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DRUG ABUSE ADVISORY COMMITTEE

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Building A, Lecture Room C
Uniformed Services University
of the Health Sciences
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Bethesda, Maryland

P A R T I C I P A N T S

Sidney Cohen, M.D., Chairperson

Reese T. Jones, M.D.
Jo Ann Nuit, Ph.D.
Donald W. Goodwin, M.D.
Robert L. Balster, Ph.D.
Don Phillips, P.D., M.P.A.
Stanley Wallenstein, Ph.D.
Donald R. Jasinski, M.D.
Mitchell B. Balter, Ph.D.
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FDA STAFF:

Frederick J. Abramek, M.S., Executive Secretary

Paul Leber, M.D.
Edward Tocus, M.D.

C O N T E N T S

P R O C E E D I N G S

DR. COHEN: I think we will begin. There are two Committee members not yet present. We have given them 10 minutes to find their way through this new installation, which we are very pleased to meet in, and so I will call the meeting to order now, and welcome you to this, the 13th meeting of the Drug Abuse Advisory Committee.

My name is Sidney Cohen. I am from Los Angeles and I am Chairperson of the Committee. The last time I spoke with you, I said "for the last time," and this, I again say, "for the last time," without possibility of contradiction.

DR. BALSTER: Do we have to thank you again?

(Laughter)

DR. COHEN: Will the staff and the Committee members identify themselves?

DR. TOCUS: Ed Tocus, Chief of the Drug Abuse Staff, FDA.

DR. LEBER: I am Paul Leber, Director of the Division of Neuropharmacological Drug Products from the FDA.

DR. VOCCI: I am Frank Vocci. I am a pharmacologist from the Drug Abuse staff.

DR. JONES: I am Reese Jones from the University of California, San Francisco, psychiatrist, doing clinical pharmacology.

DR. BALSTER: Bob Balster, Pharmacology Department,

Medical College of Virginia, Richmond.

DR. BALTER: Mitchell Balter, National Institute of Mental Health, Chief of Applied Therapeutics and Health Practices Program.

DR. NUIT: Jo Ann Nuit, Pharmacologist, N.B. Associates.

DR. GOODWIN: Don Goodwin, University of Kansas, Department of Psychiatry.

DR. PHILLIPS: I am Don Phillips, pharmacist for the Arkansas Department of Health.

DR. WALLENSTEIN: Stan Wallenstein from Memorial Sloan Kettering, psychologist.

MR. ABRAMEK: I am Fred Abramek, the Executive Secretary for the Drug Abuse Advisory Committee.

DR. COHEN: Mr. Abramek, you have some comments to make. Why don't you go ahead and make them?

Don Jasinski has arrived from the National Institute of Drug Abuse.

MR. ABRAMEK: I ask your indulgence while I make a few announcements. First of all, thank you all very much, and special thanks to members of the Advisory Committee for being able to come back into town so soon. As Dr. Cohen indicated, we had said our goodbyes about a month or so ago, but it is good to see you again, and thank you very much for adjusting your schedule to accommodate us.

This is my first experience with the room -- I hope I am heard in the back of the room and I hope that we can all be heard without the microphones -- it may be of benefit to our transcriber-recorder. However, it will make her job a lot easier if people who do come forth would address their comments into the microphone in back of me.

I have been advised that Drs. Anthony, Baselt, Pruitt, Rose, and Schoolar will be unable to attend this meeting. One additional comment about Dr. Paul, his wife is having a baby one of these days this week, so I am not sure whether his absence is because of that.

If anyone in the audience has comments to make during the open public session, again, if you would come forth and speak into the microphone in back of me -- however, make sure that the Chairman does address you, recognize you, and then state your name and affiliation.

I hope everyone did grab an agenda and the list of the members on the table at the rear of the room as they came in. Smoking also is not permitted in this room, and we ask that if you do need to smoke -- very ironic for this meeting --

(Laughter)

-- that you do so outside in the appropriate places.

Also, the cafeteria is in the next building, Building B, which is the building that probably most of you came

into, the building above the parking garage. I have made arrangements for us to use the cafeteria at any time for breaks, any time anyone wants to take a break, just leave, get your cup of coffee, come back, et cetera.

We also have arrangements for lunch if we are through here at that point in time. Since we are guests of the University, I would ask you indulgence, also, and assistance in helping me bus this room after the meeting. A reminder, also, that this is an open meeting and anyone may record the transcript of the meeting, with the knowledge that it is not official until such time as the Commissioner has approved the transcript.

At this point in time I am not aware of any member of the Committee who has any direct conflict of interest with any of the topics for this meeting. However, for the record, I would like to ask the question, are there any Committee members who feel that they have any potential or real conflicts of interest that I am not aware of at this time and who would prefer to make that known at this point in time?

DR. JONES: For the record, it is probably important to mention that there is some potential -- or at least the appearance of a conflict of interest in my case, in that a few years ago our research group at the University of California in San Francisco did receive some support from Merrell-Dow

for studies with Nicorette.

The data in those studies is not part of what we are considering today. We are no longer receiving support from them for any studies, though we are being supplied with some Nicorette chewing gum for other reasons, for other stuff. I in my own mind sort of balanced what I could contribute to the discussion versus the appearance of conflict of interest and decided that the balance was such that I had no personal problems with it.

The Committee, or the staff, may feel that it would be wiser that I not participate in the vote. I will leave that up to you for your decision.

DR. JASINSKI: Yes, I don't think it is a conflict of interest, but we have been studying nicotine and tobacco as a dependence process over the last few years and I guess about nine or 12 months ago we decided to investigate the Nicorette chewing gum.

Dow Chemical has supplied us with the gum and allowed us to cross-reference their IND -- it is a National Institute of Drug Abuse IND, there are no funds involved. So, we have been studying the Nicorette gum on our own, and they have cooperated with us.

I also now have a relationship with Dr. Jones, and that is that he is conducting his studies and we have a collaborative relationship to study the Nicorette chewing gum.

He is now currently going to study the Nicorette chewing gum under a collaborative study under our IND.

MR. ABRAMEK: I would like to make an additional comment that the Agency is aware of the participation of both Dr. Jones and Dr. Jasinski and has ruled favorably on their participation.

At this point in time I would like to then make a few remarks about the packet of information that was sent out to the Advisory Committee members and the confidentiality aspects of that. This will be for the benefit of all the sponsors or potential sponsors who may be in the audience.

This is what I call the Committee member review packet, and this is sent to the Advisory Committee members prior to the meeting of the Advisory Committee. They may include such documents as clinical reviewers' reports, the pharmacologist's review, consultants' review, some things which have been prepared in-house within FDA that may have participation from the sponsor; we may have participation from outside groups.

The information in the packet is such that we feel it must be known to the Advisory Committee members if they are to be knowledgeable about a particular subject. Such a review packet was prepared for this meeting. We occasionally get comments or requests from sponsors asking if they could in turn have a copy of this internal review publication.

We have checked with our legal people and been informed that all such reports which are prepared in-house, within Food and Drug, are considered to be interim internal agency documents from which no official position could be made. They are confidential in nature and they are not releasable.

We try not to be secretive, however, about the information which is sent to the Committee members. Agency personnel frequently meet with sponsors, we telephone sponsors and have phone conversations. We frequently commit things to writing between the Agency and the sponsors, some of these which may be addressed in various aspects within a Committee, Advisory Committee meeting.

There are times when such packets, however, do not contain this type of confidential information. At these times we are more than willing to give a sponsor a copy of what is sent out to the Advisory Committee members. On the other hand, such as this case, the packet contains information which is not releasable.

So, we hope that you will all -- and this is not intended for the Dow-Merrell, not specifically geared toward them at all -- it is just, hopefully, our way of letting sponsors know in the future that when we say no, that we can't release some information, we hope that you will understand our reason for doing so.

I would like to make one last comment, and the people from Dow-Merrell are aware of this. In case someone does have additional slides or will be presenting in the open public session, the pointer that we have is a laser pointer and I would just ask that everyone be sure not to point it toward any member of the audience.

(Laughter)

With that, though, I will then close my comments and turn the meeting back to Dr. Cohen.

DR. COHEN: Thank you. Dr. Leber, you had some remarks?

DR. LEBER: Yes, in the first place, I would like to explain why you are back here. I had given some very wise advice to a member of the Committee, telling him that there was no chance that we would be meeting again before Dr. Cohen left us -- that is when we all said such nice goodbyes. It is all my fault. I made a managerial misjudgment in predicting the future -- those happen often.

I was absolutely wrong. We are back here today, and I welcome you and, as a matter of fact, I am not so disappointed, because I think it actually turned out to be a very good idea to be back. That is the first point.

The second is that I would like to welcome you all personally. I think this should be an interesting topic to discuss. It certainly covers a spectrum of issues and I would

like to take advantage of my position as Director of the Division and the person in the end who implements and takes advantage of your counsel and advice and, finally, has to make a recommendation upon it, to deliver what I traditionally do, and that is called the charge to the Committee.

Now, a lot of people don't like being charged at or pushed, but I feel like I ought to do it for the record to try to clarify what kind of counsel information we want from you. Also for the record I would like to make it clear, perfectly clear, that we are well aware as a federal agency that there are very few people in our time who don't know there is a morbid risk associated with smoking cigarettes as a life-long habit, whether you are talking about lung cancer, cardio-vascular disease, stained teeth or fingers.

I think almost everyone is aware that something is bad about the habit. Indeed, I think anyone who bothers to read the cigarette package from which they draw their daily ration knows that the federal government has an official position warning you that it is not a wise thing to do, to smoke, it is not good for your health.

Unfortunately, we live in, I think, a real world where smoking, like overeating, as everyone on this panel knows, is a habit that is hard to break. Many people who claim they want to stop find it difficult to do so; in fact, they fail to succeed even though they claim to have tried time and

time again.

Others, who have succeeded in stopping smoking, obviously lapse, just like people who overeat too much. Thus, being against smoking and trying to find an effective means to encourage smokers to stop smoking is, I think, a bit like being in favor of God, flag, apple pie, and everything good at a Fourth of July celebration in a small hometown in the 1940's.

DR. COHEN: You forgot motherhood.

(Laughter)

DR. LEBER: Motherhood, yes.

I don't see how anyone could possibly think that we are not concerned as a federal agency about smoking. We would like to do what we can to get people to stop smoking in the interest of the public health, and I think as a physician I also share that view independently.

Unfortunately, and this is where the hooker comes, merely wanting to find a treatment for something does not mean that one has a treatment. Furthermore, and this is probably more apropros of today's discussion, even because one claims to have a treatment that is logical by scientific and medical rationale, that even has a pathophysiologic explanation for its mechanism of action, that is not enough under our federal system of laws to allow the marketing of a drug product.

And that is more precisely why we are here today.

Merrell-Dow has submitted a new drug application for a product which consists of a resin-bound buffered nicotine-containing chewing gum which they claim, when used under the directions that we will write some time in the future, will increase the chances of a smoker who is determined, in quotation marks, to stop smoking, to indeed stop smoking.

Now, this kind of a claim without further elaboration and explanation begs a very critical definition of what we mean by, quote, stopping, close quote, smoking. Now, stopping is, we would think, a pretty straightforward word, but I think it actually has a lot of different interpretations and meanings.

One of the things we had to do as a Division before we could even assess the information in front of you today is to set up an operational definition of what it means to stop smoking. Now, one of the important inputs from the Committee is do you agree with the operational definition that will be discussed later that we have used in evaluating the data?

Because, otherwise, we have an undefined term which means nothing. So, one of the things I would like to get your specific comments on in the process of answering the single question we have raised is, is our outcome definition of stopping appropriate? Is it a wise one and is it a valid one?

Now, another point that is critical and I think possibly controversial is that we are in an unusual situation, for a drug, in quotation marks..

Nicotine, the presumed active component of the gum, is itself what we would call a toxic substance; that is, it is pharmacologically active and produces effects on the normal body system in most people that most reasonable persons would conclude is not good for you. In short, most physicians would recommend that individuals shun the casual use of nicotine.

The Agency understands this. It also believes that most people who smoke cigarettes obtain not only nicotine, but nicotine plus other nice "bennies" like ionized air, coal tars, smoke, and a variety of other phenomena, and I guess we have made an implicit, and I am now making explicit, judgment that it is better to obtain nicotine for a short period of time within the structure of the labeling that we will write, from a gum than from a cigarette, if that is the quid pro quo, presuming, of course, that you can get the same amounts of nicotine and that you do not smoke during that period.

Another point that you have to address as a Committee -- and I think before I go on that I would certainly like your opinion of that expressed in today's discusssion -- another point, I think, is the discussion, of course, of evidence. Our laws say very clearly, our regulations, that before you as experts can conclude anything, that you must have looked at evidence obtained from what are called adequate and well-controlled investigations that allow you fairly and reasonably to conclude that the product will do what it claims it is going

to do in the labeling, again, that we will eventually write.

Now, you are allowed to do this in part on the basis of what we have defined in the past as adequate and well-controlled investigations. And our regulations, which are in front of me, specify a whole list of things that you can go through to test whether or not a trial is adequate and well controlled.

This is an issue that is easier solved in the prospective than it is retrospectively, and for reasons that will become clear in the discussion, this became an issue and, again, we would like you to listen to our internal decisionmaking process on this issue, because it is critical for the record that we understand that the approval of this product is based on adequate and well-controlled investigations.

Also, this has to allow a quantitative estimate of this difference between treatments, the evidential base on what you are going to be dealing with. There are going to be other things the Agency wants to determine about this product before it is actually marketed, so I want to carefully distinguish between the question that we have posed to you today; that is, specifically, do you think the evidence in the clinical studies before you persuades you that Nicorette will aid people to stop smoking in the behavioral programs that were used, as distinct from whether or not you want to have the application for Nicorette gum approved.

Approval is still the process that is reserved to the Agency, so even though you may privately believe that we ought to approve the application, we still have other things to satisfy, labeling and certain other issues that we will negotiate, if your guidance is that you think the product works and is safe.

Now, I will tell you this at the outset. The Division of Neuropharmacological Products and its statistical consultants, which represent the level of the Agency that has assessed the data to this date, is preparing to conclude, is the best way I can put it, that the evidence presented by the sponsor has been obtained from adequate and well-controlled investigations -- emphasis on plural -- and the evidence supports, beyond the vagaries of chance, that Nicorette does enhance the quit rate among smokers trying to stop smoking and seek -- and I think that is our bottom line, and that we would really like your specific advice and counsel on whether we are corret. We are preparing to make this decision, and obviously we would like your input on that, and that is really the bottom line.

Now, you should be aware that we were not initially of this opinion; in fact, we earlier refused to accept the filing -- not officially the filing -- but we refused to approve this NDA when it was based on studies that actually provided fairly good evidence, but the studies themselves failed to meet our fairly, I think, demanding standards for adequate and

well-controlled investigations, and the Committee is aware -- I suggest you look at the nonapproval letters -- of what some of the reasons were that we turned down two of the studies which we would now view as supportive and perhaps with further elaboration that cannot be presented today, because we don't have time to do it, perhaps also may come up to the standards of some of the studies discussed here.

We had just simply chosen a different route to go with the firm, that having turned it down, we agreed that we would prospectively try to look at two studies, one in progress at the time, conducted by Drs. Russell and Jarvis and their associates, and the other, that I think was also in progress, that we could have more input into the actual outcome and planning of, a study conducted by Dr. Christen at the Indiana Dental Clinic.

These two are the major source of evidence that we wish to discuss today; there is other evidence available, but we would like your opinion specifically on those. Certainly anything else is open for discussion. Our analysis of the strengths and weaknesses of the evidence and how we reached our conclusions about it is going to be the subject of various presentations made by FDA staff; that is, Drs. Vocci and Dassler will discuss the clinical evidence, and Dr. Marticello from the Division of Biometrics is going to discuss how we went through our statistical modeling and analysis of the evidence

to reach our conclusions.

Following that, I think you will have a chance to hear your own Committee discussants. One final word, I don't think these are as trivial or easy decisions as I might have thought not so long ago. In properly placing the FDA's imprimatur on a toxic product of dubious worth would certainly not be in the interest of public health.

Therefore, it is very critical that you, as our advisers, certify to us that you think we are doing the right thing -- more than think, that you are willing to vote that we are doing the right thing. Now, remember, there are other things that are to be involved before the product is approved, but on the basic issue where you are truly experts, whether this will aid in people stopping smoking, we want your advice.

With that, I would turn the Chair and the meeting to our able Chairman, Dr. Cohen.

DR. COHEN: Thank you. Ed, do you have some remarks?

DR. TOCUS: Yes. This, the 13th meeting, represents another facet of the activities of the Drug Abuse staff and the involvement of this particular Committee. The Committee started as the old Psychotomimetic Advisory Committee and then became a Drug Abuse Research Advisory Committee, and at one point we had two committees, the Drug Abuse Research and a Controlled Substances Advisory Committee, and those were combined and became the Drug Abuse Advisory Committee.

We have done a lot of the investigations and we have gotten a lot of advice from this Committee on the research. We have gotten a lot of advice from this Committee on controlled substances. Rarely have we come to you for this type of an evaluation and decision, but this is the third facet of our activites in the Drug Abuse staff.

You might -- I would just like to put for the record that this product, and we have alluded to the nicotine-containing chewing gum as a drug, we at the Drug Abuse staff are prevented by law from dealing with alcohol or tobacco, but we are not prevented from dealing with anything, any drug or substance that is used to treat dependence on alcohol or tobacco; therefore, this now becomes a drug and the FDA has authority over substances used to treat.

These substances usually come to the Drug Abuse staff and that is why we are here with the Drug Abuse Advisory Committee. I second what Dr. Leber has said. We do welcome you. We weren't expecting this, but it is nice to have a committee that can convene and tackle issues such as this. Now I will turn it back over to Sid.

DR. COHEN: I think we will open the meeting now to the public and Fred has informed me that there is one individual who has requested time to make a presentation.

OPEN PUBLIC HEARING

MR. ABRAMEK: Dr. Cohen, Dr. Blum was not sure

whether or not he would be able to make it to today's meeting. However, in his absence, he did send us in the mail an article or a statement which he would like circulated to the members of the Committee as well as to the audience.

I will just briefly paraphrase what he had to say. Dr. Allen Blum, B-l-u-m -- and he is associated with DOC, or Doctors Ought to Care, a membership, nonprofit organization of approximately 1000 members. Its objectives are threefold, to curtail public health costs, to educate the public, and encourage dialogue within the health professions about major killer habits such as cigarette smoking, alcohol dependence, and other drug abuse and, three, to counteract the promotion of such lethal life-styles.

It is the opinion of this group that the available data are insufficient to permit approval of the drug at this time. Dr. Blum then goes on to cite studies by Russell, Fee, and Stewart, and points to other raw data. I will leave it to each individual person to read what he has to say, but I would like it entered as an official document.

DR. COHEN: Thank you. Are there any members of the public who have a comment to make, a brief comment to make? This is the time in which it could be done.

(No response)

There seem to be none, so we will now proceed with the first item of business, and the last, namely, is Nicorette

Gum approvable under the conditions that Dr. Leber mentioned. Leading off the presentation for the sponsor, Merrell-Dow, will be Dr. Ohye.

PRESENTATION OF MERRELL-DOW

MR. OHYE: Thank you and good morning, everyone. Mr. Chairman, members of the Committee and the Agency, ladies and gentlemen, I am George Ohye, Vice President, Regulatory Affairs, for Merrell-Dow Pharmaceuticals, Inc., and on behalf of Merrell-Dow I would like to take this opportunity to thank you for this opportunity to present data on Nicorette, nicotine resin chewing pieces, an adjunct to smoking-cessation programs that is helping hundreds of thousands of people who want to quit smoking in Canada, England, Ireland, Germany, Austria, Sweden, and Switzerland become ex-smokers.

It is my pleasure to introduce our first speaker this morning, Dr. Bill Martz, who recently retired as Medical Director of Merrell-Dow to return to academia. Dr. Martz is Professor of Medicine at Indiana University School of Medicine and a past President of the American College of Cardiology.

We felt it is particularly fitting that Dr. Martz is our first speaker and the moderator for our presentation, because it was under his leadership that Nicorette was first studied by Merrell-Dow in the United States. Dr. Martz?

PRESENTATION OF DR. MARTZ

DR. MARTZ: Chairman Cohen, we are very pleased to

have the opportunity to review the data on Nicorette for this group. I apologize for reading my comments -- Mr. Ohye, in the interest of time, has insisted on it -- I think Dr. Leber has covered many of the points in my presentation, so I also apologize for the repetition.

I believe all of us in this room would readily agree that cigarette smoking is a habit easily acquired and, for many, one quite difficult to break. Nicotine-dependence, at least in many smokers, is a significant factor in the continuing use of cigarettes.

Serious smokers appear to regulate their smoking, their brand, frequency of cigarettes, depth of inhalation, to experience pleasurable CNS effects and prevent the unpleasantness of withdrawal. Such a dependence was operative before cigarette smoking became popular, but in the form of chewing tobacco and, for the ladies, the more easily concealed use of snuff -- habits I understand are returning.

If Dr. Ebert were here, and he had planned to be and was prevented by illness, he would probably point out that the magnitude of tobacco use in our nation really didn't change much when our society switched from a chewing to a smoking one.

Inhalation of cigarette smoke provides a rapid delivery system for nicotine, with high brain levels quickly achieved. However pleasant, the inhalation route carries with

it carbon monoxide irritating gases, carcinogenic tars, and other components of cigarette smoke which have contributed significantly to toxicity and morbidity in the form of chronic lung disease and cancer, as our nation's vital statistics dramatically show.

Approximately 14 years ago a distinguished scientist in Stockholm, Professor Ove Ferno (phonetic) -- and I wish so much he could be with us today -- began working with nicotine-containing chewing pieces as an alternative route of administration as a means of helping smokers break the habit.

At the Second World Conference on Smoking and Health held in London in 1971, data were presented on the use of this gum. Although somewhat effective, to accomplish a uniform release rate in the mouth required not only complexing the nicotine to resin, but also critical buffering.

The rationale of the chewing gum was that this vehicle would provide a means of accomplishing slow absorption through the buccal mucosa, bypassing liver destruction, with the possible additional virtue of partially substituting for the oral gratification cigarette.

It was shown by Dr. Russell, who is present with us today, early that a piece of gum providing 4 milligrams of nicotine chewed slowly every hour provided blood levels which approximated those achieved when a strong cigarette was smoked every hour -- of course, without the peaks of nicotine levels

that inhalation of cigarette smoke produces.

The AB LEO Company of Sweden, developer of the nicotine-resin buffered complex, five years ago surveyed approximately 100 Swedish physicians who had had experience with the gum in their patients. In this study there was an overall effectiveness of 34 percent, not controlled by placebo.

Ninety-three percent of the responding physicians said they found it useful in their practices. Dr. Ferno concluded from this study and survey that, and I quote from him, doctors can be stimulated to take an active interest in smoking cessation by the existence of a pharmacologically active product like nicotine chewing gum, end of quote.

Subsequent to this indication of interest by Swedish physicians, the AB LEO Company began licensing efforts. The Dow Chemical Company in Canada obtained approval for marketing in that country, and there has now been a four-year marketing experience with good acceptance and no unexpected problems with the use of Nicorette.

The acceptance by Canadian physicians stimulated our interest in the U.S. and an IND was filed on June 23, 1980. The Merrell-Dow Pharmaceutical Company sponsored additional bioavailability studies in the U.S., documenting that the chewing gum produced blood levels in the same range as cigarette smoking and that there was no unusual metabolism associated with this route of administration.

These data, together with results from several U.K., Scottish and Swedish efficacy trials, were presented as a new drug application in March of '81. I should make it clear that these studies were initiated prior to U.S. licensing of the product without the rigor of joint sponsor-FDA-investigator protocol review and planned documentation.

This resulted in certain logistic difficulties, as Dr. Leber has already referred to. For example, in the case of the Fee study, in Scotland the Health Service found it inappropriate to send case-report forms to the sponsor for detailed analysis -- these were sent directly to the FDA.

In the case of the early Russell studies, some of the data usually incorporated in the U.S. case report forms were provided retrospectively. I should point out that Professor Russell is in the fortunate position as a long-term established investigator to have program rather than contract support, and his studies have at times, have not been supported by pharmaceutical sources.

He studied nicotine gum because he had interest in it from his long-term behavioral modification programs and does not have the bias of industry support. This carries with it the problem of some of the documentation that we are accustomed to in NDA applications.

The sponsor felt at the time of the new drug application, obviously, that support for efficacy and safety

was adequate. The FDA requested that additional data of U.S. origin be submitted. The study by Christen, which you have had an opportunity to review, is response to that request. You will hear directly from Dr. Christen a bit later. The FDA reviewers have been in phone contact with Professor Russell regarding his studies and we present this morning to your Committee -- he is here to give firsthand details of his experience, if you care to hear them.

We should emphasize that the sponsor is proposing the modest claims that nicotine chewing pieces provide a delivery system for nicotine free of the noxious respiratory-tract toxicity of cigarette smoking. The gum has been demonstrated, we feel, to be a valuable adjunct to a cessation program in the smoker who is well motivated to stop.

No suggestion is made that it will work in a poorly motivated subject. Current data suggest that the highly nicotine-dependent smoker is the most likely to benefit. Also, as in most behavioral modification programs, it would seem essential that it be acknowledged that continued motivation, social support, and encouragement to tolerate the unpleasantness of the gum is essential in preventing return to the habit.

These considerations, we feel, make it imperative that nicotine chewing gum be a prescription item and be used in conjunction with appropriate motivational and support efforts.

In addition to the data contained in the new drug application, your Committee has further safety and utility assurance from the marketing experience in several sophisticated countries, which George alluded to.

As indicated, Canadian physicians have found Nicorette useful, as evidenced by good market acceptance and steady sales over the past four years. In Sweden, its country of origin, the use of Nicorette is at the highest level per capita of any country in which it is available. It has been estimated by the producers of the gum that approximately 1.2 million people have had experience with the gum at this point in time.

Acceptance in the U.K. market has also been good. We will comment later on side effects. If any of you have the erroneous impression that nicotine chewing gum might be considered in the confectionary category, George, would you mind -- we have brought a supply of placebo gums, so you could see and taste it, if you care to.

You can judge for yourself its palatability. The nicotine-containing gum, at the suggestion of FDA, if marketed, will be in a child-proof package. We made these placebo simpler to get to.

SPEAKERS: Which are the placebos?

DR. MARTZ: This is all placebo.

(Laughter)

SPEAKER: Is this the placebo used in the Indiana study or in the Russell study?

MR. OHYE: This is the Indiana placebo.

DR. MARTZ: We think you will agree with us that it is not a very pleasant confectionary-type product. We will talk about this a bit later, but we feel that if we get to the marketplace, our problem will be helping physicians keep their patients on it long enough to really get the job done, that the abuse potential is relatively minimal, partly by nature of the gum.

Early in the U.S. evaluation of Nicorette, we were fortunate to enlist the collaboration at the University of Arkansas of Drs. Ebert and McNabb. I am sure all of you are aware that they are 20 miles away from the Pine Bluff Laboratory, and that Laboratory had developed prior to our and their interest in Nicorette a very sensitive and reliable assay for nicotine, and these do not exist in very many laboratories, we found.

Dr. Eugene McNabb, who works with Dr. Ebert, will next review their data on comparative nicotine blood levels on gum versus cigarettes. Dr. McNabb is Director of the Pulmonary Laboratory, VA Hospital, University of Arkansas.

DR. COHEN: While we are waiting, I might for the record mention that Dr. Steven Paul has arrived from the NIMH, adding to our Committee numbers.

DR. GOODWIN: Are the placebos indistinguishable from the 2-milligram-containing nicotine gums?

DR. MARTZ: Dr. Russell, would you want to comment on that?

DR. RUSSELL: I don't know whether these placebos are the same as ours, so I couldn't answer.

DR. GOODWIN: Well, can you tell the difference between them and the active drug? That is what I am asking.

DR. JONES: I have chewed the 2-milligram gum, which is what we are using. I have not chewed this placebo before, and this is quite distinguishable. I find this not unpleasant.

(Laughter)

You are quite right, the gum -- I assume because there is nicotine in it, which is a bitter alkaloid -- has --

DR. GOODWIN: Because there aren't side effects with the gum or because it has a different taste?

DR. JONES: A different taste, plus you do get, you know, effects -- I would call it side effects -- you get the effects of nicotine, at least I, as a nonsmoker, do. I don't know about the 1 milligram on buffered gum that Dr. Russell and others have used as, quote, placebo. I have never tasted that.

DR. MARTZ: I am pretty sure the person can, by pharmacologic effects detect, but the taste is -- we put as much nastiness in this as we could get.

DR. LEBER: This issue is one of the subjects we were involved in, we will get into it later, but it occurs to us unless the subject has had both gums, he really has no reference or comparison. However, there is another issue labeled blinding of the investigator, and that is something I think our statisticians will discuss a little bit later.

But I think we were convinced if no subject has had repeated exposure to different sources of gum, the issue of taste wouldn't be as critical as it would be, unless they had contacted them to discuss how it tastes. Now, try to describe the taste of this gum to someone else.

DR. COHEN: Let's continue.

DR. NUIT: Wasn't there one other type of placebo, though? Before, I thought it mentioned in the material we were given that there was another placebo that incorporated cathepsin or a similar product.

DR. COHEN: Let's continue. I am sure a lot of the questions in everybody's mind will -- some of them -- will be resolved with the discussion that is going to occur.

PRESENTATION OF DR. McNABB

DR. McNABB: Dr. Cohen, members of the Committee, Dr. Richard Ebert, who was to be here, has been active in studying and writing about smoking cessation in this country for several years, one of the few internists engaged in that sort of activity. He is not here today because he became

acutely ill.

I have worked with Dr. Ebert as a medical student and as a house officer, and in later years as a research associate. I hope I don't add to his symptoms by standing up here and quoting some of his remarks that he was to make to the people here.

As you know, cigarette smoking is the principal cause of lung cancer which, in turn, is responsible for 100,000 deaths per year in the United States. Lung cancer is not only the most common cause of death from cancer in men, but now equals breast cancer in terms of cause of death from cancer in women.

Chronic bronchitis and pulmonary emphysema are also directly related to cigarette consumption and are a major cause of disability and death in the United States. Finally, cigarette smoking greatly increases the risk of developing coronary-artery disease.

In a perfect world, the solution to the problem of cigarette smoking and disease would be abolition of cigarettes. In this imperfect world, it is impossible, for a variety of reasons. The physician, in his practice, must deal with persons who are addicted to cigarettes. There is evidence that if these individuals can be induced to quit smoking at the appropriate time, smoking-associated disease can be prevented.

An example of this is the early treatment of chronic

obstructive lung disease. It is now believed that individuals with incipient disease can be identified by detecting more rapid annual loss of pulmonary function. There is evidence that detecting these individuals with early evidence of airway obstruction and inducing them to quit smoking will prevent the eventual development of disability and death.

In 1980, we began our studies and we are happy to be studying an agent, the chewing of which didn't lead to spitting on the sidewalks and from which carcinogens had been unloaded, and which, according to studies by me, created blood levels of nicotine no greater than that produced by chewing tobacco, and which did not pollute the air space of other persons.

You may know that in 1910 there was very little smoking of cigarettes and tobacco was consumed mainly as chewing tobacco. That began to change in 1920 and then some 20 years later began the epidemic of lung cancer. But it is true that throughout the history of this country that the consumption of tobacco products and the consumption of nicotine has mainly been by the oral route.

So, in 1980 we began a series of studies on this agent to determine the suitability of it for use by practicing physicians. We were specifically interested in comparing blood levels produced by the chewing gum and those sustained by cigarette smoking.

Twelve patients, whose lung functions were slightly

less than half of normal on average, participated in our initial study, which was a nine-day study. Over the initial three days of the study, the individuals smoked, and we set out to determine trough levels from smoking their usual brands in the usual fashion on the first two afternoons.

May I have that first slide, please.

Just to point out, here are some curves of nicotine in the plasma. Each dot represents a single determination of plasma nicotine level. The slide displays one individual smoking a cigarette, which happened to be the first cigarette of the morning, and then another individual chewing a piece of nicotine chewing gum which contained 4 milligrams of nicotine.

What we were doing was determining the trough levels. We were measuring the plasma nicotine in this zone in individuals who smoked cigarettes, and then I will come to this momentarily, but we were also drawing blood at this time period in individuals who were chewing the nicotine chewing gum.

So, all along I am talking about trough levels. Now, on the third day of the initial three smoking days individuals continued to smoke, but this time they smoked on an hourly basis, using a common brand which yielded 1.1 milligrams of nicotine, and then specimens were drawn in the afternoon, again, at 1:00 and 3:00 p.m., one hour after the previous cigarettes. Again, those were trough measurements.

On the fourth and fifth days of the study, individuals

practiced chewing pieces of 2-milligram nicotine gum and, after practicing, on the following day, they were asked to chew a piece of 2-milligram gum hourly, starting at 7:00 a.m. Blood specimens were drawn at 11:00 a.m., 1:00, 2:00, and 3:00 p.m.

The same regimen was followed for testing the 4-milligram gum, again providing two days of practice chewing of the 4-milligram dose.

We can have that slide off, please.

Every time blood was drawn, the specimen was also analyzed for carboxyhemoglobin for the purpose of separating out nonabstinent subjects from the assessment. Thus, eight abstinence subjects provided data for the assessment of 2-milligram nicotine chewing gum, and 9 abstinence subjects for the 4-milligram dose.

Nicotine determinations were by the gas chromatograph technique of Fireben (phonetic) and Russell, with the very minor modification of changing the internal standard and using ethyl nornicotine in place of quinoline.

Subjects were given lists of possible side effects associated with the gum and asked to check those they had experienced.

(Slide)

Looking at the results of this study, then, as far as the levels of -- we may need to have more lights out.

("We can see.")

We are looking at the results of the plasma nicotine determinations in abstinent subjects chewing both doses of the nicotine chewing gum, and on the Y-axis plasma nicotine level in nanograms per milliliter, and on the X-axis, time of day, 11:00 a.m., 1:00, 2:00, and 3:00 p.m.

(Slide)

Now, the mean of the nicotine levels chewing 2-milligram gum at 11:00 a.m. was 11.8 after four pieces of 2-milligram gum; at 1:00 p.m., 11.1 after six pieces of gum; at 2:00 p.m., 11.4 after seven pieces; and after eight pieces of gum at 3:00 p.m. the level was 12.8.

Nine abstinent subjects used the 4-milligram gum and the mean of their plasma nicotine levels at 11:00 a.m. was 21.8 nanograms per milliliter after four pieces of gum; at 1:00 p.m., 23.2; at 2:00 p.m., 22.1; and at 3:00 p.m., 25.7.

If you took all of those levels and took a mean of all the levels that you saw in the previous slide, the mean of all levels for 2-milligram gum was 11.8 nanograms per milliliter, and the mean for 4-milligram gum was 23.2 nanograms per milliliter.

These were compared to the mean of all trough levels from smoking in the usual fashion, the usual brand of cigarette, and there were 36 of these measurements, 36 individual plasma nicotine measurements, to give this mean of

15.2 nanograms per milliliter.

There were 18 individual measurements when subjects smoked a common brand on an hourly basis, and that means for 18 measurements was 18.3 nanograms per milliliter.

(Slide)

Side effects are listed in this table, and this number should be 12 instead of 13. Some patients with dizziness and nausea on the 2-milligram dose did not complain of those symptoms on the 4-milligram dose. Duration of these symptoms was brief, with the exception of sore gums in wearers of dentures.

Recurrence of the symptoms was usually controllable by slower chewing. None of the participants stopped chewing the gum during the course of the study, and all subjects wished to continue the gum over subsequent weeks to promote their efforts to stop smoking.

In summary, plasma levels of nicotine may be readily produced by chewing nicotine gum, and individuals chewing one or the other dose of gum on an hourly basis developed steady-state plasma levels which matched those trough levels from smoking.

This group of patients with chronic lung disease found the gum to be acceptable, despite a few mild controllable side effects.

DR. MARTZ: Thank you, Dr. McNabb. Are there any

questions for Dr. McNabb at this point?

DR. COHEN: Well, perhaps we could hold the questions until you have completed your remarks.

DR. MARTZ: As was already mentioned, the studies by Dr. Russell have been the most extensive with Nicorette, and we felt it was appropriate to ask Dr. Russell to be with us today. We have asked Dr. Michael Russell to be present and review his experience with Nicorette.

Dr. Russell is responsible for the Addiction Research Unit,Institute of Psychiatry at the Malmsley Hospital in London. Dr. Russell, we are happy to have you with us, and we appreciate your coming the long distance to be here.

PRESENTATION OF DR. RUSSELL

DR. RUSSELL: Dr. Cohen, ladies and gentlemen, I am going to present briefly the results of our double-blind placebo-controlled trial of nicotine gum as an adjunct to group support in a smoking-cessation clinic.

Firstly, I would like to say that we are very honored that a committee such as yours is prepared to make an exception and give serious consideration to a study conducted in a foreign country. We are confident that our methodology, data, and conclusions are sufficiently robust and stringent to withstand any scientific scrutiny.

Secondly, I would like to apologize that our protocol and system of data collection and recording were not in the

usual format for clinical trials submitted to you. Our protocol was handwritten for internal discussion and planning within our own research group. Perhaps it would help if I could explain why this is so. The study was funded by the Medical Research Council, which is the main body for allocating British Government funds for medical research.

Support from the pharmaceutical industry is confined to the supply of the active and placebo gum. Now, most Medical Research Council grants are short-term project grants of two to three years, and these do require detailed and very specific research protocols.

Fortunately, for us, we are funded on a longer term basis by the more coveted and prestigious program grants. These program grants give the grantholder freedom and almost carte blanche to choose what studies to do and how they wish to do them.

So, we chose to do this study and also how to do it, without having to submit any protocol at all to the Medical Research Council, or anyone else. Hence the fact that our protocol was handwritten for internal purposes only.

Before going on to actually turn to the study itself, I would like to say that we have been engaged in smoking research since 1969, and the treatment has been one of our main interests. We have had a smokers' clinic running throughout this time.

At first, its scale was modest, but now we see about 300 smokers a year and have had experience with a total of about 2000 smokers at our clinic. Now, like others, we have tried all kinds of treatment methods. We have tried individual and group support, we have tried hypnosis, we have tried pharmacological approaches such as lobeline, nicotine aerosol, tranquilizers.

We have tried behavioral methods such as electric-aversion therapy, rapid smoking, covert sensitization, and Q-exposure (phonetic). But like others, we found that none of these methods does any better than the intention placebo, and support element that is involved in any treatment situation.

Success rates on these other methods, which were not always chemically validated in the old days, ranged between 15 and 25 percent not smoking after one year. But the advent of Nicorette has changed all this; it has doubled the success rate, and we believe that it is a genuine breakthrough in the treatment of smoking cessation after years of frustration.

We first tried it way back in 1974 and we weren't impressed at that time. In a placebo-controlled crossover study, although it suppressed inhalation during ad libidum smoking, the inhalation was measured by carboxyhemoglobin levels, and people who were smoking and having active gum had lower carboxyhemoglobin levels than people who were smoking and having placebo gum.

So, although it suppressed inhalation, it did not increase the success rate at that time in 1974, and it was also not at all acceptable to our smokers. So, we lost interest in it for a while. However, the product was modified. Flavoring and buffering capacity were improved, and we took an interest in it again, in the first instance, by doing absorption studies to see whether or not nicotine was adequately absorbed.

And we did studies of the kind that Dr. McNabb has so clearly presented to you. Having satisfied ourselves that nicotine was adequately absorbed, we then tried it again clinically during 1978 to '79, and to our surprise and interest it doubled our success rate to 38 percent of 69 subjects who were abstinent one year after treatment, and that compared to 14 percent for the previous rapid-smoking trial that we had just completed.

So, to see whether or not this was a placebo effect, we started on the present randomized controlled trial.

If I could just have the first slide, please.

This shows the methods of the study and you can see that there were 116 smokers recruited and they were treated in 12 groups or cohorts of approximately 10 subjects each. The actual numbers ranged from 8 to 11, with a mean of just below 10.

Each group or cohort was randomly allocated to the active or placebo gum. I gather that there have been some

questions about our randomization method, and we will be very happy to attend to any of these in the discussion afterwards in any amount of detail you wish. The study had two therapists, both experienced clinical psychologists, and I am pleased that we have got one of them here today to answer any questions in more detail that he could answer better than I.

Both the psychologists, the therapists, and the patients were blind as to gum allocation. Each therapist treated six groups of patients, three with active and three with placebo. So, there were altogether 12 groups, six placebo gum groups, six active gum groups, each comprised of 58 subjects. The active gum was a 2-milligram commercial preparation, the placebo was the 1-milligram unbuffered gum, and the lack of buffer meant that even the lower dose of nicotine was much less well absorbed.

So, we did this to match the nicotine taste without giving an appreciable pharmacological effect.

(Slide)

The next slide shows that subjects were treated with six weekly group therapy sessions, but before the first group, they had an initial individual session with their therapist, at which the gum was given out with clear instructions, and they were also instructed to stop smoking over the next three days and to then start using the gum ad lib as they needed, and to try to come up to the first group the following week

off cigarettes, but on the gum.

During the course of the six sessions, subjects completed weekly questionnaires which contained withdrawal symptom ratings, ratings of acceptability of the gum, and a checklist of unwanted effects. They also completed diary cards on which they put cigarette consumption and gum consumption.

For follow-up they returned at three months, six months, and one year, and verification was by carbon monoxide measurement or third-person testimony in a few cases. Of the successes, third-person testimony was only required in three in the active group, and four in the placebo group; all the other successes were validated.

(Slide)

The next slide shows the patient characteristics -- that is an error, that is not statistically significant, it doesn't even approach it -- the only significant difference was in cigarette consumption, and that was to the disadvantage of those in the active group.

All these are pretreatment variables, with the exception of attendance at pyschological sessions, and you can see that -- that is, group meetings, the six group meetings -- the average attendance was only 2.4 of them.

(Slide)

This is the main slide of interest and shows the main outcome in terms of percentage abstinence at one month

and one year. The actual success rate, you can see, has been doubled, 24 percent at one month in the placebo group, 48 percent in the active group; 14 percent versus 31 percent. These are significant statistically at the .01 level here and the .025 level there.

Now, I would like to say that these criteria of abstinence were extremely strict ones. These are the ones who were abstinent by the first group meeting, that is,during the first week, and didn't have any lapses whatsoever until the follow-up period at one month or one year.

I should also mention that none of these successes were actually still chewing the gum at one year following. All these strict criteria successes were off the gum at that time.

In most withdrawal studies cited in the literature, they don't use such strict criteria. The usual criterion is validated nonsmoking status at one year follow-up, and by those criteria the placebo group were 21 percent versus 47 percent for the active group. So, this is the main outcome finding, but strong other supportive evidence comes from the fact that the active gum group had significantly less severe withdrawal symptoms and also found the gum significantly more helpful.

(Slide)

This last slide shows the checklist of checking the unwanted side effects. The only differences that were

statistically significant were the hiccups and the indigestion. The rest were not statistically significant between the two groups, although some of them clearly occur more frequently. I should emphasize that to get on this list, you just had to have said you had a symptom once very mildly over the course of six weeks.

In general, the symptoms were very mild, they were short-lived, and in no case did they cause -- were they the reason for dropping out or termination -- for dropping out. So, that is all the slides. In conclusion, we are satisfied that the active gum was substantially more effective than the placebo in enhancing short-term and long-term success rate at smoking cessation and that those who received the gum had less severe withdrawal symptoms and found it more helpful.

DR. LEBER: Mr. Chairman, do we have permission to ask some clarifying questions at this point?

DR. COHEN: Have you finished your presentation?

DR. MARTZ: No, we have two other speakers.

DR. COHEN: Can we wait until the two other speakers have finished? Then we will have a discussion.

DR. MARTZ: As we indicated earlier, the Agency asked that we have additional well-controlled studies, preferably of U.S. origin. Our next speaker, Dr. Christen, will present data on a study completed. Dr. Christen is Director of the Preventative Dentistry Section of the Indiana University School

of Dentistry. Dr. Christen?

PRESENTATION OF DR. CHRISTEN

DR. CHRISTEN: Dr. Cohen, ladies and gentlemen, I am Dr. Arden Christen, Associate Professor and Chairman, Department of Preventive Dentistry, Indiana University School of Dentistry.

Could we have the first slide, please.

Here is an aerial view of the Indiana University campus from downtown Indianapolis. Our research team and faculty members are housed in the Oral Health Research Institute, in this building right there. We are right across the street from the Dental School.

(Slide)

Our Institute, directed by the well-known and respected dental researcher, Dr. George K. Stookey, is a Division of the Indiana University School of Dentistry. The Institute is housed in a separate building located adjacent to the School of Dentistry, and contains about 20,000 square feet of space which is devoted to laboratory animal and clinical dental research.

I thought it advisable to speak to the Committee and give you a little bit of background, because I don't know how familiar you are with our operation. We have eight full-time Dental School faculty, 23 full-time staff members, plus about 25 part-time staff members, including dentists, dental assistants, hygienists, undergraduate and graduate students.

For the past 20-plus years, we have completed numerous research projects, receiving financial support from a wide variety of governmental and commercial sources, including the National Institute of Dental Research, the Indiana State Board of Health, the American Dental Association, General Mills Foundation, Procter & Gamble, Johnson & Johnson, and many, many other sources.

I am the principal investigator of a project entitled Clinical Investigation of the Nicotine-Containing Chewing Gum, Nicorette. This longitudinal study was designed as a randomized double-blind placebo-controlled trial of three months' duration, with the primary objectives of assessing the influence of chewing 2-milligram Nicorette gum on the oral soft tissues.

We were concerned about the oral use of a product like this, since we know that chewing tobacco and snuff and smoking tobacco do have some problems with the oral cavity. So, we were interested in assessing safety considerations. We were also concerned with various dental and health and cosmetic parameters and to assess the effectiveness of the gum in helping smokers quit.

(Slide)

As shown in this slide, after subjects were selected they were randomly allocated into either the Nicorette or the placebo gum group. After six weeks of tretment they were asked

to return for a smoking status evaluation -- this point right here. The study was then allowed to continue to completion. I was kept blind throughout the entire study. The purpose of my briefing today is to report six-week smoking-cessation data for your consideration and some other preliminary oral findings.

Of the 208 smokers recruited, 103 were allocated to the placebo group, and 105 to the Nicorette group. Throughout the study, efficacy was assessed by means of self-reporting and a breath test in which expired carbon monoxide was measured by an analyzer.

(Slide)

The base-line characteristics of the test and placebo subjects in our study were essentially comparable, although there were some marginally significant differences between the groups. The placebo group was several years older in age and had smoked longer by an average of two years.

However, it can be generally stated that the two treatment groups were found to be essentially homogeneous in character relative to demographic, clinical, psychological, and gum usage characteristics -- these were the two areas where the average age had a slight difference there and the average years of smoking here.

(Slide)

As shown in the next slide, the results are clear and straightforward. Incidentally, I would like to mention for the

group that we were mainly interested in the oral ill effects and the study was not designed primarily to determine quit rates. This was really a spinoff, because we were really interested initially and this sort of evolved.

At six weeks, the Nicorette group quit rate was 34.3 percent versus 10.7 percent in the placebo group. This represents a threefold superiority of Nicorette over the placebo gum. Quit rates were defined by self-report and an expired carbon monoxide measurement in all cases. We just don't believe anyone who says he is not smoking, unless it can be verified.

At six weeks, around 70 percent of both groups were still chewing gum, with an average usage of seven to eight pieces a day. Although not shown here, and if you would care to later, we have some slides of 12-week data, but although we are not showing it here, the results after 12 weeks in the program also indicate a significantly higher quit rate for the Nicorette treatment group compared to the placebo group, although the quit rate in both groups was smaller.

We can ascribe this to the fact that a minimum of reinforcement occurred in our study as compared to the study previously described by Dr. Russell. In fact, our study was really a minimal intervention study in which they received one brief session with a facilitator to describe how to quit and given a pamphlet and so on, and after that, that was it.

Further, gum usage dropped off to an average of two pieces a day -- this was after 12 weeks. Consequently, motivation to quit smoking was probably considerably lower in our group of subjects.

(Slide)

The next slide shows the degree of nicotine dependence, which was measured by means of the Fagerstrom questionnaire, resulting in a Q score. Dr. Fagerstrom, who is in the audience, he would be glad to discuss this, I am sure, at a later time, if you so desire.

You will notice one thing needs some clarification up in here. "Hard to refrain from smoking in public" is how it should read. It was dropped out, those words.

This evaluation asks eight questions pertaining to the subject's smoking habits, which are then scored and totaled to yield a 0 to 11-point scale. Values greater than 6 are considered to be high nicotine-dependent smokers. Down in here we can see the scale -- the high nicotine-dependent smokers.

These would tend to represent more hard-core smokers.

(Slide)

Examination of data based on nicotine dependence are shown here. The low-dependent smokers achieved a quit rate of approximately 29 percent, while the high-dependent smokers achieved nearly a 46 percent quit rate. We found these to be

particularly interesting data, in view of the fact that people who tend to gravitate to clinics seem to be perhaps the more hard-core, dedicated, if you will, smokers. These data suggest that the more nicotine-dependent subjects have a greater success in quitting than the total population.

If we could have the lights, please.

Now, a few words about the dental findings which I think are important. Concerning the safety evaluation, a tally of adverse experiences shows that no unusual or serious side effects were found in the course of the trial. The reported adverse experiences identify nonspecific gastrointestinal symptoms, nausea and hiccups as reactions likely associated with Nicorette gum.

Mouth ulcers, called aphthous ulcers, as you are aware, jaw-muscle aches, appeared to be the result of active gum-chewing, whether it be with placebo or the nicotine gum. The data from the examinations, the dental data, we looked at four parameters.

We looked at gingival inflammation, dental plaque, calculus or pellicle, and staining data. We wanted to know whether the gum stained teeth, for example. These four parameters, although we have not completely analyzed these statistically, we have done a preliminary inspection of the mean values and standard errors, and we can support the following statement concerning the oral findings.

The base-line data. The group assignment procedure did provide two groups of smokers which were alike -- in other words, not significantly different -- at the outset of the trial with regard to these four variables. So, we had patients put into four categories based on the amount of stain, the amount of gingivitis and so on, all of the dental parameters.

We also had rather stringent requirements for entry into the study. They had to have so many teeth, so many front teeth, and not too much dental infections, and so on.

Test data. With regard to gingival inflammation, which we term gingivitis, those subjects who continued to smoke continued to have a slightly higher level of gingival inflammation than those subjects who quit smoking, regardless of whether they used the placebo or nicotine-containing gum.

On the other hand, there was no difference in the level of gingival inflammation between those subjects who used the placebo gum and those who used the nicotine-containing gum, regardless of whether they quit or continuted to smoke. The same trend held partially true for the staining data.

Smokers had more stain than those who quit smoking. With regard to calculus and plaque, there was a definite trend for those subjects using the test gum who quit smoking to exhibit less plaque and calculus than any of the other groups of subjects.

To summarize, we found that Nicorette was demonstrated

to be an effective agent for smoking cessation during the period of time that we tested it. Further, our clinical evaluation of the oral cavity indicates that Nicorette does not cause detrimental changes in the mouth.

DR. MARTZ: Our next speaker is Dr. Robert Powell, who is Director of Regulatory Affairs for Merrell-Dow, and he will present the data on two additional studies that are part of our new drug application.

PRESENTATION OF DR. POWELL

DR. POWELL: Thank you, Bill. Dr. Cohen, Panel, as Bill mentioned earlier, our new drug application was submitted some time ago and contained some 14 clinical trials and approximately 1000 patients. Later on Bill will summarize the safety data from this submission. I would like to summarize just two additional studies that we think show the consistency of the action of the gum across studies.

The gum has indeed been on the market in several countries, also, and Bill will allude to that in terms of the safety of the compound. The first of the studies I would like to discuss was a study conducted by Dr. Karl Fagerstrom in Uppsala, Sweden. Dr. Fagerstrom , incidentally, is the individual who developed the nicotine-addiction rating scale that Dr. Christen used in his study.

In Dr. Fagerstrom's study, patients were randomly assigned to active Nicorette or matching placebo groups and

entered into a series of sessions of individualized counseling which was tailored to the needs of the patient by the counselor. Patients were given in the study chewing gum on the first visit and supplies were replenished ad lib for about four weeks.

Then patients were encouraged to reduce gum use, with the ultimate goal of total elimination of such use. The double-blind code was broken only after the patient had remained abstinent for three months, at which time most had ceased chewing the gum.

May I have the first slide.

The first slide summarizes the patient characteristics on entry into this study. You will note that they were essentially the same with respect to age, cigarette consumption, nicotine dependence, and number of years that they had smoked.

A total of 100 subjects were entered into this trial, 50 placebo and 50 Nicorette. Prior to the first meeting, 3 Nicorette and 1 placebo patient dropped out and, therefore, there were 47 Nicorette and 49 placebo subjects who entered the trial.

(Slide)

There was a comprehensive smoking-cessation program that was used, which consisted of 10 days of recording of tar and nicotine intake, a medical check-up, carbon monoxide concentrations pre- and post-cessation, review of motives,

feedback to the medical motives, recording of weight.

(Slide)

There were some fundamental premises that led to the study, that is, complete abstinence should be reached within at least 20 days of the program. Highly dependent nicotine subjects cannot take occasional cigarettes, gradual reduction is not a serious alternative to cold turkey, and a high degree of individualization was considered to be required.

(Slide)

Treatment components consisted of general medical health information, nonspecific support, encouragement, reinforcement, warm, accepting atmosphere, patient decided when he was going to quit, and education in self-control techniques.

(Slide)

The administration of Nicorette or placebo, sensitization of how smokers relapse, personal contact for four to six months with six to 15 sessions, and after six months, participants were requested to contact the clinic by post card as an additional reinforcement.

Patients had the opportunity to smoke whenever they desired at the clinic.

(Slide)

The results of this trial are depicted in this graph, which shows the high initial rate of smoking cessation, which deteriorates over 12 months, but the difference between

the control group and the drug group remains essentially the same as the failures developed.

(Slide)

The second trial that I would like to discuss briefly was a study conducted by Dr. W. M. Fee in Ninewell's Hospital, Dundee, Scotland.

(Slide)

This study was a double-blind placebo-controlled evaluation of Nicorette 2-milligram gum as part of an anti-smoking program consisting of 10 group therapy sessions over a five-week period, so this differed from the Fagerstrom study in that it was group sessions as opposed to individual sessions.

Three hundred fifty-two smokers entered into the trial and, following randomization, 180 received Nicorette gum, 172 received placebo. Gum was provided ad lib with the caution not to chew more than 20 pieces per day.

Verification of quitting was confirmed by carboxy-hemoglobin levels.

(Slide)

Of the 180 and 172, respectively, who started the trial, 114 and 90 completed the 10-session five-week program, 63 percent of the Nicorette and 52 percent of the placebo group. Verified nonsmokers at this point were 46 percent in the Nicorette group versus 33 percent in the placebo group, statistically significant.

In addition to the information from these trials, safety information was gathered on up to 1000 patients in our NDA, and Dr. Martz will address that subject.

PRESENTATION OF DR. MARTZ

DR. MARTZ: In regard to adverse reactions, George Ohye is handing out a summary of our total NDA-covered experience on this first sheet, labeled Exhibit A, in the 959 subjects receiving Nicorette gum as a part of our new drug application.

There was a relatively high incidence of, we feel, relatively mild kinds of side effects. Nicotine, as you know, is an irritating substance, and 13 percent of these people had some GI symptoms, 18 percent at some time or other complained of a problem with sore mouth or throat, 1 percent had hiccups. These are relatively innocuous side effects, but to be expected of a substance like nicotine.

On Exhibit B, at the request of FDA, we have divided the U.S. and British studies into those subjects reporting side effects on placebo and true gum, and I think you would agree that under the gastrointestinal side effects that eructation is higher in the true gum than in the placebo gum, nausea and vomiting more common in both the U.S. and British studies.

The British used a classification called "indigestion." It was twice as high in drug as in placebo. It is difficult, as you might guess, to separate air-swallowing and mechanical

problems of chewing -- there certainly is some soreness around the temperomandibular joints with vigorous chewing. Hiccups is a real phenomenon, probably both a central and a local component.

But, all in all, we feel that these side effects are the ones that would be expected and not at an alarming rate. We are prepared in proposed package literature, and certainly more work needs to be done in conjunction with FDA personnel on what sorts of questions should be incorporated in the package insert, we are certainly are prepared to say it should be used with caution in people with cardiac arrhythmias and other cardiovascular problems, pregnant women, lactating women.

We must caution people with esophagitis and gastric problems that they will get irritating effects from the gum. But we think the adverse reactions are a relatively mild problem in regard to this product. Mr. Chairman, this completes our presentation, and we are ready for questions, or however you want to do it next.

DR. COHEN: Thank you. I think we should have a short question period now, but please remember there are four more presentations and the questioning now should be directed only at the material that has been presented by Merrell-Dow.

I would like to ask the first question. What do I do with this placebo gum I have in my mouth?

(Laughter)

DR. OHYE: You can put it behind my ear.

(Laughter)

DR. LEBER: This will obviously come out in the discussion, but I just want to raise sort of a generic question to each of the people who presented data. You have things like percent quit and p values. Obviously, the percentage quit depends on a numerator and a denominator. It also depends upon what you declare an evaluable patient to be, and the p values that you get, that is, the estimate that these differences couldn't have been observed by chance, depends very much on the model you use to calculate.

So, if you look at the data presented, I just simply caution us, and I think I ought to go through each investigator and ask them what they used for the rule, because simply to say I had a percentage of quitters, without defining what you mean, without saying you are talking about the percent of those who began, the percent of those who completed, the percent of those who were available, there are a lot of missing data.

Also, you have to talk about time point. So, I am just -- I, at one point, wanted to ask specifically of Dr. Russell, in the figures that you presented that gave 50 percent differences, were you talking about percentage of those who entered, those who completed? I am getting a nodding to both.

DR. RUSSELL: Fifty percent of those who entered.

DR. LEBER: So, the denominator is those who entered

and the number of people that you still have contact with. There is no adjustment for --

DR. RUSSELL: All our success rates, they are all based on those initially starting a treatment.

DR. LEBER: And the same question, of course, would be directed at the assessment of data that were presented. What were the calculations based on?

DR. CHRISTEN: We have used both determinations, but prefer to use the all patients that started the study -- all people who began the study -- and we believe we would rather err on the conservative side, realizing that ours was a minimal intervention type of clinic.

DR. LEBER: I had one other point which is just for the record -- I am sorry, Mr. Chairman. You presented data from the Indiana Dental Clinic on safety, which is yet to be presented to the Agency, and it is really not the proper subject for discussion -- not that we question your results, but we have not yet had a chance to review it.

So, the Committee should not really take that evidence into consideration as part of its assessment. It certainly is one of the items that remains to be resolved between the corporation and ourselves, if we do get to that stage.

DR. COHEN: Dr. Paul, and then Dr. Jones.

DR. PAUL: I am a little concerned that these studies

were really sort of placebo-controlled due to the incidence of side effects on placebo, which, presumably, these were informed consent studies and people knew what kinds of side effects they were going to have, if they had them, on Nicorette, and a lot of them, like hiccups and things, didn't occur at all in the other placebo groups.

How well did your patients -- how well could they predict whether they were on placebo, how accurately could they predict whether they were on placebo, or did you do any of those kinds of experiments? Because the differences, although they are significant, maybe twice in terms of abstinence, are still relatively small, and I am really concerned that these are real drug-placebo differences, drug/inactive-placebo differences versus active placebo, and I am curious as to whether patients could retrospectively reliably tell, or whether that was even possible in the design?

Presumaly it would be difficult, if there was a crossover.

DR. RUSSELL: We did not actually tell patients they were receiving the placebo. In a way, ours was better described as a dose-response study. We said we were trying out nicotine, would they enter for a trial of nicotine-containing chewing gum. We were interested in the success rate, and we were also trying out different strengths.

DR. PAUL: The patients did not know that they were

potentially going to be in the placebo group?

DR. MARTZ: Maybe it is not fair that the placebo he used contained 1 milligram of unbuffered nicotine. I am not sure you were aware of that.

DR. PAUL: Right, but presumably that didn't cause the same sort of side effects as the 2-milligram Nicorette, in that the incidence of hiccups and many of these things were statistically different in certain groups. I guess any time I see a drug-placebo difference of this magnitude, I worry a little bit about whether an active placebo might have given you almost comparable results.

DR. RUSSELL: In some ways our whole analysis would have been much easier if we had been able to randomize by individuals rather than by groups, and one of the reasons we opted for randomizing by groups was that we felt we couldn't have individuals meeting in the same group who were having different gums.

So, I think, as far as the subjects were concerned, the patients were concerned, they had --

DR. PAUL: Let me just ask you, then, a general question. Do you think your patients knew when they were on placebo or when they were on Nicorette? I mean, you really think that they didn't?

DR. RUSSELL: No, I don't.

DR. JONES: I had two separate questions, or one is

sort of a series of little questions, about placebo-gum issue that I am increasingly getting confused and just a little bit concerned about. Perhaps Dr. Russell or Dr. McNabb -- what are the blood levels that one sees in the English placebo gum, that is, the unbuffered nicotine, 1 percent nicotine-containing? What are the trough levels?

DR. RUSSELL: We did not systematically study the trough levels of the unbuffered 1-milligram gum. We assumed it would be a good deal less than half the buffered 2-milligram gum. We did, however, just see whether extremely heavy use could perhaps generate levels that might have had some pharamcological effect, and so we just did in one private testing someone who chewed one gum every half-hour for four hours, so eight gums in four hours, which would be the equivalent of about 30 a day, and that generated 19 nanograms per mil.

So, with that heavy degree of use, it is possible that they got a pharmacological effect. As it turned out, there weren't heavy placebo users like that.

DR. JONES: Of course, 19 nanograms would be in the range where you would expect an effect, since that is what the 2-milligram --

DR. RUSSELL: Once again, we thought that that would be a very conservative element. That is why, perhaps, we didn't look into it more stringently. They were getting some pharmacological effect --

DR. JONES: Related to that, is the nicotine in the unbuffered gum in the form of base or is it a salt? Or, for that matter, is it a salt or a base in the resin complex? That would have great relevance in terms of whether the buffering is all that important or not.

DR. RUSSELL: I would rather let someone --

SPEAKER: The nicotine is bound to an ion-exchange resin, and that holds true for the active preparation used in Dr. Russell's study and for the placebo used in his study. So, there is no difference in that respect.

DR. JONES: In terms of how it would dissociate in either acetic or basic media, would it make any difference?

SPEAKER: The dissociation would not be the difference between the active and the placebo. It is the absorption that is the difference, the active being buffered to pH 8.

DR. JONES: Related to the placebo gum, I am struck on the side effect list and then in the material we were provided that the low-dose gum, I prefer to call it, and the real placebo, both produced a surprising, to me, number of side effects that maybe are unrelated to the nicotine in the gum, and I say this in that some of these side effects, certainly the aphthous ulcers, the hiccups to some extent, some of the other effects, rarely are encountered in people chewing tobacco.

Now, maybe the tobacco chewers may be quite a

different situation, but the one thing in common is the nicotine. It seems like even the nonnicotine-containing placebo gum may have some mild, albeit, toxicity of its own. I don't know if that has to do with flavoring agents, or whatever, but it certainly confounds things.

My third question, and the last one, Dr. Chairman, is that I am surprised at the quit rates in the Russell study at the early point, which seems to be the most impressive demonstration in the placebo group, or the low-dose group, if you prefer. Twenty-four percent of the smokers were abstinent. Now, maybe these are different quit rates -- you know, we are using different criteria for quit rates -- but I assume there was an ancillary treatment; that is, these people were meeting in weekly groups, besides getting the gum.

That 24 percent is low compared to most studies I am aware of, certainly, in this country, and even if you compare it to Dr. Christen's data, where there was minimal intervention besides the gum, they had a 34 percent quit rate at that early point. Was there something funny or strange about the low-dose placebo group in your study, Dr. Russell, or am I being just a little bit too harsh?

Isn't that an unexpectedly low response? And if you had a real placebo, might there be a higher response, the logic being that the low-dose gum doesn't provide enough nicotine to really be therapeutically effective as compared

to the high dose, but it contains enough nicotine to be aversive and maybe taste a little worse, et cetera, than if a real placebo would be done?

I am just trying to build a case where does one really need a real placebo treatment to make sense of your data?

DR. RUSSELL: No, I don't think so. I don't think the success rates of the placebo group were atypical of the support control groups that we have used in previous studies. I think it is difficult to compare success rates in different groups of clientele.

People who come into our clinic are obviously a different kind of person than in other studies, so I think you can only be happy comparing the same population who have been subjected to different treatment processes. I don't think our placebo group was at all atypical of our clientele.

If I could just come back to that question you raised just before about the side effects on the placebo gum. Quite a number of those side effects were related to chewing, and anyone who is going to be chewing a lot and are not used to chewing, might have sore tongue and burning throat for a little while.

But, again, these symptoms need only to be recorded once in six weeks. There was a checklist providing all the suggestability elements. They had a checklist listing all these symptoms, and they just had to put a tic if they felt

any of them at all. Now, I suggest that if you have got a group of heavy smokers, mainly middle-aged, and you got them to rate over six weeks and you gave them a checklist of things like headache, feeling faint, a lot of them might say so.

As regards mouth ulcers, mouth ulcers is actually a known side effect of giving up smoking with no gum at all, so I don't think there is any real evidence that placebo was having significant side effects due to the small dose of nicotine it contained.

DR. COHEN: Thank you. Dr. Leber, and then Dr. Wallenstein.

DR. LEBER: I would like to make a point of something that I consider us, as the Agency, somewhat expert on, and that is the issue of how reliable are the incidence numbers one obtains in controlled clinical trials for any type of adverse reaction associated, presumably, with product use.

I will tell you, we are impressed always by the large variation. If you look at page 2 of B, the sponsor's handout, you will see what things like criteria variance, just not using the same terminology, will do to a particular rate. For example, look at headache, the incidence in the United States versus the incidence in the British studies.

This isn't unusual even when you are using the product in many different centers, and one of the reasons recent adverse reaction sections of product labelings emphasize

that one cannot compare two products or even two different centers too easily from these incidence data sets is that because of the variation, depending on how you inquire, how you define, how frequently you ask, whether you use systematic survey or casual reporting, all influence incidence rates.

So, we have taken the stand that only if you use trials of the same design, really poolable by the same rules that you would pool efficacy trials, can you fairly really compare incidence rates of ADRs.

Otherwise, they vary all over the lot, so I wouldn't be too impressed by them. Certain things do stand out in this list, that there are things that happen, for example, like hiccups, that do not in both countries happen with the so-called placebo gums.

But I think there is great variation in rates of ADRs.

DR. WALLENSTEIN: I have some questions for Dr. Russell concerning the cohort design. I presume that patients were assigned to the cohorts in groups, so that they could participate in group support and therapy, and this can in a study produce placebo effect, halo effects, where you have individual groups being affected by varicus methods in that group.

Now, what I was wondering was whether or not you have analyzed the data in terms of the responses within each

of the 12 cohorts to see how consistent responses were within the cohort, because one of the things that can happen is that one or two cohorts can influence your total data one direction or another, and from the way the data were presented we have no way of knowing this.

DR. RUSSELL: If I may, Mr. Chairman, I would ask my colleague, Dr. Jarvis, to address this point.

DR. JARVIS: We were, of course, aware of the possibility that you could get group effects like this, so we looked at possible between-group differences in the process measures we took during group meetings, their rates with the gums or withdrawal, and we found no significant differences there, nor did we find any significant group differences in outcome in the early stages of treatment.

So, we didn't find any evidence for those group processes affecting major variables in a way that would suggest -- nor, in fact, did we find between-group differences in pretreatment patients.

DR. LEBER: Partly speaking to your question, though, is the analysis used by Drs. Russell and Jarvis is not the analysis that is used by the FDA. When we present the FDA's analysis of the data, we will try to take into account the method of randomization for cohort in our analysis, and we will explain why.

I think it does deal in part, not with all of your

question, but perhaps you can then ask it of our statisticians.

DR. COHEN: Jo Ann?

DR. NUIT: Relative to that, I believe, if I interpreted your data properly, you had six different sessions where people could come back, your cohorts, but you had a mean of 2.4 that people actually did come back. That is less than 50 percent of the sessions they attended.

So, how do you interpret that in terms of the efficacy of whatever therapy you were giving them or whether there were any cohort effects? In other words, whether certain cohorts liked to come back together. Did you analyze that? Did certain cohorts all come back and other cohorts hate each other, so they didn't come back? Was there any of that kind of effect, such as what Stanley is talking about?

DR. RUSSELL: Certainly some cohorts were better than other cohorts in terms of the group process and their sticking together. One cohort in particular had a very high success rate and also the attendance rate was generally the most successful of all cohorts. The attendance rate is composed not only of those who attended any, but also includes those who dropped out before attending any group sessions. So, that dilutes the overall average attendance somewhat.

DR. NUIT: Do you think the validity of showing those data as a mean, though, makes any sense? For me, to see a mean when you have cohorts, and you are expressing it as

individuals, really. What you really have is cells of individuals. Aren't those data a mean of individuals --

DR. RUSSELL: The 2.4 is a mean across all individuals.

DR. NUIT: Well, what if you took the mean of cohorts?

DR. RUSSELL: I don't believe that we have analyzed the data in that way. Perhaps the FDA has, or others, but we haven't done that.

DR. LEBER: We didn't do that specifically, but we are trying to look at it as a cohort model of treatment, because presumably -- I don't want to steal Dan Marticello's thunder, and I won't -- he is going to try to decide and explain to the Committee why we believe what the data are and what they are useful for. It may not be precisely what Drs. Russell and Jarvis believe, but I think it comes out in a given direction, and I think the Committee is anticipating many of the things that the FDA went through when first looking at these data, and maybe it is appropriate to hear the FDA's analysis and then come back to the Committee discussants.

DR. COHEN: I agree. I think you are quite right that we ought to go forward. First, I would like to hear a last question from Dr. Jasinski.

DR. JASINSKI: Just in terms of perspective, I too have tried the gum with the nicotine, and this is sort of a simple-minded question to put some of this in perspective from

Merrell people. If somebody would have had 4 milligrams of nicotine available from a piece of chewing gum or 2 milligrams, if that is marketed, if someone goes into the store and buys some chewing tobacco and takes a wad of chewing gum of normal size, how much nicotine is available to them buccally in that instance?

DR. McNABB: May I have slide 69, please?

(Laughter)

I am offering a comment or two that Dr. Ebert was going to make in his remarks. We do see a number of tobacco chewers on the ward of our VA hospital, and about half of those people are chewing tobacco because that is the way they stopped smoking cigarettes, and the other half have been life-long chewers of tobacco.

We have drawn blood specimens while the individual was chewing tobacco from 20 to 25 individuals and the mean of those afternoon plasma nicotine levels, while the person had the chew in his mouth, was 24 nanograms per milliliter for 20 to 25 subjects.

(Slide)

Now, this particular slide here, these are studies from two different individuals, plasma nicotine on the Y-axis and time on the X-axis. I don't have the pointer, but the solid line represents an individual putting in a chew of Red Man Chewing Tobacco at 0 minutes, an ordinary chew, and

then starting what he usually does with his chewing tobacco, and you see that curve over a period of 60 minutes.

Then the dashed line represents an entirely different individual chewing one piece of 4-milligram chewing gum. So, it seems that the chewing tobacco may even create a level a little faster and perhaps a little higher, or about the same as the 4-milligram gum.

DR. COHEN: Thank you. At this time we would like to hear from Dr. Frank Vocci on his impressions of this submission.

PRESENTATION OF DR. VOCCI

DR. VOCCI: The first thing I am going to do is review the chronology of the submission and discuss what FDA said about the Fee and Fagerstrom studies.

(Vu-graph)

The initial submission came in March 17, 1981 and, as Bob Powell told you, there were 14 studies submitted, and this was the review by Dr. Barrett Scoville. Twelve of these 14 studies were rejected either for lack of efficacy or critical flaws in either design, conduct, or analysis. This left us with two studies that Barrett pegged out to show some evidence of efficacy. These were the Fee study and the Fagerstrom study.

The Fee study I will discuss first. We commented to the sponsor regarding the deficiencies in the Fee and the Fagerstrom studies in the not approvable letter of July 23rd.

Merrell-Dow at that point requrested a meeting and they met with FDA on August 12, 1982. At that meeting we discussed the requirements for NDA approval and the following agreements were reached.

The Fee and the Fagerstrom studies would not serve as primary evidence or, in FDA terminology, as pivotal studies to determine Nicorette's efficacy. Two adequate and well-controlled studies, and I emphasize the plural there, would be required.

The Company said that it already had obtained the data from Dr. Russell, the 12-month study, and asked that one U.S.-based study be done, and this was the study done by Dr. Christen. At that point in the meeting we decided that we had to come up with a definition of a smoking cessator, what do you mean when you say someone has quit smoking versus a smoker who quits and then backslides into smoking again.

We came up with the following operational definition. A person was declared a cessator if he stopped smoking within 24 hours of study and remained abstinent until the rating period. Those failing to stop smoking within 24 hours or who lapsed from abstinence prior to the rating would be considered treatment failures.

The claims of smoking cessation would be verbal self-report with a carbon monoxide verification. The primary efficacy variable to be decided in the studies was defined as

a statistically significant difference in proportion of subjects who achieve cessation on drug compared to placebo at one month after initiation of treatment. Now, obviously, you have heard the studies that were given today. Dr. Russell encouraged his people to stop smoking within three days, so there is obviously one deviation, but this was done and I don't think that is a critical deviation at all.

Dr. Russell did not do carbon monoxide verification at the one-month or the six-week time point, and I don't think that is critical. In the Christen study it was done.

(Vu-graph)

This is the Fee study. The design was a random double-blind randomized trial comparing Nicorette versus placebo. One of the problems with analyzing this was again alluded to by Dr. Powell. Dr. Fee sent the data directly to FDA and a protocol was not submitted with the application.

It becomes a little difficult to decide exactly whether or not the randomization, for example, was performed correctly. Dr. Fee did not send in his method of randomization, so there is no way of knowing. There are 352 patients in three different cohorts.

It was a five-week study and the efficacy criteria in this study, patient diaries were evaluated for smoking cessation, carboxyhemoglobin levels, and urinary nicotine. Other data gathered were adverse effects, the amount of gum

used per day and the feelings of the patients about the gum.

Nicorette was superior to placebo with respect to dropout rate, which is not a good primary efficacy variable, but it was also superior with respect to those claiming abstinence as a percent of starters, those claiming abstinence as a percent of completors, and one odd or curious result that shows why you do need some biochemical validation was that there was a differential deception rate; that is, 26 percent of the group who claimed to quit who were on Nicorette actually had not quit, and 12 percent on the placebo who claimed to quit were also still smoking.

Dr. Scoville's comments were directed toward the method of randomization, which is really unknown, and there was a question about the adequacy of the blinding, because these patients were, again, in cohorts and there is a question as to whether or not the patients could have broken the blind.

We could possibly get Dr. Fee to address these issues, but we haven't as yet. Dr. Hauptman is in the audience here, the statistician who did the first analysis, and he came up with some comments, also. He thought the biochemical validation data were confusing.

A certain subgroup had biochemical analyses, 145, and 207 patients did not. We had some questions as to which ones and why and of the group who didn't have the analyses, how do you verify that they really had quit, given the fact that in

those that you did validate, you had a differential deception rate.

The second question that Larry brought up was, again, a cohort question. Here is a study that is designed as a cohort study and they were apparently analyzed by individuals. We thought the study should be reanalyzed taking into account the patients were in three separate cohorts.

(Vu-graph)

The Fagerstrom study. This was double-blind randomized trial, blocks of 10 patients randomized, comparing Nicorette versus a flavored placebo in a smoking cessation program. I think this has the obvious strength of having a flavored placebo.

There were 100 patients in the group, six-month treatment with six-month follow-up, and the follow-up was apparently done by post card.

DR. POWELL: After the six months, yes.

DR. VOCCI: The efficacy criteria in this study were, number one, retention in treatment, completion of six-months of treatment and return for follow-up. This was one that we had a little difficulty with. Return to old smoking habits. This was determined monthly.

We weren't quite sure what Dr. Fagerstrom meant by that. For example, did this mean total abstinence, or could someone go from being a two-pack-a-day smoker to a 2-cigarette-a-d

smoker and still be considered a treatment success? That is just one kind of question. Abstinence claims were verified by end-expired carbon monoxide concentrations, which had to be less than 4 parts per million, which I think is pretty stringent.

The results, this is at six months, in the Nicorette group were that 13 of 49 had returned to smoking and, in the placebo group, 27 of 49 had returned to smoking. The dependence questionnaire, which has been alluded to by Dr. Powell and shown by Dr. Christen, the Q score for determination of biological nicotine dependence was used in this study.

Dr. Scoville had the following comments. He was unclear as to what the definition of recidivism really meant. He wanted to know how often carboxyhemoglobin was measured, what the dosages of Nicorette were, and the intervals at which the gum was discontinued, and he also had a question about the quality control of the tabulated data versus individual records.

Dr. Hauptman's comment was again directed towards carboxyhemoglobin. He wanted to know whether a single or multiple analyses of carboxyhemoglobin were performed. Again, I will redirect you up to efficacy, comment B, the return to old smoking habits was determined monthly, and we are unclear as to whether biochemical validation was obtained monthly or only at the six-month time point.

Dr. Fagerstrom is here and he may want to addresss some of these issues.

(Vu-graph)

This is the Christen study. As Dr. Christen pointed out, this is really a modified protocol on dental pathology parameters that he had originally started. The modification was incorporated on July 27th of last year, and the modification was to have participants return at six weeks to assess smoking behavior.

Dr. Christen already had designed, as he told you, a double-blind placebo-controlled randomized trial in a smoking-cessation program. The smoking cessation, as he said, was really the, the program aspect, was rather minimal. There was a psychological intervention and a videotape viewing and counseling from the American Cancer Society.

At that point the patients were allocated to either Nicorette or placebo gum. This was a true placebo, there was no nicotine in the placebo gum. The number of study participants, there were actually 250 study participants, 200-plus received gum.

The efficacy parameters were those which FDA and Merrell-Dow had agreed upon, verbal self-reports of abstinence validated by end-expired carbon monoxide concentration, in this case less than 8 parts per million. Other data gathered were the Fagerstrom Q scores for nicotine-dependence and the amount

of gum usage.

Now, some of the data. The dropout rates were not significant. This is something we always look at. The placebo dropout rate was 8.7 percent, Nicorette, 12.4 percent. Sample sizes by Q stratum or dependent stratum, there is a slight tendency here, which is marginally significant, the Nicorette group had a greater number of highly dependent subjects than the placebo group.

(Vu-graph)

If you look at the demographic and behavioral characteristics across groups, as Dr. Christen told you, the Nicorette group was somewhat younger, marginally significant, and they had less years of smoking, again at marginally significant level.

I guess the main point I would like to stress is that these people were chronic smokers, you are talking 15.2 years in the Nicorette group versus 17.6 years for the placebo group. If you look at gum usage as a function of dependence stratum, the high-dependence Nicorette group chewed the gum more often. That is, I guess, an indirect measure. I guess you can interpret that a couple of ways, but I found that kind of interesting, it is 9.7 versus 6.3 sticks per day, and that was highly significant using a t-test.

Looking at the primary variable, abstinence for six weeks across groups, the Nicorette group had a 34.3 percent

abstinence rate versus a 10 percent abstinence rate for placebo. Using chi-square analysis, this gave a significance probability at the .001 level. If you break it down and as abstinence as a function of the dependent subgroups, as Dr. Christen told you, the drug appears to be more efficacious in the high-dependence group, but still shows efficacy in the low-dependence group.

(Vu-graph)

Now, the Russell study. Most of what we got from the actual design was from the British Medical Journal publication by Drs. Russell, Jarvis, and associates. I guess perhaps I should explain that FDA usually previews protocols and in this instance obviously we could not, because they study had already been completed.

As Dr. Russell told you, in the academic setting he and his colleagues had a handwritten protocol which they followed. There was some question about the randomization scheme. It actually was submitted by the sponsor. This was a classic card shuffle without replacement for the clinical trials. This is a very acceptable method.

Each cohort, which consisted of, again, about 10 patients, was assigned to either Dr. Jarvis or Dr. Raw, and each patient in the cohort received the same treatment, either Nicorette or thel-milligram unbuffered gum.

Now, I think in this type of a design it is more

critical to have, number one, the cohorts all receive the same treatment, and possibly to have a quote-unquote active placebo, because the patients were going to be meeting weekly for six weeks, as opposed to the Christen study, where the patients came in, received their treatment, and came back six weeks later.

So, there was -- what you would surmise from that, I think, was that there was a lack of a group effect or a potential group effect of breaking the blind in the Christen study, whereas the Russell study you would be concerned with the patients breaking the blind, and I think Dr. Russell opted to do it in this manner.

There is a secondary concern of the therapist possibly breaking the blind, and I think Dr. Marticello is going to speak to that. There are 58 patients per group here, which is three groups per treatment per therapist. Chemical verification was done in a nonsystematic way; it was used as a motivational tool.

The subjects were told that Dr. Russell had a "chemical lie detector" to ensure accuracy of self-reporting, and they used end-expired carbon monoxide.

The efficacy analysis in this instance was abstention from one week to week four. This was the primary efficacy variable. We had agreed to the one-month time point as opposed to the one-year time point in that meeting in August of last

year.

Now, we get to the analyses. The demographic and pretreatment smoking characteristics, the Nicorette group smokes slightly more cigarettes. If you look at the proportion of gum users by group or by therapist, there were no significant differences.

These are the success proportions as a function of therapist and cohort and also treatment and, Dr. Wallenstein, you can see that one group here and the Nicorette group did have a very high success rate, an 80-percent success rate. The success rates in the Nicorette groups went from 22 to 80 percent; in the placebo groups went from 10 to 40 percent.

(Vu-graph)

If you look at overall abstinence proportions, and these were analyzed by individuals rather than cohorts, there is no difference across therapists, but there is a difference across gums. Nicorette has approximately a twofold increase in abstinence proportions.

These data are categorical data and if you look at an odds ratio, you get 3.28. If the cohorts were pooled, a Mantel-Haenzel yielded a 6.54, a one-sided significant value of .005. There is a question as to whether or not the statistical analyses should have been one-sided or two-sided, and my feeling was that the hypothesis here was that Nicorette would increase the likelihood of smoking cessation; we were not

looking at a null hypothesis in terms of whether Nicorette would possibly decrease or equally likely cause a decrease in smoking cessation. So, I thought a one-sided significance analysis was appropriate.

There was an alternative analysis done, a weighted least-squares analysis, performed by the Company, with cohort replicates, because of the large difference in cohort success rates. And here, again, it shows a significant effect at the one-month time point by gum, but not by therapist or lack of gum-therapist interaction.

When the cohorts were pooled, this also yielded a significant value by the gum but not by therapist or lack of -- also not significant. There were some questions that our statisticians had about the analysis of the Russell study, and Dan Marticello is going to go over that. He will actually give his reanalysis of the Russell data.

But I think our Division has concluded that the Christen and Russell studies are adequate and well-controlled studies which demonstrate the efficacy of Nicorette.

Before Dan gets up to speak, Dr. Dassler is also going to discuss some of the side effects.

DR. COHEN: Dr. Dassler --

DR. LEBER: It might be more useful, actually, to have Dan go, because he is looking at efficacy data, and have Brigitta -- that is what I had hoped I could do, because I

think yours will logically follow Frank's.

PRESENTATION OF DR. MARTICELLO

DR. MARTICELLO: I will start off by considering the domestic study conducted in Indiana. As has already been mentioned, 208 smokers were randomized to placebo, 103 subjects, or Nicorette, 105 subjects. Twenty-two subjects, 13 on Nicorette and 9 on placebo, dropped out of the study and did not participate in the six-week evaluation.

Of these 22 subjects, 17, 7 receiving placebo, 10 receiving Nicorette, did not receive any treatment. Subjects that self-reported as not smoking and who were evaluated with an expired carbon monoxide level of less than 8 parts per million at the six-week visit were considered successes, all others as failures.

Based on these criteria, the sponsor reported that 36 Nicorette and 11 placebo subjects had successfully quit smoking. In my analysis, I excluded the 17 pre-gum dropouts from the analysis, those 17 subjects that did not receive any treatment.

In doing that, I obtained smoking cessation rates of 37.9 percent, that is 36 of 95, for the Nicorette group, and 11.5 percent, that is 11 of 96, for the placebo group, a highly significant difference, a p value of one in 50,000, in favor of Nicorette.

In this analysis, the 5 remaining dropouts -- recall

I said there were 22 -- were treated as failures, an assumption that does not alter the highly significant results detected in favor of Nicorette. In total, 62 subjects, 44 on Nicorette, 18 on placebo, p value of one in 10,000, reported that they were not smoking at six weeks, although, as I have already mentioned, only 47 of these were validated by the expired carbon monoxide test of less than 8 parts per million.

I conducted a further analysis which indicated that the significant results obtained with respect to the non pre-gum dropouts are not sensitive to the less than 8 parts per million criteria. The reason I did this is because I didn't find any mention in the protocol of this cutoff, 8 parts per million, but no matter where I put the cutoff, it doesn't affect the results of highly significant differences in favor of Nicorette.

As far as side effects go, 6 Nicorette subjects reported hiccups at the six-week visit, no such reports from the placebo subjects, a p value of .013. In addition, at two weeks, significantly more, p value of .001, Nicorette subjects reported hiccups and nausea than did their placebo counterparts.

However, in comparing success proportions between subjects who experienced side effects and subjects that did not, I did not detect any differences which might indicate that the blind had been broken, which was one of our initial concerns.

So, as far as the domestic study is concerned, in conclusion, based on the data supplied by the sponsor, a significant difference in favor of Nicorette 2-milligram chewing gum over a placebo chewing gum was demonstrated with respect to six-week quit proportions.

One other concern I had was that neither the protocol nor the study report submitted by the sponsor indicated whether or not there was a discernable difference between the taste of Nicorette and placebo chewing gums. This is a factor that could possibly have affected the blindedness of the study. I guess some individuals have tasted the placebo already, although not the Nicorette.

That concludes my remarks on the Indiana study.

DR. COHEN: Thank you. Dr. Fagerstrom has to leave early and would like to respond to some of the remarks already made.

DR. LEBER: He is not finished with his study.

DR. COHEN: Oh, I am sorry. I thought I heard you say --

DR. MARTICELLO: That is just with respect to the Indiana study.

Okay, on to the Russell study. As has already been mentioned, a total of 116 smokers, 58 receiving the Nicorette 2-milligram chewing gum, the other 58 the unbuffered nicotine 1-milligram chewing gum, were randomized by cohorts rather

than by individuals. Each of two therapists was randomly assigned to six cohorts, three on each treatment.

The cohort sizes ranged from 8 to 11. Initially, each investigator was assigned four cohorts, and this was subsequently increased to six. Smoking cessation proportions were statistically analyzed at the one-month and one-year evaluation points.

The sponsor defined an abstainer as one who had been substantially free from smoking throughout the study period from week two to the evaluation time of interest, and a quitter as one who was not smoking at the time of evaluation, but who had not necessarily been abstinent throughout the prior study period.

At the one-month evaluation point, which we are concerned with today, only abstainers were considered.

The sponsor reported that 11 subjects, 6 on Nicorette, 2 milligrams, and 5 receiving the unbuffered nicotine chewing gum, were lost to follow-up and were considered treatment failures. Consequently, the one-month abstainer proportions, as you have already heard, are 48 percent, 28 of 58 for the Nicorette, 2 milligram, group versus 24 percent, 14 of 58, for the 1-milligram unbuffered nicotine group.

This resulted in the sponsor reporting a one-sided Mantel-Haenzel p value of .005 in favor of Nicorette. However, we felt that this method of analysis is incorrect in that it

assumes that patients are independent of each other, which is not the case, due to the method of randomization employed -- remember we randomized by cohorts. For this reason, in order to determine if a dose-response existed, I conducted a Wilcoxon ranked-sum test on the cohort success proportions, treating the 12 cohorts as the experimental units and ignoring therapists, because there does not appear to be a therapist effect.

In this case, I obtained a one-sided p value of .032 in favor of the Nicorette 2-milligram chewing gum. I also noted that the largest differences between treatments and the number of side effects reported at least once during the first six weeks of treatment were with respect to hiccups, 29.8 percent versus 4.5 percent, p value, one-sided, of .027; indigestion, 51.1 percent versus 27.3 percent, one-sided p value of .047.

The higher percentages, now, are associated with the 2-milligram treatment group. Nausea, 38.3 percent versus 20.5 percent, a one-sided p value of .066. This raised the concern of whether or not the blind was affected by these different side-effect-incidence rates.

But in performing an analysis, I did not detect, a p value of .36, any indication that the side-effect incidences influenced success proportions. Consequently, it does not appear that the blindness of the study was influenced by side

effect rates.

In conclusion, my analysis of the Russell study results in a marginally significant difference, a one-sided p value of .032, in favor of the Nicorette 2-milligram chewing gum with respect to one-month abstainers.

DR. BALSTER: Did you look at any time at the effect of the number of sessions, even on an individual basis, with respect to outcome?

DR. MARTICELLO: No.

DR. COHEN: Do you have anything further?

DR. LEBER: There is an exaplanation for that. The sessions were every six weeks, every week for the first six, so you could have looked at three by our time, a four-week analysis.

DR. MARTICELLO: We looked at four weeks, yes.

DR. LEBER: So, there were only three sessions for those four weeks.

DR. COHEN: Does that conclude your report?

DR. MARTICELLO: Yes, it does.

DR. COHEN: Dr. Fagerstrom?

DR. FAGERSTROM: Thank you very much for allowing me to speak at this time. Unfortunately, I have to leave this interesting meeting, and I think it will be even more interesting as the time goes on. I think I could clarify some of the questions that were raised according to my study.

According to dosage, it was only 2-milligram gum used in my study, just 2 milligrams. Carbon monoxide tests, when were they made? It was always carbon monoxide values taken before smoking cessation, just before and just after, but that was for therapeutic reasons to show the patients what was happening.

But for reasons of control, it was made at six months. The carbon monoxide test was made on every patient at six months. By return to old smoking habits, which is an unprecise statement, I apologize for that, I mean that almost every one of those who didn't succeed to abstain returned to their old smoking habits.

It was very, very few that reduced their smoking for any long time.

DR. VOCCI: The question was whether this return to old smoking habits was taken in some sort of a continuum sense, a qualitative continuum, or were these people totally abstinent at six months?

DR. FAGERSTROM: Those were counted as successes. I haven't applied the same conservative and stringent criteria as Dr. Russell. They were abstinent by means of the carbon monoxide value and I regarded them as nonsmokers, but some had had occasional cigarettes, and even in my clinic they could have an occasional cigarette.

DR. LEBER: I think what we were trying to get at

is how you declared winners, not so much how you declared losers. In other words, could someone who entered with a three-pack-a-day habit go to one pack a day and be declared a winner?

DR. FAGERSTROM: No. No, never.

DR. LEBER: What was the minimum amount of smoking that you would allow that would still allow a patient to be declared a winner at any particular time point?

DR. FAGERSTROM: I applied a criteria that they should, with verbal statement, at least not have smoked anything at all 14 days prior to the carbon monoxide test, and since I had personal contact with these subjects during the whole period, I knew fairly well their kind of relapses, if they were long or short and how intense, and so on.

I think this is a very serious matter for short follow-up points, but when we go so long as six and 12 months, smokers don't relapse and quit again, relapse and quit again. But they may do so for a couple of weeks.

DR. COHEN: Thank you very much. It is a pleasure to have you here.

I think this is time for Dr. Dassler to present the view of the FDA Drug Abuse staff.

PRESENTATION OF DR. DASSLER

DR. DASSLER: I have only to make a few remarks, since I evaluated the safety data of the two studies, two new studies submitted, and several of the things I am mentioning have

already been mentioned, but just to be complete and be on the record, there is, of course, no doubt that smoking behavior is a risk to public health and there is also little question that nicotine intake, regardless of the route, causes many pharmacological effects and many of these are known to be harmful.

We also expect that Nicorette gum is likely to be highly promoted and widely used, so, therefore, any assessment of the risk-to-benefit of Nicorette must consider two factors. The first one, whether or not the gum is effective and then, second, how safe is the gum when used as prescribed.

Seen from this public health perspective, the first factor has been presented to you by Dr. Vocci in the affirmative. As to the second factor, I have the following comments. Nicorette gum, as used in the two studies, contained 2 milligrams of nicotine bound to an exchange resin and is released only during chewing.

Pharmacokinetic study results provided to us by the sponsor showed that blood levels of nicotine obtained with the Nicorette gum, with the 2-milligram Nicorette gum, were half those obtained from smoking a cigarette, and the pronounced early peak in nicotine blood levels seen with the inhalation of cigarette smoke was not observed with chewing of the Nicorette gum.

Nicorette gum is an adjunct to smoking-cessation programs under medical supervision for short-term use in

normal heavy smokers that primarily has its advantage by removing the exposure to carbon monoxide tars and various noxious agents contained in cigarette smoke, but leaving exposure to nicotine, a known potentially harmful substance.

Therefore, I would consider Nicorette contraindicated in nonsmokers. There have been no studies demonstrating the safety of Nicorette in disadvantaged smokers such as subjects with known or suspected coronary heart disease, including myocardial infarction and/or angina pectoris, or in patients with vasospastic disease states, just to mention a few of these subjects at special risk.

Therefore, no judgment could be provided as to the safety of Nicorette in smokers with systemic disease. On the other hand, the side effects observed and reported by the investigators of the two studies under discussion in the target population of the 324 healthy smokers, half of whom smoked the 2-milligram Nicorette gum, consisted mainly of local effects within the oral cavity and soreness of the jaw from the chewing and of gastrointestinal symptoms, including, as we heard now, vomiting and hiccups, none serious enough to require discontinuance of the use of Nicorette.

With the exception of the incidence of hiccups which were reported more frequently with Nicorette when compared to the placebo gum, there were no significant differences. Little information is available on long-term

safety or on Nicorette's potential to cause dependency.

Also, the results Dr. Christen told us on the oral pathology testing we have not had a chance to review and so we have not completed this aspect.

In conclusion, the substitution of Nicorette chewing gum for cigarette smoking is expected to eliminate the elements of carbon monoxide and tar inhalation with their attendant pulmonary and circulatory effects, while leaving the systemic effects of reduced amounts of nicotine.

Considering the overall benefit-to-risk ratio for the 2-milligram nicotine-containing buffered chewing gum as a source of nicotine for a limited time, up to three months, as an adjunct to smoking cessation programs in healthy heavy smokers, I consider it acceptable.

DR. COHEN: Thank you. We want to hear now from the Committee discussants. Dr. Jasinski?

PRESENTATION OF DR. JASINSKI

DR. JASINSKI: As a discussant, let me tell you where we are particularly coming from. As the scientific director of an intramural laboratory in the National Institute on Drug Abuse, our mission is to study the causes, treatment, prevention of substance abuse.

About four years ago, the National Institute of Drug Abuse took the position of trying to be the lead agency in investigating tobacco dependence, and this came about for a

number of reasons, so that we started a particular program as part of the Institute.

Can you flip on the first slide.

The purpose of these studies was to investigate -- I want to go through this, because I think it is important to the discussion, because I think there are some unresolved issues that are at least alluded to -- and investigate the mechanisms underlying compulsive tobacco use.

Our hypothesis, to begin with, is that nicotine is a dependence-producing substance, and this is somewhat important, because when you start talking about tobacco-smoking or cigarette-smoking, there are certain biases which are social biases that tobacco is somewhat different and is not a dependence-producing substance.

Our basis for this was to compare tobacco, which contains nicotine, versus opium, and cocaine and alcoholic beverages, and cannabis, each of which contains a substance which has certain properties, and it was hard for us to see that God would make tobacco somewhat different from other substances which people ingested compulsively.

(Laughter)

Part of this is that in terms of looking at this as a dependence-producing drug where there is this particular confusion, is on the relationship of what are some of the behavioral effects in the relationship?

From the study of other dependence processes, the pharmacological effects are necessary, but are not sufficient. The whole process of addiction involves a process of learning, as my friend Dr. Balster will tell us, environmental factors, and biological factors which may predispose, and there is this complex interaction when one looks at this.

However, if one is interested in developing therapy and using the model of narcotics and other substances where we have made this in developing rational therapy, it has been basically pharmacologically based in chemotherapy.

(Slide)

If one looks at the characteristics of dependence-producing drugs, one is they are psychoactive, and by this I define it when given versus placebo under various circumstances they have the ability to alter mood, feeling states, thinking, and perception.

Two, they have the particular ability, at least in our population and addict populations, to act as euphoriants, and by this I mean produce feelings of well-being and people like the effects of the drug better than placebo or some other drugs. There are particular states which are reproducible.

Thirdly, in models they serve as positive reinforcers and some, but not all, produce tolerance and physiologic dependence.

DR. COHEN: Give me an example of one.

DR. JASINSKI: LSD.

DR. COHEN: That produces enormous tolerance.

DR. JASINSKI: But not physical dependence.

DR. COHEN: Oh, yes, of course.

DR. JASINSKI: Now, we have conducted large numbers of studies in human volunteers and also in animals, and these are my colleagues: for the animals, Dr. Steve Goldberg and Dr. Jack Henningfield for the human studies.

This is just a basic summary and these have been conducted on a research ward, a closed research ward, using the paradigm we have had for many years, and we basically looked at the abuse potential of nicotine as a dependence-producing drug.

Now, we have studied this both intravenously, by giving boluses of nicotine and by smoking, and these are basically the summary and conclusions which are important. Delivered intravenously or inhaled, it is psychoactive and physiologically active; that is, people can tell it from placebo and they can discriminate the content of cigarettes when you smoke them under certain characteristic ways, and they can discriminate among different nicotine contents of cigarettes and they can discriminate among boluses of saline and various doses of nicotine given intravenously. It is a euphoriant, and by this I mean that the people like the effects of nicotine given intravenously, the group responses

show increasing rates on liking scores.

Most importantly, we get many of the scales which we validated with cocaine and morphine and the amphetamines. When you take people and abstain them overnight and give them boluses of nicotine, you can produce euphoric responses which are similar.

If you ask people to identify what the effects of nicotine are given in intravenous boluses, they say it is very close to cocaine, that it is cocaine-like.

Now, the other experiment is, it can serve as a positive reinforcer. We did large numbers of subjects and experiments. It is a simple paradigm, essentially have cigarette smokers abstain from smoking and we put them into a chamber and we put in an intravenous line which is gravity-fed and going into the intravenous line are two infusion pumps.

One has saline and one has various doses of nicotine and these are hooked to two levers and they have access and when they press the lever 10 times, they get an infusion of nicotine. The question is, will people take intravenous nicotine in preference to saline offered alternatively when they are abstaining from cigarettes and, yes, they do.

We published this. Then we get very high reinforcing rates and the pattern of taking is very similar to that seen with animals taking cocaine under similar paradigms, or if you watch people smoking cigarettes, it is about the same rate

of smoking cigarettes. It is also dose-dependent. You get the very nice curves very much like the animal experiments. It goes up and, as you increase the dose, it goes down. We have met all of the criteria for defining a positive reinforcer for our friends in behavioral pharmacology -- I won't go through that, all of this has been published.

(Slide)

If you give a larger dose of nicotine in some subjects, or if you increase the dose very rapidly, in other words, give them access very rapidly to large doses, it is also a dysphoriant, that is, it produces aversive effects, and can serve as a negative reinforcer, that is, it can suppress behavior.

This is not different from other substances of abuse. All substances of abuse do this, if you take too much or too little and it is within a particular dose range.

The fourth point that is important, and this gets to be somewhat confusing and it will be important for the discussion to come, if one gives boluses of nicotine or watches somebody smoke, nicotine has very profound effects, but they are short-lived.

By this I mean that the most profound effects are within 45 seconds after the bolus or within the first minute after smoking or puffing on cigarettes. There is predominantly an increase in blood pressure, there is a pupillary dilation

which lasts for 45 seconds, then followed by a longer lasting pupillary constriction. There is usually a tachycardia. With a very large dose of nicotine, one, or puffing very rapidly on a cigarette, one can get a bradycardia. The autonomic effects are quite complex.

There are also different pharmacodynamic half-lives. For example, if one measures -- with the blood levels, if one measures the skin temperature effects, there is a hysteresis. By this I mean that the skin temperature effects do not correspond in time with the subjective effects or the euphoriant effects.

They come on much more slowly and last much longer. I won't go into this, but we have shown that mecamylamine blocks the responses and attenuates the subjective effects and euphoric effects and alters self-administration behavior.

Now, we have done nicotine delivered i.v. and buccally and by inhalation. We show that it decreases reported desire to smoke and a rate of cigarette smoking, and on the basis of this we concluded that nicotine is a dependence-producing substance which is similar to prototypic substances of abuse.

I would like to discuss the gum from this particular perspective.

(Slide)

This is a poor slide -- it is a new process and it

didn't work too well. We have done some experimental paradigms and, I am sorry, this is from another presentation. The hypothesis is that nicotine should substitute and decrease smoking behavior.

We have evidence from other studies that we did that after people would inject intravenous nicotine in the self-administration paradigms where we give it to them, that their smoking behavior would decrease, and we have done it in two populations.

On is in our post-addict population who are paid volunteers to study drugs, who have no interest in quitting smoking. They are just there and they reside on the research wards, an in-patient controlled access research ward. The other were out-patient female hospital employees.

I will just give you -- this is from a presentation I gave about a week ago down at the Committee on the Problems of Drug Dependence -- and these people on the ward chewed Nicorette chewing gum in two doses and placebo. The doses were the 2 or 4 milligrams and placebo and these were daily, and these were given in seven doses at two-hour intervals, and each dose in placebo was replicated three times each.

The measures were taken all day in a controlled ward and, in fact, under this condition -- I am not going to present all the data, just to show you that if one looks at all of the measures which we had, and they all were in

particular concordance, one can reduce the smoking behavior in this group who is not motivated to quit smoking when one particularly compares this.

One does not, even with this, however, abolish smoking; one reduces the smoking. This is not very different from what people have shown with drugs such as methadone in animals which are, for example, self-administering narcotics.

One can suppress the behavior, depending upon the dose, but one cannot usually abolish the behavior. I think that is somewhat important in many of these considerations.

(Slide)

The conclusions after all of our studies is nicotine administration suppresses cigarette smoking behavior. Nicorette chewing gum appears to be efficacious in delivering nicotine. Now, we found that from the nicotine chewing gum that it has a nicotine-like side effects which in some subjects may limit its utility, because they just won't like it and won't chew it, and they will go back to cigarettes. Basically, it is the nausea and the unpleasant taste -- the stuff tastes pretty bad.

Can you turn off the slides and put the lights on.

The other issue is a question which was raised in that letter which we address, coming from our particular perspective, is the abuse potential of this stuff. We have attempted to do this, and that is, we have attempted to study

it in the same paradigm as we studied the intravenous and the smoking of the nicotine.

Here we were also faced with the placebo issue. One issue which has not been addressed, which we have had to address in this, in the particular question, if you listen to the gum, the rate of release of nicotine is compression-dependent, so that if you chew the gum faster, you get nicotine out faster than if you chew is slower.

So, we have done a controlled experiment and we have had people chew the gum for 10 minutes; however, we have had this done under a nurse-observer in controlled circumstances with a timer, where this a crossover study where they chewed at one-second intervals, and two-second intervals, and four-second intervals, and eight-second intervals -- again, because many times the blood levels don't help, because the question is whether you can get this bolus effect if you chew rapidly.

Briefly, even though one can chew at one-per-second, one shows a greater degree of effects chewing at every eight(sic) seconds, but in contrast to the intravenous or the inhaled, one, we cannot, even at this rapid rate, show a euphoric response.

What we basically see is essentially a slight degree of effects, which are in the same trend, but they are not as great as with the intravenous, and we tend to get an

accumulation more of what we see, the dysphoric effects, with -- rather than the euphoric effects. We could not get the quick release with chewing the gum through the buccal absorption, even chewing at one per second.

However, it is psychoactive. Subjects can discriminate, and they can report a greater effect at one-second than at the eight-second intervals, and there are slightly greater effects, but we cannot get the same jolt that you get from the intravenous or the cigarette. Thank you.

DR. COHEN: Thank you. Reese Jones?

PRESENTATION OF DR. JONES

DR. JONES: It is hard to follow a set of slides like that. We have been looking at nicotine in our laboratory for five years, even before NIDA decided to support such work, which sometimes leads a lot of people to start doing nicotine studies, or whatever.

I can't add much to what Donald said. We find surprisingly similar sorts of things and it poses some interesting sort of conceptual, almost philosophical, issues in terms of dealing with something like Nicorette and nicotine gum, in that nicotine clearly is a drug of addiction, it is a very potent drug.

I don't have a slide, but if you give nicotine to nonsmokers intravenously, the threshhold dose is somewhere around 1 microgram per kilogram i.v. You know, it is getting

in the range of LSD and other drugs that we think of as being incredibly potent drugs. I will bet you it could even be in the range of LSD.

So, the smoker is someone who has a fantastic level of tolerance, if that is true. That becomes an issue, and I would rather just make a few points about the data at hand here, rather than the research data, which will only confuse some people more.

But that tolerance issue raises at least one point that troubles me, that I think we need to consider -- the FDA has already considered -- what do you really need for a placebo? Should it be a real inactive placebo? Is any placebo inactive in this day of endorphins and enkephalins? Or should it be a placebo with a little bit of nicotine in it? How much nicotine should be in it? And since we don't know the bio-availability at that dose at those levels in the unbuffered form, really, I think Dr. Russell's data are reassuring, but they are certainly not the sort of data I think we would demand if this were almost any other drug, treating almost anything other than tobacco dependence.

The fact that tolerance develops so rapidly and so profoundly, it may well be that inactive placebo is inactive for the first week or so of treatment, as the tobacco smoker loses tolerance from the decrease in the tobacco smoking. Perhaps there is enough sensitivity that develops to that

dose that it is no longer a placebo, and I do have some continuing concerns about sort of a trade off between aversive and reinforcing qualities, depending on as the sensitivity changes.

Our group has been looking at tobacco dependence in treatment programs for some years. That leads me to be increasingly concerned about the short-term assessments of efficacy. Nicorette clearly, no question about it, looks good at one month, better than other treatments that have been studied in comparison to it, better than whichever placebo we are considering.

But is one month an adequate assessment period? I am not so sure. But if we were considering a new anorexic agent and the efficacy data mainly made it look good at one month in terms of weight control, I don't think we would be terribly impressed, and this is very much the case with the treatment of tobacco dependence.

There are lots of things that look good at one month, ranging from acupuncture to hypnosis to most any sort of mumbo-jumbo you want to put the tobacco addict through, but they all look very good and better than no treatment at all.

What is an adequate difference? We have already heard different groups in different countries, presumably for all sorts of different sociological and pharmacological and cultural reasons have different sort of base-line rates for

no treatment versus various treatments.

It makes it even more necessary to consider whatever data one is considering and comparisons, whatever one is making, draw it from the same data pool. I am not at all certain that smokers in England are anywhere like the smokers in Indianapolis or the smokers in San Francisco in all respects -- I am quite sure they are different in many respects.

The one thing that puzzles me in the material we were given as a Committee to review is if 1.4 million people throughout the world indeed have been given Nicorette, why are there so little data presented in terms of its effects in special groups, especially in special groups that it is going to be prescribed for?

And here I refer to people with a variety of cardiovascular diseases, pulmonary disease, pregnancy, adolescence, a number of -- I won't go through the special considerations in such special groups, but many of them are obvious and important.

Maybe it is not the custom when an NDA is approved with a new drug to worry much about that and say, well, the data will be accumulated. The problem is, Nicorette is not a new drug, if we consider that 1.4 million patient experience But I am getting a mixed message in terms of whether we should consider that or not.

Given the very limited charge to our Committee, and

it is stated a couple of different places, but most succinctly, I think, it is under Tab R, that what we are being asked to consider is can one conclude that Nicorette increases the likelihood of smoking cessation among participants in behavioral modification programs?

This term, "behavioral modification programs," is used slightly differently in a few different places in the material, ranging from adjunctive treatment to psychological treatment, et cetera. Well, the answer to that very limited question, if we are talking about the short-term treatment, is, yes, probably.

But there are these other considerations that I don't see alluded to in the material that we received, particularly the issue of special groups and risk versus benefit and efficacy. If this advertisement that we were sent by the DOC organization, which I gather is an advertisement from a Canadian medical journal, is typical, it exemplifies some of the concerns I have of introducing a drug at the state Nicorette seems to be at.

It says it is going to be an aid that will help, but it doesn't give -- now, maybe there is a package insert disclaimer along with this ad that gives the busy physician some guidance as to who and what should provide the help.

It sort of lumps cardiovascular patients all together and says, implies Nicorette is a useful help for this. Does

this include people with vasospastic disease? I think people with such diseases can have a lot of problems with Nicorette. Should this be considered in terms of data provided for an NDA? I don't know.

It talks about impressive success rates. I don't think we would be having this meeting if all of us were as impressed with the success rates as this ad says they are. I wish I hadn't seen this, really, because I felt a little bit differently before I saw it.

But this sort of raises the spectre of what should the process we are doing now provide in terms of making something a little bit more explicit and helpful than this? Thank you.

COMMITTEE DISCUSSION

DR. COHEN: Thank you, Reese. On the other hand, Reese, consider the alternative, that is, continued smoking versus Nicorettes.

DR. JONES: If the alternative is one month or even six months continued smoking versus Nicorette, I don't think that is much of a concern to me. If it is a question of smoking or not smoking, no question; I am willing to accept all sorts of toxicity for the treatment.

But I am not sure that is the data that we have here.

DR. LEBER: I think it is important that I frame this question for you, again, because I think, as Ed Tocus

suggested, this Committee is not used to dealing with efficacy matters that come before the Food and Drug Administration. The law, in the first place, does not set out very clearly what is meant by efficacy. It really says evidence of efficacy that will allow experts to conclude, on the basis of evidence from these controlled trials, including clinical investigations, and to conclude fairly.

The magnitude of the treatment effect is not one that we have ever solved. No one ever specified how much effect a drug must have. The conditions that lack treatment, the argument is often as long as a drug can help someone out there, that was the intent of the Congress in the efficacy requirement in the '62 amendments.

It doesn't have to be like an OTC product where a substantial proportion of the individuals have to experience the effect in the labeling, only that the drug is effective enough to produce a change in the right direction which is not due to chance and which can be accounted for by the drug, by whatever mechanism that drug works.'

In other words, a lot of the discussion today that has been dealt with deals with the rationale, the, if you will, explanatory pathophysiology, the mechanism of how the drug might work. Actually, if we didn't know how this drug worked, it wouldn't make any difference. That may help you in making a decision, but the basic question is, can you

conclude from the evidence presented that the drug will have the effect it is alleged to have under the conditions of labeling and purported use?

There are all sorts of concerns that everyone gets into in answering that question, which is part of your role as an expert, of saying not how the drug will actually be used -- that is an issue always beyond us. How things are actually used is not really an issue here; it is something you have to consider, but not in a direct way. I want to make that point.

Another issue, do we, in a typical NDA drug, look at every special disadvantaged population? No. It is impossible to do so before marketing. If we did, we would have drug lag that would be unbelievable. A lot of what is learned about a drug is often learned because the drug is studied in a population where the drug is going to be used.

What is so exceptional and different about this, which I think Dr. Jones recognizes as well, is that we are not dealing with the traditional model of a drug. We are dealing with a model of a substitution of something people are already getting for something in an effort to reduce an alternative source of the same substance, and to provide it, if you will, even for a short period of time, in a vehicle or format that we think is slightly less toxic.

I don't think the model of anorectic drugs is exactly the same, even though it has some parallelism. The

difference would be that most people who are obese, trying to lose weight and have a high degree of recidivism, are not taking flurfenamine (phonetic) or amphetamines all the time, and when they do take them, they take them for a short time which has short-term effects that may not be good, and then they may lose some weight and become recidivistic.

Here the patients involved, the people involved, they are already taking the nicotine and they are taking the nicotine plus something else, so that applying the standard that we use, that you don't have to be totally efficacious, that you don't have to have some minimum degree of efficacy, that the risk-benefit seems to be, on base grounds, reasonable, given fairly restrictive labeling, and that is the position we have taken, and I think it is partly the position that we would like you to address this in.

There are much broader societal issues, and I am not trying to suborn your testimony. If you were to conclude that this is a horror for the public health, by all means say so and tell us not to proceed, because we don't want to make any mistakes.

DR. COHEN: Thank you. Before Dr. Paul makes his remarks, I would like to ask the Committee whether they would like to break for lunch or continue the discussion and close the meeting.

DR. GOODWIN: Continue.

DR. COHEN: Thank you. It is unanimous.

(Laughter)

DR. PAUL: Paul answered my question. I mean, I think we should be able to get some data, as Dr. Jones said, about those 1.4 million people. There is one thing worse than -- I mean, it is clear if you have the alternative between smoking or abstaining, I think it is obviously much better to abstain, and certainly the alternative is bad.

As the case with benzodiazepines and many of these drugs, you end up getting a population of patients that are taking both. The question I would have, is there any chance that people could actually increase their nicotine consumption and maybe make things worse, you know, outside this very limited sort of indication? I don't know if there are any data from those 1.4 million people, whether you get a population like that.

DR. COHEN: Would the sponsor like to respond to that?

DR. OHYE: With reference to the 1.2 million that Dr. Martz referred to in his opening remarks, it is our intention to go to the sophisticated countries, for example, Canada, U.K., and Sweden, where they have adverse drug reaction reporting systems, and just prior to FDA's action on the drug seek a computer printout from these various sources, so that with reference to any blips that might be out there

we will certainly obtain those.

Incidentally, in the case of the CSM or the U.K. FDA, we asked for their cooperation just prior to this meeting and we were told, well, there really isn't anything there. It is not an important issue at this point for us to run our computers.

But we will ask for that information and with respect to any ongoing studies that we are sponsoring, we will gather up all data and submit them at the last moment. Now, with reference to your second question about these special groups, if in our discussions with the Food and Drug Administration they identify areas for Phase IV studies, as is the custom between FDA and the industry, we have agreed to perform studies as a condition, if you will, a condition subsequent to approval.

On your third question with reference to data on people who both chew and smoke at the same time, we do have some data on that, if you deem it important to show it on a slide, but, in summary, the data show that there are no major differences or spikes in the data with reference to people who titrate their nicotine levels by smoking or titrate nicotine levels by chewing and smoking a bit, too.

DR. LEBER: I think I would like to do another point again, directed to Dr. Paul. I think there are perhaps 1,200,000 people exposed to Nicorette throughout the world. The situation isn't so different with many other drugs we deal

with.

However, the question is, even with that presumed source of data available, what use can one make of it and how would one do it? We have enough problems, in a way. We are dealing with domestic inferences from fairly well-controlled data bases where people actually make a great effort to link events to drug exposure from automatic prescription lists.

It is very, very hard to assign, unless you have a denominator, what is going on. For example, let's assume that 20 percent of the people who smoke and 20 percent of the people who used Bendectin had myocardial infaractions in a particular data-reporting system. How would you interpret that?

The problem always is denominator and the issue of compared to what, and I am not sure how we would make use of data from around the world, unless we found specific things. For example, let's define diversion, misuse, covert sales, theft, a higher rate of dying in people compared who are taking smoking within six weeks of myocardial infarction versus using Nicorette.

Those would be planned, almost epidemiologic studies rather than, I think, casual surveillance of --

DR. PAUL: Well, the beginnings of --

DR. LEBER: But that is not something we are likely to get before the fact in a realistic way. I am just trying to put limits on what our expectations are for foreign data,

that is all.

DR. JONES: I can see the problems with the surveillance data, but -- and you will have to inform me here, because I don't know about this efficacy business -- these are not normal, healthy people that this drug is going to be prescribed for. They are going to be people with varying degrees of cardiovascular disease and pulmonary disease and other diseases that bring them to the attention of the physician and the physician thinks that somehow tobacco is associated and will prescribe it.

Is it customary when a drug is going to be prescribed to non-normal healthy people with various diseases, take cardiovascular disease, to do at this stage of the process some experimentation? I don't see any good electrocardiographic data anywhere in the file.

The one study from the Forney group was good so far as it goes, but it didn't go very far. Since this is going to be given to people, and since we know from years of experience nicotine has acute cardiovascular effects, whether such data should be provided or, if not, why not.

DR. LEBER: Well, I guess the question I ask you is the logic of asking for such data. If this population that is using Nicorette had never taken nicotine before, what you say makes entire sense. I think even when we prepare a drug like an antidepressant or anxiolytic for marketing, we have

only limited Phase I and Phase II data, perhaps, on EKG performance, and the most cursory type of supervision, that really tells you what would happen if you went out and used somebody who had Mobitz-type block with this drug product.

We are just not going to know that. It is true, after the fact people begin to develop that kind of information. As a general thing, I think, drugs are developed with some understanding from clinical pharmacology of what effects they have on various organ systems and then you go into the population at risk.

The population at risk for depression certainly includes, for example, patients who have heart disease. A significant number of them are older men who are depressed and living alone, with multiple diseases, and yet the antidepressant would be used.

We decry the lack of information, but we would not use that as a reason to keep the drug off the market. Now, what I see as the exception with Nicorette, and I would like to hear this argument, is that we are willing to waive all sorts of things we normally do with a drug product, because we think we understand the pharmacology of nicotine.

We think we know that nicotine is a cardiovascular poison, if you will, something that increases afterload, something that is bad for you. So, what is the point of comparing Nicorette gum with cigarette smoke that is already providing

what we think, on the basis, say, of the studies that were presented earlier, 2 milligrams versus cigarette smoking, the same load?

DR. JONES: Well, I guess the only problem is that if people are dying of the nicotine they are getting in their cigarettes -- and I am not sure that nicotine in cigarettes is interacting with carbon monoxide, it is a complicated situation and maybe the nicotine is relatively nontoxic -- but if they are dying, say, they are developing arrhythmias and dying from smoking tobacco, does that justify marketing something that does the same thing?

The logic of that somehow escapes me. Maybe I am missing some point there.

DR. PAUL: I am still concerned about how the drug is going to be used. You have sort of set these limitations about this drug is prescribed in smoking-cessation programs and with behavioral modfication -- I mean, almost any drug prescribed doing that would have a markedly limited use potential relative to just without these kinds of limits, but I don't see anything in these advertisements to indicate that -- I mean, is that what the FDA is going to do or demand?

DR. LEBER: Again, this is partly -- let me start, first, with what is legal and what is advertising puffery, and what is American advertisements and what are non-American advertisements. I cannot speak for the journal editorship,

the type of advertisements that are accepted, and whether or not we would want advertising. Clearly we control one thing in the federal government, under our regulations we can control what the labeling of the drug product says, that is, professional package insert.

In theory -- I say in theory -- you are only allowed to advertise what we say about the drug product in the official labeling. In practice, it often appears that other things appear in labeling, sometimes with photographs, using photo-montage techniques to suggest the use of the drug product in a population that nobody has any data on.

Those things go on. That is life. And I don't know whether or not we will effectively regulate that as much as we would like to. But we are not discussing that here. I don't think -- that is a general class problem of advertising, advertising puffery, and the use of drugs beyond their labeling.

We even have an official FDA statement. It says even though we approve a drug for a given use, it is understood that the physician has the right to use this product any way he wants in his reasonable practice of medicine under the community in which he operates.

For example, there were a couple of letters to the editor saying that nicotine suppressed, or there seemed to be an association with less ulcerative colitis in people who

smoke a lot of cigarettes. What happens if some guy decides to take his ulcerative colitis patients and use Nicorette? That is perfectly reasonable, he can do that in the practice of medicine, because he has that information.

Let's assume that you get a foolish physician and he decides to put all his patients on Nicorette. The FDA's role is not to protect society from foolish physicians, and a lot of this has to do with the societal question of where you put the controls on the practice of medicine.

Are they going to be distally between the diad of the physician and the patient, or up here in Washington between ourselves and the release of the drug to the public. Those are such broad questions, that I tried to steer you away from them in the way I pharsed today's question.

Now, clearly, the Committee doesn't want to stay away from that. The Committee has a very broad interest and I will, having said that, go back to your discussion, but I think we try to focus on the issue of in the evidence presented to you, do you believe you can conclude something?

DR. PAUL: I guess most of us may not have much trouble with the way the thing is phrased, but have a lot of trouble with how the drug might be potentially used. I guess that doesn't bother you, for some reason.

DR. LEBER: Officially --

DR. JONES: It can't bother him.

(Laughter)

DR. VOCCI: Just to address one of Steve's questions. This NDA is unusual from several aspects. Usually you have pharmacology and toxicology data in preclinical studies which address some of the long-range toxicity issues. There are toxicity data which speak to some of the issues in the NDA, but it was essentially a literature survey.

So, what we decided to do was, we are going to time-limit the indication on the basis of the clinical studies and we will ask that people use the gum for no longer than three months -- I think this is what we have agreed to.

Again, and you have to keep going back to this, you are always talking about giving this to a smoker or someone who has quit smoking and is trying to stay off cigarettes. We see this, not in the classical sense of a drug, but in the sense of more of a methadone model, where you are doing a substitution procedure. I think this is the proper context.

DR. JASINSKI: Do you want another methadone?

DR. COHEN: You are out of order.

(Laughter)

DR. COHEN: Reese, did you still want to ask your little question?

DR. JONES: Well, it is a little point, but now Dr. Leber, I think, has convinced me, but a point that hasn't been made so far. Most smokers who want to stop smoking stop smoking

without any particular professional intervention, is my guess. I have seen good data on this and perhaps Dr. Russell or someone else may have some data on how many smokers are able to stop without any intervention.

What the availability of this will do, the gum will do, is more incline people to resort to pharmacotherapy when odds are they don't need pharmacotherapy. Now, agreed, this is the problem of the physician and the patient, and I am now convinced it is something that cannot be regulated and it is not our province, but it is a consideration in terms of perhaps demanding the best evidence of efficacy that we can.

DR. COHEN: Dr. Jasinski?

DR. JASINSKI: I want to come back, and I would like to get out of here, too, but going back to your efficacy issue, I will tell you one thing, I am amazed that Nicorette looks so good, and I will tell you this on the basis of my experience looking at years of studies with neltrexone (phonetic) and methadone which, again, is a particular model.

First of all, what strikes me with regard to the efficacy issue, you have a drug which is active, which has a known pharmacology. Secondly, whether rightly or wrongly, and this is true for most drugs you introduce into therapeutics, which we use in therapeutics, the way they are eventually used may not do this, but you need at least a rational justification for this use, and there are enough basic science data which

gives a rationale for its use in medicine. I think that is a second issue in terms of efficacy.

The third issue, given the particular state-of-the-art of looking at suppressing what is essentially a behavior and measuring this in long-term studies -- I speak again for the methadone -- this drug looks awfully good, because I came expecting to see that there were two studies that didn't show anything and two studies that didn't do anything, and what is quite clear, apart from all the statistics, is that what appears to be the most significant factor across all the studies is the presence of the drug versus other factors.

I am amazed, because in the experience of looking at methadone and neltrexone, all of the other variables tend to negate the methadone and the neltrexone in terms of incidence of cures -- you know, different programs have a very marked difference in the drug, it isn't particularly effective.

Fourthly, with Dr. Jones I will point out that I suspect that in most of his practice he will use methadone at times to treat certain people who are using narcotics, recognizing that the toxicity of methadone may be equal to or greater than heroin, but hopefully to achieve certain issues within this.

And I suspect that the role of this -- we are not talking about this type of efficacy -- and I will suspect that, very much like this, he and I and most of us who treat

drug abusers, would be using this drug for heavy cigarette smokers in this manner, to attempt to detoxify people or at least to suppress some of their behavior.

DR. COHEN: Dr. Goodwin, you have been unusually silent.

(Laughter)

DR. GOODWIN: I want to move that, considering the evidence presented, one can conclude that Nicorette^{R} gum increases the likelihood of smoking cessation among participants in behavior modification programs.

DR. NUIT: I second that.

DR. COHEN: It has been seconded. Further discussion is allowed at this point, but only to the motion.

DR. BALSTER: I would like to just make a comment for the Committee and to the FDA and bring to their attention some additional support for that motion that Dr. Goodwin has made, and that is that I, being a laboratory scientist, I was impressed with direct laboratory studies showing that a manipulation can affect smoking behavior.

I am thinking particularly of the study that Don just showed us of some data where Nicorette gum, namely, 4 milligrams in his particular case, could affect smoking behavior when it is given in a preload in a situation which is not a smoking cessation program.

There are many studies -- in fact, Dr. Russell is a

leader in this field -- and there are probably a good half-dozen or dozen studies in which attempts to look at the role of nicotine preloading in affecting cigarette smoking behavior have been carried out. My impression of these studies is, in general, they support the notion that giving nicotine by some preload or some other route of administration does, even in a nonsmoking-cessation situation, alter cigarette smoking behavior.

I am looking at a paper by Koslowski (phonetic), Murray Jarvik, and Ella Gritz in the January, 1975 Clinical Pharmacology and Therapeutics where, again, they fooled people into thinking they were doing some kind of mouth-muscle test and had them chew something for an EMG, but really what they were doing was slipping nicotine into them and then laying some cigarettes around and looking to latency to smoke and, sure enough, the latency to pick up a cigarette when they got a dose of nicotine was longer.

These kinds of studies are particularly convincing to me that it is the nicotine in the Nicorette gum that is responsible for what is going on in these elegant and long-term double-blind studies.

DR. BALTER: To the motion I have one residual problem. This is supposedly adjunctive therapy in motivated people who came to stop smoking. I am a little bit bothered by the behavior modification and I hope we don't reify a

particular kind of therapy. I don't think we have the kind of data before us that would say if you are not practicing behavioral modification, there is no indication for this Nicorette gum.

DR. GOODWIN: I would accept an amendment to the motion that you would delete the term "behavior modification" and substitute the term "smoking-cessation program."

DR. JONES: How about acceptable adjunctive therapies, or something as broad as possible, because I don't think anybody has --

DR. GOODWIN: Yes, something broader than behavior modification. Can you word that?

DR. BALTER: Well, we are talking about psychosocial at the moment. You don't mean another drug. Some effective psychosocial therapy.

DR. GOODWIN: Counseling.

DR. COHEN: Are you ready to vote on the motion?

(No response)

Apparently you are. Those in favor of the motion as amended to broaden the scope of the type of therapy with which Nicorette is supposed to be used, please raise your hands.

(Show of hands)

Those opposed?

(No response)

Those non-voting?

(No response)

It is carried. Please keep your seats.

(Laughter)

The motion is carried, 10, 0, 0.

I would like to ask someone to make a motion regarding either that this drug should be scheduled or should be unscheduled.

DR. GOODWIN: I move it should be nonscheduled.

DR. NUIT: Second.

DR. COHEN: Any discussion? Those in favor of --

DR. JONES: Wait, wait, wait. This formulation I have no problems with. I am not sure if when someone brings out the aerosol that you spray in your throat that I would go for that.

DR. NUIT: We already have that. It is smoking.

(Laughter)

DR. JONES: I am quite comfortable with the gum being nonscheduled. I am not quite --

DR. GOODWIN: I move the gum be nonscheduled.

DR. TOCUS: We have been talking about reinforcing substance and we are talking about a substance that has, as you just said, has a reinforcing and an abuse liability, and as such we must address, before we can deal with a new drug application approval, the question of whether we would

recommend control or not, and that is what we are trying to do here.

DR. VOCCI: One of the things that hasn't been brought out is that this is going to be a prescription drug product. It hasn't been stated, but it is. We consider prescriptions a form of control.

DR. COHEN: No, it would be in scheduling --

DR. VOCCI: I know, but this is something that you were asking about, a little bit of drug abuse philosophy --

DR. JASINSKI: Just for clarification, the FDA's position is that the drug does not require control and they are not proposing this for control. Is that --

DR. LEBER: The NDA (sic) does not have a position.

(Laughter)

The FDA. The FDA does not.

DR. COHEN: Was there any further discussion?

DR. BALSTER: This seems to me to be a bigger question than we should pass by with a five-minute kind of a thing. I am going to vote against that motion. I believe that nicotine as a pharmacological agent possesses some of the properties under which the Controlled Substances Act requires us to make scheduling decisions, and I am going to vote against this motion.

I didn't realize this was a question for discussion today. I think it would have taken a lot more discussion to

work through all the issues related here.

DR. COHEN: Apparently this is arousing more than a five-minute discussion.

DR. BALTER: Apropros of Reese's point earlier, if you look at prescription as a form of control, but not the one under discussion, the likelihood that it will only go to decrepit people is also not true, because then if this is advertised and it becomes clear it is effective, you may have young people going to physicians to get the thing. That is another point.

I didn't hear much data, except Reese's reference to naive -- take the model of the naive person who is exposed to the gum as opposed to the smoker who has a history of habit-reinforced as well as, possibly, dependence on the medication. We haven't heard much about what happens in naive people if they chew this gum.

I am not saying that I necessarily would vote against this motion on that basis, but this quickie is worrying me a little bit.

DR. GOODWIN: I view it as grandfathered. Tobacco and alcohol have been excluded in certain ways from FDA control. This is the nicotine in tobacco and, also, I think we were ill-prepared for this. I think if we debated it all morning, we would still vote noncontrol. But if we are going to have more than a five-minute discussion, I withdraw my

suggestion that we don't have lunch.

(Laughter)

DR. LEBER: I would make another suggestions, and this is just a thought. Usually, when we come with official questions to you, we have had a good time to think about it and develop an in-house position on it and, very frankly, we did not come to discuss the issue of control today.

I think that in fairness to everyone, the people who were saying wait a minute, let's not jump, and I think it is always better to consider things -- remember, we always have the option to control anything any time we want to, if it turns out to be diverted and abused.

We will counsel among ourselves and perhaps independent with you outside of this forum, which we are allowed to do, try to get some sense of where things stand and, if need be, at our next meeting -- it may not be the same set that examines the issue -- but we would have to have a submission, we would have to have data, we have several points of analysis that would be necessary, and you would have to consider evidence.

Because, again, if you remember, the philosophy is you just don't do this from the top of your lip; in theory, you are supposed to be looking at evidence.

DR. GOODWIN: I withdraw my motion.

DR. COHEN: Do you withdraw your second?

DR. NUIT: Withdraw the second.

DR. COHEN: Any other business?

(No response)

Is there a motion for adjournment?

DR. GOODWIN: Anybody going to National?

(Laughter)

DR. COHEN: Apparently the meeting has adjourned.

(Thereupon, at 12:40 p.m., the meeting was concluded.)