I would encourage you to -- I know it's
25 a whole separate study and I'm not sure the FDA has --

1 I'm not sure we have the mechanism in place to test a
2 relapse prevention agent, but I think this would be a
3 real unique place for it.

4 I think the problem that you're running up
5 against is that the people are unwilling to take the
6 lozenge once they've had the taste, if they're
7 actually still dependent.

8 DR. FEY: Yes again, let me point out that
9 most people are unwilling to repeat that response, but
10 there are some people who can use this and it will
11 help them -- a small percentage out there.

12 And what we've always told them on the
13 relapse prevention side is, once you experience the
14 lozenge, keep it with you. If you find yourself in a
15 social situation and you've decided to quit, and
16 you're not smoking but you find yourself in a social
17 situation -- perhaps among a group of friends and
18 people that are lighting up and smoking and you have
19 that urge to smoke -- use a lozenge instead.

20 And if you happen to smoke it will let you
21 know, it will remind you, and will prevent you for up
22 to a couple of hours, in not smoking. It will help
23 you to get over that hump, that particular urge at
24 that time.

25 CHAIRMAN SCHNEIDER: Ms. Cohen.

1 MS. COHEN: I had some questions if I may.
2 How did you pick your cross section of the population?
3 For instance, what did you determine was the amount of
4 cigarettes that a consumer was to use in order to
5 enter into your trials?

6 DR. FEY: Yes, this was -- first of all, we
7 were given guidelines by NIH to include minorities and
8 what was our program going to be in terms of minori-
9 ties. We had to have a certain number of representa-
10 tion in the study. And then we had a questionnaire
11 that was developed that basically defined how much
12 people would smoke, and that was used as a screening
13 criteria by Dr. Hymowitz in the study.

14 MS. COHEN: Did you verify, during these
15 trials, whether people started to smoke again?

16 DR. FEY: Yes. Dr. Hymowitz had the people
17 come in periodically on a regular schedule and had
18 given them a questionnaire to fill out to find out
19 whether they had smoked or not. Now, the way the
20 program was set up, if somebody had one cigarette
21 within the period of time that we were looking at them
22 over this 21 days -- and actually we went out to 28
23 days -- if they had one cigarette they were considered
24 a treatment failure.

25 The fact of the reality is, that smokers

1 normally don't quit like that. There are stops and
2 starts and stops and starts until they eventually
3 stop. But if they had one cigarette they were
4 considered a treatment failure in this particular
5 study. So the data you see reflected here includes
6 that as a failure.

7 MR. LUFKIN: But in terms of whether they
8 quit or not -- I think you're asking was the expired
9 CO₂ measured and the urocotinine measured?

10 DR. FEY: Yes.

11 MR. LUFKIN: There was objective measures.

12 DR. FEY: And the saliva cotinine.

13 MS. COHEN: This is not asked as a humorous
14 question, but is your lozenge so repulsive that people
15 won't use it?

16 DR. FEY: There will be many people who will
17 find it so repulsive they won't use it. But like
18 pain, pain is something that's remembered very
19 strongly in the mind. When you experience that you
20 try to avoid it. I think -- there are people out
21 there who will try to avoid this product, who will not
22 use it, and will go back to smoking.

23 There are people who are out there, if
24 they're motivated to quit and have tried this product
25 and remembered the experience that they had, will keep

1 it with them and will use it to help them to help
2 themselves to quit.

3 So you're asking, how do you define that,
4 it's very difficult to define that particular issue.

5 MS. COHEN: I looked at your package and I
6 see that it's sugar, corn syrup, etc., etc. What
7 about for diabetics, and have you tested this in
8 relationship to other medications that people might be
9 taking?

10 DR. FEY: We have not done any tests, per
11 se. We have done a literature search and we have not
12 found it contraindicated with anything else. But
13 specifically for diabetics, we've had that question
14 asked of us a number of times. We do not have the
15 resources to -- and we can develop another product
16 that would be a sugar-free-type product -- but we do
17 not have the resources.

18 We're just trying to get over the hurdle of
19 getting this back into the marketplace at this point
20 in time, and we need some help. We need financial
21 help, we need technical help, and quite frankly, if we
22 don't get some help, this is all going to be a moot
23 issue and the public will not see this product again.

24 CHAIRMAN SCHNEIDER: The Chair has a couple
25 of questions; one to follow up. What's the caloric

1 content?

2 DR. FEY: Oh, it's I think nine grams, so
3 we're talking very minor caloric content. It's a
4 lozenge, so -- I forget but the caloric content is
5 very minimal. Fifteen calories of lozenges or so.

6 CHAIRMAN SCHNEIDER: To follow up on Dr.
7 Fey's comments may I ask, has this been used with
8 chewing tobacco users?

9 DR. FEY: Yes, unfortunately it doesn't do
10 anything.

11 CHAIRMAN SCHNEIDER: Therefore, that answers
12 your question really, doesn't it? It's the smoke
13 apparently --

14 DR. FEY: It's the smoke --

15 CHAIRMAN SCHNEIDER: -- rather than the
16 tobacco, per se, that is interacted with.

17 DR. FEY: The theory is that's it's reacting
18 -- the silver ions that are in the mouth, being bathed
19 in the mouth as silver ionizers in the mouth -- as
20 you're sucking react with sulfur-containing volatiles
21 in the smoke. Sulfur-containing volatiles are
22 ubiquitous and occur with other smokes as well, such
23 as marijuana and possibly crack-cocaine, although
24 we've never done a crack-cocaine study.

25 So this reaction will occur with other

1 smokable drugs as long as there are sulfur-containing
2 volatiles there, and they usually are present. So it
3 provides us with a vehicle, a way to obtain a repul-
4 sion or an aversion to that particular smoking
5 process.

6 CHAIRMAN SCHNEIDER: Dr. Strain.

7 DR. STRAIN: I have a question actually to
8 Dr. Wright, about naltrexone. When naltrexone was
9 going through the approval process, do we know what
10 the determination of efficacy was for those trials and
11 can we learn anything from that experience that might
12 be useful here?

13 DR. WRIGHT: Yes, the -- that's one of the
14 reasons why we brought this back to the committee. At
15 the time that naltrexone was approved, the original
16 indication for naltrexone was to block the effects of
17 exogenous opioids. It was not an addiction treatment
18 indication and it was not tested or proven effective
19 in the treatment of addition -- although it has
20 subsequently shown itself to be useful in select
21 patient groups -- but not in general, opioid-dependent
22 patients.

23 And that bothered me because we set a
24 standard for smoking cessation because of the need to
25 have a common, level playing field among a variety of

1 products; that you had to meet an initial recommenda-
2 tion by the Advisory Committee of quitting for one
3 month. I mean, it wasn't any more sophisticated than
4 that.

5 We've fancied it up since then -- we've
6 added intent-to-treat analysis and verification and
7 other things -- but the original statement by the
8 committee was that to be something other than a fraud,
9 a smoking cessation product should help enough people
10 quit for a month to be worthwhile.

11 And it's not clear to us -- and it wasn't
12 clear to us through the whole history of working with
13 this product -- that as it does not treat withdrawal
14 to our knowledge, in any way, whether the treatment
15 standard -- stop smoking for a month -- was in fact
16 the proper standard for this product or whether the
17 proper standard is a cigarette repulsiveness standard.

18 You know, does this actually make your
19 cigarette taste bad when testing in a rigorous,
20 scientific way. And is it valuable in relapse
21 prevention, as has been raised by one member of the
22 panel.

23 So one variant of the questions that we
24 asked you, and in fact inherent in the first question
25 is, is it reasonable to hold this product to the quit-

1 for-a-month standard that we have for the nicotine
2 products given its mechanism of action and presumed
3 mode of effect? And we don't know.

4 DR. STRAIN: A question, perhaps both to Dr.
5 Wright and Dr. Fey. First Dr. Wright. Again,
6 naltrexone but now switching gears for alcoholism.
7 Was one of the things that came out of the two studies
8 -- the Volpicelli and O'Malley studies -- one of the
9 things noted was that there was decreases in craving
10 for alcohol. Was that considered a primary outcome
11 measure in the approval for naltrexone in alcoholism?

12 DR. WRIGHT: It was considered --

13 DR. STRAIN: Or could craving be considered
14 a primary outcome measure?

15 DR. WRIGHT: There's no intrinsic objection,
16 although there's not a tight linkage between self-
17 reported craving and actual use of drugs in many
18 settings, so it's a tricky outcome measure.

19 What was operative in the Revia approval was
20 documented evidence of improvement for the patients in
21 a whole variety of outcome measures. In the compli-
22 ance-enhanced setting -- because over time Revia has
23 not shown itself to be particularly useful if you're
24 not enhancing compliance in some way, usually by good
25 concurrent behavioral therapy -- you saw improvement

1 in liver function tests, you saw decreased drinking
2 days, you saw decreased general use of alcohol, you
3 saw decreased day sampling alcohol.

4 So there were a variety of things that all
5 got better. Craving was, I believe, a secondary
6 measure. I'd have to check the record, though.

7 DR. STRAIN: Have you looked at craving at
8 all? Some ratings of craving?

9 DR. FEY: No sir. My background is in the
10 food industry, having studied up at Cornell University
11 where I got my Doctorate. But my approach to this has
12 been through taste and aversion, and to rate this on
13 what I've learned and that is, a taste test and scale.
14 But we've not looked at craving, per se.

15 DR. STRAIN: At first I thought part of the
16 problem here was that you were having differential
17 dropout, but that's not the case; at least in your
18 large study, your 500 population study.

19 DR. FEY: Define differential dropout.

20 DR. STRAIN: Well, that you had more dropout
21 from one of your conditions rather than the other, but
22 in actuality it looks like you had very similar rates
23 of -- at least to study visit 3, which was four weeks
24 into treatment?

25 DR. FEY: Visit 3 was three weeks, and 3A I

1 believe was four weeks -- 28 days, yes.

2 DR. STRAIN: So you had actually -- it
3 wasn't a case that you're having higher rates of
4 dropout in the placebo group because it doesn't work,
5 for example. And they're recognizing that placebo
6 because they smoked and they don't notice any differ-
7 ence.

8 DR. FEY: Let me just --

9 DR. STRAIN: Both are staying -- a little
10 over 50 percent of the populations are staying, right?
11 So what you've actually got in terms of the current
12 efficacy considerations is simply a power problem,
13 right? I mean, you've got an insufficient sample size
14 to detect a statistically significant difference that
15 you found a trend for, am I right?

16 MR. LUFKIN: Using intent-to-treat.

17 DR. STRAIN: Yes.

18 DR. FEY: But I'm not --

19 MR. LUFKIN: That's the key.

20 DR. FEY: I'm not quite sure because -- let
21 me say this. That we were asked to make the placebo
22 taste very similar to the active. The active has a
23 slight medicinal taste to it, a slight, bitter taste.
24 So we had to go back and add quinine to the placebo to
25 make it taste bitter in and of itself. So the spread,

1 the difference between the two was lessened and not
2 enhanced, or not kept as large as it was, so that also
3 went against us in this particular study.

4 DR. WRIGHT: I'd like to raise a point at
5 this point and that is, this is another problem that
6 has concerned us mightily which is, the notion of
7 potentially overmatching of the placebo for products
8 like this. Because there are certain effects on the
9 clinical trials that take place when you start making
10 the placebo repellant. And it is a -- you can get, as
11 you might expect, depending on the relative palatabil-
12 ity of the product and the placebo, you can get quite
13 complex interactions in terms of the clinical trials
14 outcomes.

15 DR. FEY: Well, the other thing we wrestled
16 with that went against us in this particular study is
17 that we could not screen out and keep the integrity of
18 the double-blind. We could not screen out non-
19 tasters, so before we even started the study we were
20 about 20 percent -- having 20 percent of the people
21 going against us in the particular study because we
22 couldn't screen out those who were non-tasters.

23 DR. WRIGHT: And I need to ask a question.

24 DR. FEY: Yes sir.

25 DR. WRIGHT: Have you personally observed a

1 large number of people get the taste aversion re-
2 sponse?

3 DR. FEY: Yes sir.

4 DR. WRIGHT: Can that response be blinded?
5 Is there any way to --

6 DR. FEY: What do you mean, be blinded?
7 Blindfold blinded, or --

8 DR. WRIGHT: No. Is it an unmistakable
9 response?

10 DR. FEY: Absolutely.

11 DR. WRIGHT: You simply can't mimic that
12 with anything else?

13 DR. FEY: That's correct. It's like a light
14 switch. It's an on-and-off thing; you either see it
15 or you don't see it. And when you see it -- and
16 people are strong tasters -- it's obvious. You see by
17 the expressions on their face, by the reactions that
18 -- it's absolutely unmistakable and it's unique. The
19 taste is unique.

20 DR. YOUNG: I agree with one of the earlier
21 comments from the committee that there's a definite
22 place for adjuncts to relapse prevention. But in
23 looking at your preventive medicine study in '96, the
24 paper that reports on the 500-patient trial, it
25 strikes me that one of the most marked characteristics

1 is that nobody is using lozenge; that you've got 90
2 percent of the patients say they use the lozenge on
3 three or more occasions, but in general, patients in
4 neither group are using the drug, and the biggest
5 effect is a dropout from lozenge use.

6 And so unlike many other treatment condi-
7 tions where you know the patients in the group are
8 taking the drug, in this case you have a fair number
9 of patients who may be assigned to your treatment
10 product but take it once and never take it again.

11 And I wonder how you've chosen the 2.5
12 milligram dose. Is there a way to alter -- and this
13 is an unfortunate term, but -- the repellent nature of
14 the product in order to increase the likelihood that
15 a patient would actually use the product?

16 DR. FEY: There is a balance between the
17 amount of silver acetate used in this particular
18 product and the effect, and one must always balance
19 that effect. But to answer your question, your
20 initial question and that is, the further out you go,
21 the less you're going to see use of the product.

22 It's either going to work for them or it's
23 not. And if it's worked, they've quit. And if it
24 hasn't worked, they may carry it around and not use it
25 again.

1 DR. YOUNG: But it appears that what
2 happened for most of the patients in this study is
3 they quit using the lozenge --

4 DR. FEY: Right.

5 DR. YOUNG: -- rather than quitting using
6 cigarettes.

7 DR. FEY: Right.

8 DR. YOUNG: Is there a way to modify the
9 product to increase --

10 DR. FEY: I see.

11 DR. YOUNG: -- the likelihood that someone
12 will take a third lozenge and actually if they carry
13 it in their pocket, use it under those conditions
14 where you think it might be quite useful?

15 DR. FEY: And the answer is, yes, we could
16 have designed this product to taste better initially
17 so people would have more of a propensity to use the
18 product. However, you must balance the fact that you
19 don't want this product to be abused long-term.

20 We don't want them to ingest silver and
21 continue to do that, particularly children, because
22 the one side effect of this particular product over
23 long-term abuse, is argyria. And silver accumulates
24 in the body over time, so you don't want to make this
25 -- you don't want to design the product for people to

1 want to continue to use it.

2 You want to design it as an aversion product
3 that has a medicinal -- you want to clearly make sure
4 they understand it's a drug and it's medicinal, but
5 you don't want them to over-abuse the product.

6 DR. YOUNG: So your goal is a product that
7 -- if I were a user, in my first or second exposure to
8 the lozenge I will have such a bad taste from the
9 cigarette that I won't choose another cigarette?

10 DR. FEY: Yes, first reaction you will know
11 that this is a tool, you will know how to use the
12 tool, and that tool will be available should you need
13 to use it. Initially you may use that tool to help
14 you to cut down on the amount you smoke until you stop
15 completely.

16 You may choose to use the tool on a continu-
17 al basis for up to three weeks, safely, as a way to
18 prevent yourself from smoking. You may use the tool
19 to prevent relapse if you get in a particular situa-
20 tion. You may not use this tool continually over long
21 term. That's basically what we want to prevent from
22 happening.

23 MR. LUFKIN: Think of it as an available,
24 psychological crutch. It's something for someone who
25 really wants help and that help is available because

1 they want to use it themselves.

2 CHAIRMAN SCHNEIDER: Any urine tests or any
3 way to determine that they actually were using the
4 lozenge?

5 DR. FEY: None to my knowledge, since silver
6 accumulates in the body and it stays there. I guess
7 some of it is excreted out and can be studied. I
8 haven't even explored that option.

9 DR. WRIGHT: Let me ask a follow-on question
10 to that. What you're telling us that compliance with
11 this product may be detectable through either study of
12 saliva, urine, or feces. You just don't know at this
13 point?

14 DR. FEY: That's correct. And I'm sorry --
15 just for one second. I don't think I answered your
16 question sufficiently. If maybe you can help me to
17 try to get out of me what you're trying to get out of
18 it, I'd appreciate it.

19 DR. YOUNG: Well, let me let him go and then
20 I'll --

21 CHAIRMAN SCHNEIDER: Dr. Lloyd.

22 MR. LLOYD: In my experience with antabuse
23 -- dispensing antabuse and sale of antabuse -- most of
24 that is not volunteer use; most of it is enforced use.
25 And I was wondering if Dr. Wright might have some

1 historical perspective on antabuse approval through
2 the Agency, and is there any parallel in that? I can
3 see as I was trying to formulate some analogies here,
4 this would be like trying to blind the study for DMSO,
5 you know, very difficult.

6 DR. WRIGHT: I can give you some history on
7 the disulfiram approval. Disulfiram was a drug that
8 was kept on the market after the DESI reviews by the
9 National Academy of Sciences, and so it was not called
10 upon to demonstrate its efficacy using the modern
11 standards.

12 There was such historical literature on the
13 disulfiram reaction -- although often in higher doses
14 than currently recommended -- that no one questioned
15 that if you gave enough disulfiram to a patient and
16 they drank, they would get a disulfiram reaction.

17 So there was no fundamental doubt of the use
18 of the existence of the disulfiram reaction. There
19 has always been considerable controversy over the
20 effectiveness in clinical use in general alcoholic
21 populations of disulfiram -- for the reasons that have
22 been so ably stated today.

23 CHAIRMAN SCHNEIDER: I'd like to, unless
24 there's further questions of Dr. Fey -- poll the
25 committee so we can be specific in replying to the

1 questions that have been posed to us. How would the
2 committee suggest that the sponsor proceed with the
3 clinical trial design? Dr. Strain?

4 DR. STRAIN: Let me clarify. So is the
5 sponsor at this point, preparing to conduct another
6 clinical trial? Is that the implication?

7 DR. WRIGHT: Let me take a crack at that and
8 then Dr. Fey can take a crack at it. If the barrier
9 remains, quit for a month, intent-to-treat, probably
10 not. That may be too great a barrier to get across
11 for this product. I'm not sure that the resources are
12 available for 1000-patient clinical trial.

13 So from our perspective, we need advice on
14 how to advise him should he wish to do additional
15 studies. Then I believe it's up to you, Dr. Fey.

16 DR. FEY: Yes, I think I want to just point
17 out that we cannot continue to go much further than we
18 have. We have certainly had tremendous support from
19 the National Institute of Health, National Heart,
20 Lung, and Blood Institute. We certainly thank you for
21 allowing us to present here and we certainly thank you
22 for the comments that you've made at FDA and the help
23 that we've had.

24 We're essentially asking you to bring this
25 product back in the marketplace. I personally don't

1 see any good reason to hold it from the public domain
2 at this point in time. But I certainly do agree that
3 there's a lot more we need to learn about in using
4 silver acetate to help smokers to quit, and we'd
5 certainly encourage additional studies.

6 That's all I can say at this point in time.
7 The barrier has been rather substantial for us. We'd
8 like to continue with this product and continue to
9 help smokers quit. But I think that creating addi-
10 tional barriers to entry would be putting a nail in
11 the coffin for this particular product for us, unless
12 a champion out there would be willing to step up and
13 provide funding for additional studies.

14 DR. WRIGHT: I do have a question. Are you
15 able at this time, to make additional drug and placebo
16 available to individual investigators?

17 DR. FEY: Yes sir.

18 CHAIRMAN SCHNEIDER: Ms. Cohen.

19 MS. COHEN: Since the efficacy and the
20 temporary use of this is limited -- now, I'm reading
21 your label and I read labels very carefully and it
22 says, do not exceed 126 lozenges use -- why are you so
23 sure that this is going to be a deterrent to stop
24 people from smoking? Can you tell me that this has
25 stopped people from smoking?

1 DR. FEY: Absolutely. That was conducted in
2 the study. People were found to quit, using the
3 process.

4 MS. COHEN: And how long did you follow
5 them?

6 DR. FEY: They were followed for a total of
7 one year, and this was all done in accordance with the
8 Federal Register recommendations for conducting a
9 double-blind, placebo-controlled study which we
10 followed, and also with advice provided to us in
11 several meetings that we had with FDA as to how we
12 were to go about performing this study. We essential-
13 ly tried to do what we were told that we had to do.

14 MS. COHEN: And that in itself, worries me
15 a little bit coming from a consumer protection
16 background. That if we set out or they set out, all
17 the parameters that you're supposed to follow and it
18 doesn't work, what happens then? That to me, is a
19 little frightening myself. I think that -- I under-
20 stand what you said about being small and not having
21 the money.

22 DR. FEY: Well, wait a minute. The product
23 does work and it has worked in the testing that we
24 have done, but it has not produced zero cigarettes in
25 28 days, which was the criteria that we were to be

1 measured against. That's what we were able and
2 capable of doing -- we were told to.

3 We were not told to follow a track of
4 patients for four or five years and see what has
5 happened after that. I don't think anybody, including
6 the nicotine replacement products and the companies
7 that support those, were asked to do that. We've done
8 our best given the parameters that we've had to work
9 under, and are willing to try to do our best to
10 continue that.

11 DR. WRIGHT: Dr. Fey, it's probably good at
12 this point if you would have a seat and let the
13 committee discuss this issue. I think we can release
14 you.

15 CHAIRMAN SCHNEIDER: I think that's fine.

16 DR. FEY: I'd like to thank you all for
17 taking your time and energy and thank FDA for provid-
18 ing us with this venue.

19 CHAIRMAN SCHNEIDER: Thank you for the fine
20 presentation. I think that really takes us to the
21 second question and that would be: What should the
22 basis of approval be with this product?

23 What I'm hearing in contention is the 28-day
24 abstinence. Comments?

25 MS. FALKOWSKI: Yes, I think some good

1 points have been raised about, in looking at the
2 treatment of addictions, that we're starting to look
3 at them more in terms of reducing but not necessarily
4 eliminating the behavior.

5 But I also think -- and this really speaks
6 to the first question here, how would I suggest that
7 they proceed -- it's clear that they haven't had a
8 study that's under controlled conditions, where they
9 really have people and they can say, you take this
10 much of it this often and we'll compare it to people
11 who take an inactive product this much this often. So
12 to me that's what seems lacking.

13 It also strikes me that they haven't
14 controlled for a type of cigarette, which would have
15 an impact on its efficacy, depending on the brand, as
16 is suggested by another one -- I mean, just not brand
17 but menthol or non-menthol.

18 And then also I think there's a question
19 that's been raised -- and I don't know the answer to
20 it -- about if you have a placebo and if you have
21 something that's based on aversive taste as the
22 treatment, do you also have something that has a
23 similar taste as a placebo or do you have something
24 that has no taste?

25 I mean, you know, you're having something

1 with a taste -- and it's something that Dr. Wright
2 alluded to. So I don't particularly know what the
3 answer is, but I think these boil down to, what are
4 the significant issues in terms of future testing of
5 it?

6 I also don't know if you were to relax the
7 standard of zero cigarettes at 28 days, how that comes
8 to happen. I don't know the process for that.

9 DR. WRIGHT: I can answer that. We have an
10 adjunct to smoking cessation indication which we have
11 a zero at 28 days standard -- which we in fact, will
12 be forming a subcommittee of this group to address
13 over the course of this year because -- or at least,
14 that was the recommendation at the last meeting we had
15 -- because of some concerns about our intent-to-treat
16 analysis understating the actual in-use effectiveness
17 of these products.

18 We are free, and the committee is free to
19 recommend that we parse out a different indication,
20 such as was done for naltrexone, if you think that
21 that is clinically valid; that we are not promulgating
22 a sham by doing so.

23 CHAIRMAN SCHNEIDER: I've got to go back --
24 due respect, Dr. Wright -- and ask a question of the
25 sponsors. I am concerned about young people, and I'm

1 not quite sure what the term "young people" means and
2 to what extent this has been studied.

3 For instance, on secondary tooth develop-
4 ment, etc., in young people who might be asked by
5 their parents when they catch them behind the barn
6 smoking, to start taking these lozenges.

7 DR. FEY: Yes. We've not studied young
8 people, we've not discriminated among ages and done
9 any testing in that area.

10 Only to say that if this product were used
11 by a professional and a younger person would come to
12 this professional, and this younger person were to use
13 the product on a limited basis -- not abuse it -- that
14 this product would be fairly safe to use relative to
15 what's available out there -- that is, the nicotine
16 replacement product -- fairly safe to use to help them
17 to quit smoking.

18 So to that end, it depends on whether the
19 recommendation by the committee is for general OTC use
20 or for an Rx type of use among a professional prac-
21 titioner.

22 CHAIRMAN SCHNEIDER: The answer to my
23 question is, we don't know?

24 DR. FEY: We don't know.

25 CHAIRMAN SCHNEIDER: Okay.

1 DR. WRIGHT: I'm not completely certain
2 about that. There is extensive literature on oral
3 silver salts, I believe, but it is older, historical
4 literature. There were a variety of -- and you'll
5 have to help me, Dr. Fey -- were there not a variety
6 of oral silver medications, some famous, some in the
7 very historical period, infamous, that resulted in our
8 conducting a lot of toxicology testing on silver?

9 DR. FEY: Yes, absolutely. And that's part
10 of the literature review that was done on the safety
11 of silver salts.

12 DR. WRIGHT: So the sponsor has not done
13 clinical testing of silver, but it would be premature
14 to say that we do not have that knowledge.

15 CHAIRMAN SCHNEIDER: All right. Thank you.
16 Any other comments from the committee? Yes, go ahead.

17 MR. LLOYD: Having no experience in design-
18 ing any kind of clinical studies or trials or whatev-
19 er, and at the risk of being very non-traditional
20 here, is there any possibility that a provisional
21 approval could be looked at, with like an automatic
22 sunset on it, lacking any substantiating clinical
23 evidence, at a specific time?

24 CHAIRMAN SCHNEIDER: Let me raise the --
25 well, go ahead.

1 DR. WRIGHT: No.

2 CHAIRMAN SCHNEIDER: My question would be,
3 how do you put these limits and who is going to do the
4 studies to --

5 MS. COHEN: Who's going to monitor them?

6 CHAIRMAN SCHNEIDER: Yes, monitor it as Ms.
7 Cohen has said. Dr. de Wit.

8 DR. de WIT: I think we're coming up against
9 a lot of the same problems that we saw with disulfiram
10 and in fact, the controlled study comparing to a
11 placebo, in that disulfiram does not differ from a
12 placebo treatment when it's done in a properly
13 conducted trial.

14 On the other hand, I think there is room for
15 additional controlled studies with this product, and
16 I think it really shows potential for efficacy if it's
17 done in conjunction with a rigorous, behavioral
18 treatment program in the same way that naltrexone was
19 used.

20 And I think it would also be fair to screen
21 out those people that don't taste the product. So I
22 think it would be reasonable to conduct another trial
23 with this product, and I think it shows a lot of
24 potential for efficacy. And if the treatment program
25 was designed around the strengths of this product, I

1 think it has real potential to meet our existing
2 criteria for efficacy.

3 CHAIRMAN SCHNEIDER: I think this really
4 gives us an answer to question 1 and I appreciate
5 that.

6 DR. STRAIN: Let me follow up then. Yes,
7 that was very nicely put, Harriet and I agree with it.
8 I think that then, I would put forth that I don't
9 think we need to use necessarily, the same standards
10 that have been used for the nicotine replacement
11 products.

12 I think that we should maintain flexibility
13 to consider, especially for -- if this were another
14 nicotine replacement product I'd say okay, let's keep
15 it consistent, but we're talking about a product for
16 smoking cessation that we don't have an analogous
17 product that we can use an historical basis to make
18 our decision about how to determine efficacy. So I
19 think that we should remain open and flexible to it.

20 Let me also say -- and I certainly have
21 heard the comments of the sponsor today and their
22 concerns about the size of their company and their
23 ability to continue much longer in this, and it
24 certainly tugs at my heart.

25 At the same time, I think that we need to

1 ask, what would we be saying here if this were Glaxo
2 or some or other large company coming in? I think
3 that we probably would be saying, okay, you've got
4 something interesting and exciting here and these are
5 our standards.

6 And I think we need to maintain those
7 standards for what we'd like to see. And we can't
8 adjust those standards based upon the resources of the
9 sponsors. It's just -- I think that's a dangerous
10 situation to get into. And that should not be what's
11 governing our decision about what we expect to see.

12 DR. WRIGHT: I would like to second that.
13 I can assure you that if the "we're small and we're
14 broke" strategy was effective, you would see a large
15 number of venture capital spinoffs, each coming
16 forward with a balance sheet in one hand and a pan in
17 the other saying, if you put an approval in this pan,
18 Mikey will have shoes. And there is a real risk of
19 that.

20 CHAIRMAN SCHNEIDER: Yes, I think we have to
21 look at our responsibility and as I perceive it, it's
22 to protect the public in two ways: one, to protect
23 them against products that may be harmful or have no
24 efficacy; at the same time getting products to them
25 that are helpful and they are entitled to have. So

1 it's that fine line that we walk. But I think your
2 words are well-chosen.

3 Any other comments from the committee? Yes?

4 DR. YOUNG: I'll agree with Dr. Strain's
5 suggestion that the approval standards for this type
6 of product probably I don't think, need to be the same
7 as the standards for nicotine replacement product.

8 And I would encourage you to, instead of
9 looking at the 28-day cessation, especially when that
10 28-day -- when an individual is defined as a smoker
11 from a single cigarette during the period -- to
12 consider the possibility of looking at a reduction in
13 the number of cigarettes consumed per day, if there's
14 a way to objectively verify that, and/or reduction in
15 the number of days on which cigarettes are smoked, as
16 potential measures that might be useful for evaluation
17 of the usefulness of a product such as this.

18 DR. WRIGHT: Let me press you a little bit
19 on that, Doctor. If someone were to conduct adequate
20 and well-controlled trials -- predominantly of a
21 clinical, pharmacology nature such as were used for
22 naltrexone for opiod dependence -- demonstrating the
23 dose, the effective dose, the genetic polymorphism,
24 the duration of the effect, the choice of different
25 kinds of cigarette to look at the effect of brand

1 difference, and showed that there was a blocking
2 effect that had these parameters, and then a subpopu-
3 lation of smokers, either in a relapse-prevention
4 strategy or in combination with a nicotine replacement
5 strategy, showed that in clinical use there was a
6 population of benefit, would that meet your criteria
7 for approval?

8 DR. YOUNG: Of approval for the product as
9 an adjunct to other smoking cessation interventions.
10 I think at this point in our knowledge that would be
11 a useful product to have available, so given adequate
12 safety -- if the product was a product that didn't
13 have considerable health risks associated with it, I
14 would say yes.

15 But I think you have also focused on a
16 variety of ways in which the existing clinical trial
17 that was published in Preventative Medicine -- the
18 sponsors are almost fighting themselves because it
19 seems they don't know whether or not every patient --
20 every subject assigned to the lozenge group actually
21 used the lozenge.

22 You don't know how much lozenge the person
23 used so you don't know the dose assigned, and there
24 was a, I suspect, overly stringent criteria used to
25 identify you as a smoker, a single cigarette.

1 DR. WRIGHT: See, there are --

2 DR. YOUNG: Of course, you don't know who
3 takes --

4 DR. WRIGHT: There appears to be three
5 parameters that we wrestle with in these trials -- in
6 general nicotine replacement, smoking cessation
7 trials. How many of the patients actually quit at
8 all, ever? You know, perhaps as many as half of
9 patients who are recruited find they do not get
10 through as little as a single day without a cigarette.

11 How many people are quitting under treat-
12 ment? You know, if you are still giving them the
13 treatment how many of them are able to stay abstinent
14 from cigarettes under treatment?

15 And then there's the issue of, once they
16 stop the treatment, how long before they relapse to
17 their previous smoking behavior?

18 DR. YOUNG: But there's also -- you're using
19 the word "quit", and I think with a product of this
20 sort it may be useful to look at reduction in number
21 of cigarettes used, reduction in number of days
22 smoking, rather than an absolute yes/no, the individu-
23 al is quitting.

24 But that assumes that you can objectively
25 verify; that you're studying the product under

1 controlled-enough conditions that you can objectively
2 verify whether or not there actually was -- first, how
3 many cigarettes were you smoking prior to onset of
4 treatment, and then was there an actual change in the
5 number of cigarettes or the frequency -- the number of
6 days on which the product, the cigarettes are used.

7 CHAIRMAN SCHNEIDER: Let me jump in at this
8 point -- we're running out of time -- but the thing
9 that bothers me is that this product can only be used
10 for a limited amount of time.

11 So that what happens then if the person
12 hasn't quit but has just reduced their smoking at that
13 point in time, or when they run out of time, abuse of
14 the lozenge. Knowing how tobacco works a little bit
15 and how the behavioral aspect of it is, my concern is,
16 then what?

17 Have we answered the questions, or have we
18 just posed more questions? I shall read the questions
19 again, at request. Question 1: How would the commit-
20 tee suggest that the sponsor proceed with the clinical
21 trial design? I think we've answered that. I think
22 that that has -- am I correct?

23 DR. YOUNG: Yes.

24 CHAIRMAN SCHNEIDER: Any other comments on
25 that question? Second question is: What should be

1 the basis of approval with this product? And I think
2 that's what we were just debating a second ago. My
3 concern is that yes, I think it's a neat product and
4 -- this is an editorial I suppose I shouldn't be
5 doing, but I'll do it -- that I think that, while
6 being used it's going to have, for 80 percent of the
7 people using it who continue to use it during that
8 period of time -- probably an excellent deterrent.

9 What happens afterwards of course has been
10 raised, and you've looked at one year. And my concern
11 is that if it's going to be efficacious, certainly
12 it's got to be used in conjunction with some other
13 behavioral modification or educational methodology.

14 Any other comment on this question? Then
15 question number 3: If approved, how should this
16 product be used? And I think I just talked about that
17 a little bit. Any other comments about that question?

18 Again, I thank you for your presentation,
19 and we stand adjourned for 15 minutes.

20 (Whereupon, the meeting of the Drug Abuse
21 Advisory Committee, Open Session, was concluded at
22 10:15 a.m.)

23

24

25