

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
+ + +
CENTER FOR TOBACCO PRODUCTS
+ + +
TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE
+ + +

February 6, 2019
8:30 a.m.

FDA White Oak Conference Center
Building 31, Room 1503
10903 New Hampshire Avenue
Silver Spring, MD 20993

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

TPSAC Members (Voting)

ROBIN J. MERMELSTEIN, Ph.D. (*Chair*)
 Institute for Health Research and Policy
 University of Illinois at Chicago
 Chicago, Illinois

LAURA J. BIERUT, M.D.
 Department of Psychiatry
 Washington University School of Medicine
 St. Louis, Missouri

SONIA A. DUFFY, Ph.D., RN, FAAN (*Representative of the General Public*)
 Ohio State University, College of Nursing
 Columbus, Ohio

SARA (SALLY) P. HERNDON, M.P.H.
 Tobacco Prevention and Control Branch
 Division of Public Health
 NC Department of Health and Human Services
 Raleigh, North Carolina

RICHARD J. O'CONNOR, Ph.D.
 Department of Cancer Prevention and Population Sciences
 Roswell Park Cancer Institute
 Buffalo, New York

DEBORAH J. OSSIP, Ph.D.
 Department of Public Health Sciences
 University of Rochester Medical Center
 Rochester, New York

JAMES F. THRASHER, Ph.D.
 Department of Health Promotion, Education and Behavior
 Arnold School of Public Health
 University of South Carolina
 Columbia, South Carolina

KENNETH E. WARNER, Ph.D.
 Professor Emeritus/Dean Emeritus
 Department of Health Management and Policy
 University of Michigan School of Public Health
 Ann Arbor, Michigan

MICHAEL WEITZMAN, M.D.
 Department of Pediatrics
 New York University
 New York, New York

Professional Video Associates, Inc.
 2515 Saint George Way
 Brookeville, MD 20833
 301-924-1556

TPSAC Members (Non-Voting, Industry Representatives)

WILLIAM ANDY BAILEY, Ph.D. (*Representative of the interests of tobacco growers*)
University of Kentucky Research and Education Center
Princeton, Kentucky

DAVID M. JOHNSON, Ph.D. (*Representative for the interests of the small business tobacco manufacturing industry*)
National Tobacco Company
Louisville, Kentucky

WILLIE MCKINNEY, Ph.D., DABT (*Representative of the tobacco manufacturing industry*)
Altria Client Services LLC
Richmond, Virginia

Ex Officio Participants (Non-voting)

BRIAN KING, Ph.D., M.P.H.
Office on Smoking and Health (OSH)
National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
Centers for Disease Control and Prevention
Atlanta, Georgia

KAY L. WANKE, M.P.H., Ph.D.
Tobacco Regulatory Science Program
Office of Disease Prevention
National Institutes of Health
Bethesda, Maryland

Consultants (Non-voting)

LYNN KOZLOWSKI, Ph.D.
Department of Community Health and Health Behavior
School of Public Health and Health Professions
University of Buffalo
Buffalo, New York

IRINA STEPANOV, Ph.D.
Division of Environmental Health Sciences
University of Minnesota
Minneapolis, Minnesota

OLIVIA WACKOWSKI, Ph.D., M.P.H.
Center for Tobacco Studies
School of Public Health
Rutgers Cancer Institute of New Jersey
New Brunswick, New Jersey

FDA Participants at the Table (Non-voting)

MITCHELL ZELLER, J.D.
Center Director
FDA/Center for Tobacco Products

BENJAMIN APELBERG, Ph.D.
Director, Division of Population Health Science
Office of Science
FDA/Center for Tobacco Products

MATTHEW R. HOLMAN, Ph.D.
Director, Office of Science
FDA/Center for Tobacco Products

Designated Federal Official

CARYN COHEN, M.S.
Designated Federal Official
FDA/Center for Tobacco Products

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

FDA Participants

ALEXANDER PERSOSKIE, Ph.D.
Social Scientist, Population Health Science
Office of Science
FDA/Center For Tobacco Products

HANNAH DAY, Ph.D.
Epidemiologist
Office of Science
FDA/Center For Tobacco Products

Session 1 - Swedish Match Amendment

FREDRIK PEYRON
Senior Vice President of Regulatory Affairs
Swedish Match

STEVE SEIFERHELD
Director, Market Research
Swedish Match

GERRY ROERTY
General Counsel
Swedish Match

Open Public Hearing

MATTHEW L. MYERS
President
Campaign for Tobacco-Free Kids

GREGORY CONLEY
President
American Vaping Association

ALEX CLARK
CEO
Consumer Advocates for Smoke-Free Alternatives Association

CARRIE WADE
Director, Harm Reduction Policy
R Street Institute

MICHAEL W. OGDEN, Ph.D.
Senior Vice President, Scientific and Regulatory Affairs
RAI Services Company

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Session 2 - Altria Client Services LLC Application
on behalf of U.S. Smokeless Tobacco Company LLC

JOSE LUIS MURILLO, J.D.
Senior Vice President, Regulatory Affairs
Altria Client Services LLC

MOHAMADI SARKAR, M.Pharm., Ph.D., FCCP
Fellow, Regulatory Affairs
Altria Client Services LLC

GARY HARVEY
Vice President and Principal Consultant
William E. Wecker Associates, Inc.

STEPHANIE PLUNKETT, Ph.D.
Senior Director, Perception and Behavior Research
Altria Client Services LLC

RYAN BLACK, Ph.D.
Director, Regulatory Affairs
Altria Client Services LLC

TIM DANIELSON
Senior Principal Scientist
Altria Client Services LLC

INDEX

	PAGE
<u>Session 1 - Swedish Match Amendment</u>	
Call to Order - Robin J. Mermelstein, Ph.D.	9
Conflict of Interest Statement - Caryn Cohen, M.S.	10
Introduction of Committee Members	12
Swedish Match USA, Inc. Modified Risk Tobacco Product Application Amendment - Benjamin J. Apelberg, Ph.D., M.H.S.	15
<u>Applicant Presentation</u>	
Swedish Match Overview Presentation - Fredrik Peyron	21
Clarifying Questions	33
<u>FDA Presentation</u>	
Swedish Match USA, Inc. Modified Risk Tobacco Product Application Amendment: Consumer Understanding and Intentions - Alexander Persoskie, Ph.D.	43
Clarifying Questions	57
Open Public Hearing	
Matthew L. Myers	69
Gregory Conley	72
Alex Clark	75
Carrie Wade	78
Michael W. Ogden, Ph.D.	82
Committee Questions and Discussion	85

INDEX

	PAGE
<u>Session 2 - Altria Client Services LLC Application on behalf of U.S. Smokeless Tobacco Company LLC</u>	
Call to Order - Robin J. Mermelstein, Ph.D.	141
Conflict of Interest Statement - Caryn Cohen, M.S.	142
Introduction of Committee	144
U.S. Smokeless Tobacco Company LLC (USSTC) Modified Risk Tobacco Product Application - Benjamin Apelberg, Ph.D.	146
<u>Applicant Presentations</u>	
Introduction - Jose Luis Murillo, J.D.	152
Scientific Evidence - Mohamadi Sarkar, M.Pharm., Ph.D., FCCP	161
Health Risk - Gary Harvey	166
Claim Development and Testing - Stephanie Plunkett, Ph.D.	176
Population Impact - Ryan Black, Ph.D.	188
Conclusion - Jose Luis Murillo, J.D.	197
Clarifying Questions	198
<u>FDA Presentation</u>	
U.S. Smokeless Tobacco Company LLC (USSTC) Modified Risk Tobacco Product Application: FDA Scientific Presentation - Benjamin Apelberg, Ph.D.	219
Clarifying Questions	244
Adjourn	283

M E E T I N G

(8:30 a.m.)

DR. MERMELSTEIN: We're going to get the morning session started. I'm Robin Mermelstein, Chair of the Tobacco Products Scientific Advisory Committee. Thank you for joining us. A nice sunny day, better than in Chicago. Not that much. I'm going to make a few statements, and then we're going to go around and introduce the Committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by me, as the Chair. We look forward to a productive meeting today.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

You're going to read now the conflict of interest statement.

MS. COHEN: The Center for Tobacco Products of the Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the Authority of the Federal Advisory Committee Act of 1972 and the Family Smoking Prevention and Tobacco Control Act of 2009.

The Committee is composed of scientists, healthcare professionals, a representative of a state government, a representative of the general public, ex-officio participants from other agencies, and three industry representatives. With the exception of the industry representatives, all Committee members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with applicable federal conflict of interest law and regulations is being provided to participants in today's meeting and to the public.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

The purpose of this first session of today's meeting is to discuss an amendment to the modified risk tobacco product applications submitted by Swedish Match USA for these eight snus smokeless tobacco products:

- General Loose
- General Dry Mint Portion Original Mini
- General Portion Original Large
- General Classic Blend Portion White Large-12 count
- General Mint Portion White Large
- General Nordic Mint Portion White Large-12 count
- General Portion White Large
- General Wintergreen Portion White Large

Accordingly, this session of the meeting is categorized as one involving a particular matter involving specific parties.

Based on the categorization of this meeting and the matters to be considered by the Committee, all meeting participants, with the exception of the three industry representatives, have been screened for potential conflicts of interest. FDA has determined that the screened participants are in compliance with applicable federal conflict of interest laws and regulations.

With respect to the Committee's industry representatives,
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

we would like to disclose that Drs. William Andy Bailey, Willie McKinney, and David Johnson are participating in this meeting as non-voting representatives. Dr. Bailey is representing the tobacco growers, Dr. Johnson is representing the small business tobacco manufacturing industry, and Dr. McKinney is representing the tobacco manufacturing industry. Their role in this meeting is to represent these industries in general and not any particular company.

Dr. Bailey is employed by the University of Kentucky, Dr. Johnson is employed by National Tobacco Company, and Dr. McKinney is employed by Altria Client Services. Thank you.

DR. MERMELSTEIN: We're going to now introduce the Committee members and then other members around the table.

I'm Robin Mermelstein, Chair of the Committee, and I'm from the University of Illinois at Chicago.

DR. O'CONNOR: Good morning, I'm Richard O'Connor from Roswell Park Comprehensive Cancer Center in Buffalo.

DR. WEITZMAN: I'm Michael Weitzman from New York University School of Medicine.

DR. OSSIP: Deborah Ossip from the University of Rochester Medical Center.

DR. THRASHER: Jim Thrasher, Arnold School of Public
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Health, University of South Carolina.

DR. DUFFY: Sonia Duffy, Ohio State University.

DR. WACKOWSKI: Olivia Wackowski, Rutgers University
School of Public Health.

DR. STEPANOV: Irina Stepanov, University of Minnesota
Masonic Cancer Center.

DR. APELBERG: I'm Ben Apelberg, and I'm the Director of
the Division of Population Health Science in CTP's Office of
Science.

DR. HOLMAN: Good morning. Matt Holman, Director, Office
of Science in the Center for Tobacco Products.

MR. ZELLER: Mitch Zeller, Director of the Center for
Tobacco Products, FDA.

DR. MCKINNEY: Good morning. Willie McKinney, Vice
President of Regulatory Science with Altria Client Services,
and I represent the tobacco manufacturing industry.

DR. JOHNSON: Good morning, I'm David Johnson. I am
employed by National Tobacco, and I represent the small tobacco
manufacturers.

DR. BAILEY: Good morning. Andy Bailey, University of
Kentucky, representing tobacco growers.

DR. WANKE: Kay Wanke, National Institutes of Health.
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. KING: Good morning, I'm Brian King with the U.S. Centers for Disease Control and Prevention.

DR. BIERUT: Good morning. Laura Bierut, Washington University in St. Louis.

DR. WARNER: Hi, I'm Ken Warner, University of Michigan School of Public Health, and I guess I'm the rookie on the board here.

MS. HERNDON: Hi, I'm Sally Herndon, and I'm with the North Carolina Division of Public Health.

DR. MERMELSTEIN: Thank you. And we're going to move forward, then, with Dr. Apelberg's presentation.

DR. KOZLOWSKI: Robin.

DR. MERMELSTEIN: Yes?

DR. KOZLOWSKI: This is Lynn Kozlowski.

DR. MERMELSTEIN: Oh, thank you, Lynn. I'm sorry, I forgot --

DR. KOZLOWSKI: I'm also here at the University of Buffalo.

DR. MERMELSTEIN: Great, thank you for joining us, Lynn. Interrupt if I forget to ask you again. Thank you for doing that.

DR. KOZLOWSKI: Okay, thanks.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. APELBERG: Okay, good morning. I'm Dr. Benjamin Apelberg, Director of CTP's Division of Population Health Science. Thank you all for joining us for this meeting. I'll start us off today by presenting an overview of the history of the Swedish Match modified risk tobacco product applications and describing the amendment currently under review, which is the focus of today's meeting.

This is the standard FDA disclaimer, and I won't read it, but it's here in the slides.

So to provide some context for today's discussion, I'll very briefly summarize what has brought us to where we are now with a high-level overview of the history of Swedish Match's modified risk tobacco product applications. Next, I'll describe briefly the current amendment, which is the focus of today's meeting, and then introduce the question for the Committee.

So here's an overview of the timeline so far. Modified risk tobacco product applications were submitted by Swedish Match and filed by FDA in August of 2014. In April 2015 the TPSAC convened to discuss these applications. FDA completed its scientific review in December 2016, issuing a denial and a response letter. Then in September of 2018, Swedish Match

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

submitted an amendment to FDA to address the deficiencies articulated in the response letter, which I'll describe in more detail shortly.

First though, as a reminder, under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act, in determining whether a modified risk order should be issued, FDA must assess whether it has been demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population, as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. We call this a risk modification order.

In these submissions, the Applicant is seeking an order under Section 911(g)(1) for eight General Snus products. The eight products were just mentioned but they're listed here as well. They include variations in flavor and size.

In the original applications Swedish Match proposed marketing these products as modified risk through the removal or revision of certain health warnings currently required for smokeless tobacco products. In particular, they proposed removing the warnings related to gum disease and tooth loss and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

mouth cancer.

In addition, they proposed revising the warning, "This product is not a safe alternative to cigarettes," to read, "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

As I mentioned, in April of 2015, FDA brought these applications to TPSAC. The Committee discussed and voted on a range of topics in the application including the Applicant's requests to remove and revise warning labels, the adequacy of the behavioral evidence, consumer understanding, and postmarket surveillance and studies. Then, in December 2016, FDA issued a decision on these applications, which I'll describe on the next slide.

So, once again, in December 2016, when FDA concluded its review of the applications, taking into account the information submitted along with input from TPSAC and public comments, the following determinations were made.

Regarding their request to remove the gum disease and tooth loss warning, FDA issued a denial, concluding that the applications did not provide sufficient evidence to satisfy the standards of 911(g)(1), including that the implied claim resulting from the removal of this warning was not

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

substantiated.

Regarding the second two requests, to remove mouth cancer warning and to revise the "not a safe alternative" warning, FDA deferred final action concluding that, in their present form, the applications do not contain sufficient evidence to satisfy the standards of 911(g)(1). FDA deferred final action because it was determined that the applications could be amended in a way that could support an order, including by revising the requested claim and conducting additional studies.

So, in particular, regarding the risks relative to cigarettes, FDA recommended that Swedish Match consider a revised claim that was more precisely tailored to the supporting science, for example, an adequately tested explicit claim placed outside the health warning, and one that communicates information on the differences in specific health risks between the eight General Snus products and cigarettes.

FDA also recommended that if Swedish Match chose to conduct a new consumer perception study, it should address the deficiencies of its initial study, including ensuring the study stimuli test the proposed modified risk information verbatim, and if the proposed claim did appear in the warning, then the study should examine the impact of that context on consumer

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

perception and understanding.

So on September 17th, 2018, FDA received an amendment to the MRTPAs providing responses to the deficiencies outlined in the response letter. And so, in particular, the amendment proposes a revised modified risk claim, which is about the risks of General Snus relative to cigarettes, and a new consumer perception study to evaluate that claim and address the methodological issues in the original study.

Here is the revised claim. It states, "Using General Snus instead of cigarettes puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

As described, the previous TPSAC meeting involved discussion of the evidence related to the health risks of General Snus, including the risks relative to cigarette smoking, across a number of health endpoints.

With the input from TPSAC, followed by FDA's review conclusions, the Applicant subsequently revised their proposed claim with this amendment. The revised claim appears responsive to FDA's recommendations.

In addition, the Applicant conducted a new consumer perception study to assess the revised claim and to address the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

methodological concerns of their original study. Our discussion today is focused on this amendment and, in particular, on the new evidence provided by the consumer perception study.

However, in terms of our overall review process, this particular evidence and today's discussion will be incorporated into our complete review of the amended applications that will consider the broader criteria of Section 911(g)(1), including likely impacts on behavior among different groups and the potential population health impact.

So now to turn to the focus of today's discussion and our question to the Committee.

FDA's preliminary assessment of the amendment is that it addresses the concerns FDA previously identified with the claim by proposing one that is more specific, independent of the warning label, and by conducting a consumer perception study that does not suffer from the methodological flaws of their original study.

Later this morning, FDA will present the Applicant's new consumer perception study, including its design and high-level findings. We ask TPSAC to consider and discuss our preliminary assessment and further, to discuss whether the revised modified

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

risk claim raises new or additional concerns regarding the potential impact on consumer understanding and population health. Thank you.

DR. MERMELSTEIN: Okay. Thank you, Dr. Apelberg. We're going to move, then, to the presentation by Swedish Match.

MR. PEYRON: Okay. Great. Good morning, everyone, and thank you for inviting us to this TPSAC meeting. My name is Fredrik Peyron. I am the Senior Vice President of Regulatory Affairs of Swedish Match. I've been with the company since 2000 in various positions. And with me today I have Lars Erik Rutqvist and Treva Young (ph.). Lars Erik used to be in charge of our scientific affairs and he has now being replaced by Treva. They are here to answer any questions you have on the scientific support for the claim.

I also have Steve Seiferheld. He is in charge of consumer research in Swedish Match and he can -- he's been in charge for the studies, the new studies, I should say, to our application and he can answers question on that.

I also have Johan Lindholm. He is in charge of the research and development and the technical analysis related our to GothiaTek standard. So if you have any specific questions related to that, Johan would probably be the one to answer

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

that.

In 2009 when we saw the new regulation on modified risk, we felt that Swedish snus was a perfect candidate for an application and we felt that Swedish snus should have a better chance of receiving an order than any other product. We felt this because the product has been around for more than a hundred years in Sweden, and that is unique because we have a lot of population-based studies and the long-term health effects of snus are very well researched.

The MRTP regulation also tied very well into our company vision. You can see that small on the picture. Our vision is a world without cigarettes and in line with that vision, we sold our cigarette business roughly 20 years ago and we are committed to offer consumers less dangerous alternatives, which is what the MRTP is all about.

We therefore started thinking about our MRTP application almost 10 years ago and preparation started in earnest in early 2012. As you saw from Dr. Apelberg's slides, we submitted our application in 2014 and we were in front of TPSAC in 2015. It has been a very long journey with a lot of work. The most important reason for this is, of course, that the scientific criteria for an MRTP application are and should be very strict.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

I think it's also fair to say that the MRTP, we were the first to apply for an MRTP, it was a new process and both we and FDA had to learn and develop our thoughts as we went along. It is good to be back here with an application that we are proud of and where FDA has recognized, in their briefing document, that we have rectified the deficiencies they felt we had in our first application.

Before I go into the findings in our application, I want to give you a bit of background on two different items. The first item I want to shed some light on is our product standard, GothiaTek. It is referenced in the FDA briefing document that you can see at the top of the slide, and it's very important for this application, we feel.

It is through our product standard that we ensure consistency in our products. And it's because we ensure consistency in our products that we can rely on all the science on snus in Sweden over time. We know that the products we sell today are as good and actually better than the products which were the basis for the population-based research of snus in Sweden.

There are different components to this standard. Outside Swedish Match, the main focus is on the first item, the maximum

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

levels of harmful and potentially harmful components. But for us, the second and third points are also very important because that's how we achieve those levels and guarantee that -- that the consumers can trust that we won't have any higher levels.

We also believe in honest communication about the risks related to our products, and we have made that part of our standard.

Our work of reducing the health risks related to our products started already in the '80s. We were the first company to work systematically to reduce tobacco specific nitrosamines in our products, and on the next slide you will see what we have managed to achieve. There will be some bragging here.

This is a slide that we are very proud of. As you can see from this slide, we have dramatically reduced levels of tobacco specific nitrosamines and benzopyrenes, and I mention those because they are the most controversial compounds in our products. The GothiaTek standard covers a number of other HPHCs. We add new HPHCs as we go along and we continue to reduce levels of HPHCs.

As you can see, we started in the '80s, and we reduced until 2000, and we've continued to reduce, and when you see the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

slide you also see that there is a lot of variation in the old days, and that's because there is variations in the raw material, different crop years have different tobacco specific nitrosamine levels, but we have now managed to come down to low and always consistent levels.

The second topic I would like to give you some background on is consumer understanding of relative risk. That's what an MRTP is all about and you need to understand the background a little bit.

These are the consumers from snus coming out of the most recent PATH Study, when it comes to relative risk between cigarettes and snus. So as you can see, I've made a circle there to clarify that point. Very few cigarette consumers understand that snus is less harmful and therefore they have no reason to switch from cigarettes to snus.

Consumers tend to stay with their products of choice unless you give them strong reasons to switch. We are simply not giving them that reason. They don't understand that it would benefit their health to switch from cigarettes to snus.

Of course, this is not going to change overnight if our MRTP application is granted, but it will be a step in the right direction and over time consumer understanding will be

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

improved. We want to contribute to the same trends in the U.S. as we have seen in Sweden over a number of years.

On this slide you see consumer trends in Sweden and this is what I'm talking about. Among Swedish men, we have seen a dramatic fall in smoking rates as smoking has been replaced by snus. The smoking rates among men in Sweden are less than half of those of any other European country. Less than half. And this is, of course, reflected in the health statistics. You will not see these kind of trends in the U.S. unless more consumers understand that there is a difference in risk between different products.

Now to the application itself. I'm not going to read the text of the claim, Dr. Apelberg did that. But before we talk about it, we should spend some time and I will repeat a little bit what Dr. Apelberg said on the -- what is required under the statute for an MRTP application.

First of all, an application must demonstrate significantly reduced individual risk. I will not spend a lot of time today talking about this but it has been extensively covered in the FDA briefing document, which I assume that you've all read, and the FDA concludes that the claim is scientifically accurate.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

It also has to be demonstrated that there is a benefit to the population as a whole, and we have done that by demonstrating that our proposed claim leads to increased interest in snus among current tobacco consumers at the same time as it does not increase the likelihood of use among never users. And that last point is, of course, very important and it will be one of the things that FDA will keep a close eye on in postmarket surveillance.

It is important to remember that receiving an MRTP is not the end of a process, it's rather the beginning. There will be postmarket surveillance to verify that the effects that are shown in the consumer research comes true in the real world.

I promise you that I will be short when discussing the scientific support of our claim. I refer you to the FDA summary on this in the briefing document. There is a lot of science related to snus, as I said. The FDA has made a thorough scientific review and has compiled a summary on the available science for each of the disease endpoints mentioned in the claim and that is the summary you see on this slide, and if you have very good glasses, you can probably also read it.

The FDA's conclusion is that there is scientific support for the claim. To a large extent, this was also the reason for

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

General Snus being the first product to receive a PMTA a number of years ago and it's still the only one.

I will speak briefly about the claim itself and how it was developed. From the technical product review letters to the original MRTP application and from the meeting we had with the FDA following this letter, it was clear that there was apprehension about the claims on general risk reduction. It was clear that claims about specific disease endpoints would be easier to validate in science, and this played a large role in how we drafted the claim. We read what the FDA wrote and we've tried to comply.

It was also clear that we needed to prioritize consumer comprehension of the claim itself. We therefore measured the readability scores according to a recognized standard, the Flesch-Kincaid readability scores. And the claim was finalized after testing in qualitative consumer research. And when we did that consumer research, we found that the research supported the use of the word "instead" rather than "exclusively," as it felt more natural to respondents and that some respondents confused "exclusively" with "appealing" or "attractive."

On this slide you see one example of how the advertising
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

will look in real life. I think it's very important that you remember that there will always be warning labels with the advertising. These are the rotating -- you see to the left, you see the four rotating warning labels that we will have on the advertising. So the consumers will always be informed; at the same time as they see our claim, they will always be informed about the risks related to our products.

As you also see that the warning labels are also on the cans of the product and we will not put the claim on our cans, only in the marketing materials.

The consumer research was well extensive, at least to our mind. Prior to embarking on the study we submitted the study protocols to the FDA for comments and we cross did a study with those comments in mind. In the end, the study included over 10,000 recipients. Vulnerable populations such as young adults and nonusers were oversampled.

Here's the 1-minute video with or without the MRTP claim to determine the effect of the claim in the test versus controlled study format.

The study was designed to give answers on a number of issues. Specifically, we wanted to understand if exposure to MRTP claim led to improvement in the understanding of relative

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

risk compared to cigarettes and to dual use. We wanted to understand if we would see continued understanding whether General Snus carry health risks and of course, if there was an increased intent to use among current users and among nonusers.

In terms of the findings from the consumer study on understanding of consumer risks, I will again take the liberty to cite the FDA briefing document in my slide and I hope you won't repeat this, Dr. Apelberg, in your presentation.

As you can, consumers continue to perceive General Snus to be present serious health risks in the presence of the MRTTP claim. There was improvement in the understanding of relative risk compared to cigarettes, and there was also improvement when it comes to understanding that complete switching is required to obtain reduced risk.

The second question is if the improved understanding of risk translates into increased likelihood to try these products. The results set out in the table on the slide shows that the claim would lead to statistically significant increase in interest in trying General Snus among older cigarette smokers. It also shows that there is directional increased interest in trying General Snus among younger cigarette smokers after having seen the claim. Note that we did not see any

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

significant change when it comes to never tobacco users or former cigarette smokers. The conclusion is that with the claim we would see more cigarette consumers moving to snus, but we don't see any evidence that the claim would lead to non-tobacco consumers coming in.

One important factor to consider is if the claim would lead to increased dual use of snus together with cigarettes. This slide shows that this is not the case. Both among the older and the younger cigarette consumers you see increased understanding that you have to smoke zero cigarettes per day to obtain the benefit. In looking at this slide you also have to consider the background slide I showed you at the beginning, from the PATH Study.

Although the MRTP claim had possibly an effect on consumer understanding of relative risk, many of the study participants were not convinced that there is a difference and, for them, it's natural to continue to think that they may as well continue smoking or to answer that they don't know to the question.

In summary, the science demonstrates a reduction in relation to a number of very serious risks associated with cigarettes. We satisfied the MRTP criteria related to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

individual risk.

The population benefit has been shown by the points listed in the slide. The claim would lead to

- improved comprehension and perception of relative risk compared to cigarettes;
- continued understanding of absolute health risks for snus;
- improved understanding that health risks require complete switching;
- increased interest in buying General Snus among current smokers;
- no increase in the likelihood of initiation by nonusers of tobacco.

All of that, as I said before, will be verified in postmarket surveillance.

This TPSAC meeting is different to other TPSAC meetings on MRTP applications. It is not about whether it's true that the product has less risk to individual users. I think that it is safe to say that there is general scientific consensus that that is a true statement. The question is if smokers shall be allowed to hear the truth to guide their choices. We at Swedish Match believe that our application substantiates that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

that is the case.

Thank you very much.

DR. MERMELSTEIN: Thank you very much. We have time for a few clarifying questions. We're going to hold off discussion, but if the Committee has any specific clarifying questions, you're welcome to ask now.

MR. PEYRON: Yes.

DR. OSSIP: Thank you for this presentation.

MR. PEYRON: Thank you.

DR. OSSIP: Could you confirm whether the products that we're considering are completely identical to the snus products as marketed in Sweden, since most of the data provided are based on the Swedish experience, or if there are any variations in what's being proposed here to what's marketed in Sweden? Could you describe those, as those may impact the kind of messaging of health risks.

MR. PEYRON: In terms of the science, that science has been developed under -- over a long period of time. As I said, the product has been on the market for more than a hundred years and the product we're selling in the U.S. at the moment, they are lower in HPHCs than they were historically in Sweden. So they're not exactly the same, they are the same or better

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

than the Swedish product that was the basis for these studies.

DR. OSSIP: As a follow-up, sorry, is there additional -- are there any additional additives, any variation in the flavorings that go into producing the particular --

MR. PEYRON: I mean, there are different flavors. The studies that we rely on were not specific studies to a specific product but to snus, in total. So snus comes in different flavors and there will be -- there will be -- so there were many flavors in the basis of the studies, but I think it's fair to say that there are no increased controversial compounds in the products we sell in the U.S. compared to the ones that were studied in the past.

DR. MERMELSTEIN: Dr. Thrasher, did you have a question?

DR. THRASHER: No.

DR. MERMELSTEIN: Okay, Dr. Weitzman.

DR. WEITZMAN: Do you have any data specific to adolescents and their perceptions about snus relative to cigarettes?

MR. PEYRON: We don't do any research on underage. We only turn to adults in our research. I should say that, as you've seen, the claim itself does not increase the interest in never users. These were adults and young adults, but there's

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

no reason to believe that youngsters would be more susceptible to the claim than adults. Well, then we should remember that we are talking here about the claim. The product is on the market already under a PMTA issued by the FDA.

So the claim does not increase the likelihood of use among nonusers, not among the older ones and not among the younger ones, and I think it's unlikely that it would increase among youth, but we don't do any studies on those.

We should also say that FDA, when looking at the PMTA, did not find that the snus seemed to be specifically interesting for youth. Of course, this will be probably the main focus of FDA's postmarket surveillance. But the answer is we don't have any specific findings. Yes.

DR. MERMELSTEIN: Dr. Wackowski.

DR. WACKOWSKI: Hi. For your user groups you looked at results by cigarette smokers and smokeless tobacco users. Can you clarify if any of those users were dual users of both products and whether you looked at the results among exclusive smokers compared to dual cigarette and smokeless tobacco users?

MR. PEYRON: I think it's time -- when we get into the details of the studies, I think it's time that we let Steve here come up and answer that question. Do you want him here

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

or --

(Off microphone response.)

MR. PEYRON: Okay.

MR. SEIFERHELD: I was told it would be okay to use either, either one.

In response to your question, when we did the recruitment of the respondents, we recruited knowing that we would have people who do fall into both categories and so we prioritized accordingly. Incidents of smokeless users is considerably lower than smokers and so we made an effort to populate the smokeless cohort by looking at people who did not smoke combustible cigarettes. So anyone who falls into that cohort, by definition, is not a dual user of cigarettes.

Within the smoker population, we will have some incidence of dual usage, we allowed that. Their criteria for falling into the smoker cohort is consistent with the PATH Study of reporting having used at least a hundred cigarettes and currently using every or some days.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: I guess while you're up there, so I mean, don't you think it's important to look at the facts of the messaging on that particular group of dual users given that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

they're already showing a preference for smokeless products and they may be the most likely to actually make the complete switch?

MR. SEIFERHELD: I think it's -- sure, but in terms of the -- in terms of the obligation to the statute, we elected to focus in on smokers, whether or not their dual use or not, because if you are using cigarettes, whether you define it as your primary or not your primary product, you are still using what is the most harmful tobacco product on the market. And our goal, again per Fredrik, is to get people off of cigarettes.

So if we are successful in moving people away from cigarettes toward a product that's less harmful, then we feel we have met both the statutory as well as the, you know, environmentally friendly, if you will, approach to the process. It would be great if we could get dual users to drop all of their products in favor of snus, but the priority is placed on getting them off of cigarettes.

DR. THRASHER: One follow-up question, sorry. So then with regard to smokers, did you look at your data at all, looking at those who intend to quit versus those who don't since, you know, one of the things that we don't want to have

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

happen is get people to switch to snus when they would've otherwise quit.

MR. SEIFERHELD: Yeah, there is a question in the study that was asked of the motivation to stop smoking, the traditional MTSS question scale asked pre and post. Again, it was not cited in terms of a statistical analysis plan, in terms of hypotheses, as a specific cohort. It's there for post hoc analysis for people who wish to dig into the data.

What I can tell you is intent to quit is consistent across the board. We have certainly no evidence of deterring people from quitting but, at the same time, the -- you know, the focus of our analysis in our analysis plan was to motivate people who currently smoke away from cigarettes on to a product that is safer.

MS. HERNDON: Going back to the question about adolescents, what private policies are in place by Swedish Match to prevent initiation of these products by young people, and if you can comment on how the policies differ in the places where the studies were conducted compared to the United States.

MR. PEYRON: I mean, we have an under 18 no nicotine policy. It covers both our tobacco products and our nicotine products. It also says that where the legal age is higher than

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

18, and that is becoming more and more common, so we'll probably have to change the name of our policy, then that legal age is the boundary.

And that guides us in our marketing. We make sure that we restrict our marketing in various ways in order to not target youngsters. We don't need the youngsters, like from other tobacco companies, because there are plenty of cigarette users for us to find consumers.

DR. MERMELSTEIN: Dr. Warner.

DR. WARNER: Looking at the table of your results, you had only one statistically significant result with regard to older adult cigarette smokers. The young adult cigarette smokers appear to be in the right direction, but there's no indication of statistical significance. I'm curious about the category of adult smokeless tobacco users. Were you able to divide that between younger and older and did you see any difference in the non-statistically significant response?

MR. PEYRON: Steve will be back with that answer.

MR. SEIFERHELD: In the recruitment of smokeless users, the incidence was small enough that we were not able to power that group as highly as we would've liked, so I would put that again in the category of directional. So we did see, you know,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

what I would call change and relatively low p-values, but due to multiple comparisons and statistical adjustments of p-values for multiple comparisons, we did not obtain significance. That's the same as it would be with younger smokers.

If given the chance to do a study again, I would be very encouraged about the ability to show that as a difference, but having been just studied just the one time -- what I would call directional.

DR. BIERUT: So thank you for this presentation. You showed data on Sweden versus the United States, the estimated death rates in men.

MR. PEYRON: Yeah.

DR. BIERUT: Can you comment on women?

MR. PEYRON: Yeah, snus has not taken hold among women in Sweden, so women in Sweden smoke at the same levels as European women and have the same kind of health characteristics as European women. I haven't got any data comparing it to the U.S., but I would guess that we wouldn't see the same kind of difference as we see between Swedish men and U.S. men.

So does that answer your question? Thank you.

DR. MERMELSTEIN: Dr. Wanke.

DR. WANKE: Thank you.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

So I have a question that's a follow-up to Dr. Ossip's question about the formulation of the product.

MR. PEYRON: Yes.

DR. WANKE: Is your current product the same in Sweden as it is in the U.S. or have you altered the formulation to appeal to a U.S. consumer? And in specific, I'm wondering if the product is sweeter.

MR. PEYRON: I mean, we have very similar products in Sweden to the ones we sell in the U.S., so we have flavored products with mint and we don't have a wintergreen product in Sweden, but we have them in Norway. It's been developed for -- the wintergreen product is specific for the U.S. because it's a very well-recognized taste for moist snuff.

DR. WANKE: But can you characterize the other products, are they the same or different? Are each of the products reformulated to appeal to a U.S. consumer?

MR. PEYRON: In Sweden we have, I think, 50 SKUs, 50 SKUs, so we have 50 different products. And so, of course, there are a number of products in the U.S. -- or in Sweden that are in different from the ones we have in the U.S., but they are -- they don't have -- they have the same nitrosamine levels, the same and lower benzopyrene levels in the U.S. as we have in

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Sweden. I should say we have looked at the taste profile of moist snuff products and the snus products have the same as the traditional moist snuff products.

DR. WANKE: So then to clarify, that would mean the eight products that you're bringing forth now are -- each of them are unique to the U.S. Those same products would not be the same as a product that's available in Sweden.

MR. PEYRON: No, I think, yeah --

DR. WANKE: Are each reformulated?

MR. PEYRON: I mean, they are not -- I don't think that they are exactly the same and they wouldn't be exactly the same anymore, either, because when we launch a product in the U.S., then we -- it's a very, very tough job to change it. In Sweden, we keep on lowering HPHCs and trying to make the product better and better in that respect all the time. In the U.S., the process is very complex in improving the product. So over time we changed our products in Sweden, but the U.S. products are frozen in time.

DR. WANKE: Okay, thank you.

DR. MERMELSTEIN: Thank you.

We'll have time for more clarifying questions later this morning. We're going to move on now. Thank you, Mr. Peyron.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Thank you very much.

And we're going to move now to the FDA presentation.

DR. PERSOSKIE: Good morning, everybody. My name is Alex Persoskie, and I am an FDA social scientist. I'm going to describe FDA's preliminary assessment of the research that Swedish Match did on consumer responses to its modified risk claim.

So, first, how does Swedish Match propose to disseminate its modified risk claim to consumers? Swedish Match does not propose to add its claim to product labels or packaging or to provide any -- or to remove any of the required warning labels. What Swedish Match does propose to do is provide its modified risk claim to consumers through a variety of advertising channels including its branded website, direct mail and email, social media, print and online advertisements and consumer events.

So what would be in Swedish Match's modified risk ads? Swedish Match developed video, print, and online ads based on qualitative research. The ads introduce what snus is and how to use it, given that many U.S. consumers aren't familiar with this product type.

The ads then describe what is different about General Snus
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

compared to other snus, describing its Swedish origin, its ingredients and its production process, which involves steam heating and cooling. The ads also present the proposed claim and the mandated smokeless tobacco warnings.

At the bottom of this slide you can see screenshots from a video ad that Swedish Match proposes to use on its website. The video ad is about 1 minute long and includes all the features I just noted. It has a voiceover as well as visual depictions of the information. This video ad was tested in Swedish Match's perceptions and behavioral intentions study, which I will present next.

The objective of Swedish Match's perceptions and behavioral intentions study, which I'm going to call the PBI study, was to assess the proposed claim's effects on consumer understanding and intentions to use products. The study was conducted from late 2017 into early 2018. The study was an online experiment, participants were randomized to view the video advertisement with the proposed claim, without the proposed claim, or with one of two alternative test claims.

My presentation today will focus on the condition with the proposed claim and the condition with no test claim. The videos in these two conditions were identical except for the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

presence or absence of the proposed claim.

Results for the other two claims were generally similar to those of the proposed claim, but I will not discuss those conditions given that the Applicant is not proposing to use those other claims.

Participants were also randomized to view the video ad with one of the four required warning labels and one of two product flavors, mint and wintergreen. Analyses collapsed across warning labels and flavors, so I won't discuss the warnings or flavors anymore unless questions come up. After viewing the video ad, participants then responded to questions about product risks and their intentions to use products.

Participants were recruited from a variety of online research panels. The study sample included six tobacco user groups, including young adults and older adult smokers, adult smokeless tobacco users, adult former smokers, and young adult and older adult never tobacco users.

Young adults were defined as between the legal age to use tobacco and 24. Older adults were aged 25 or over. For the most part, demographic characteristics of participants in each user group were representative of those user groups in the U.S. population.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Here we see key outcomes, including understanding and intentions and how they were assessed in the PBI study. The study assessed perceptions of the health risks posed by using General Snus every day in absolute terms. These were assessed on a scale from very low chance to very high chance. The health effects included eight outcomes such as mouth cancer, lung cancer, and heart disease.

The study also assessed perceptions of health risks from using General Snus compared to smoking cigarettes using moist snuff and other snus brands and dual-using General Snus with cigarettes. The response scale for these items are arranged from much lower to much higher chance of health effects.

The study also asked participants how many cigarettes they could smoke per day when using General Snus to lower their disease risk. Options included zero cigarettes, which the Applicant defined as correct, as well as other options that the Applicant defined as incorrect, up to five cigarettes, up to 20 cigarettes, as many as you want and none of the above.

Finally, participants also reported their likelihood of buying General Snus for themselves if it was sold in a store where they usually shop. They reported this on an 11-point Juster scale ranging from no chance, almost none to certain and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

practically certain.

So let's now jump into the results. Here we see cigarette smokers' perceptions of risk from General Snus compared to cigarettes. Specifically, these figures show the percentages of cigarette smokers who perceived General Snus as lower or much lower in risk than cigarettes. The top figure shows the results for young adult smokers and the bottom figure shows results for older adult smokers.

In each figure, the light blue bars show perceptions among smokers who viewed the video ad without the proposed claim. Dark blue bars show perceptions among smokers who viewed the video ad with the proposed claim.

Along the x-axis you can see the eight health effects that were assessed. These include respiratory effects, lung cancer, chronic bronchitis and emphysema; cardiovascular effects, heart disease and stroke; and oral effects, mouth cancer and gum disease. Also, it includes the general risk, serious health problems.

For all health effects, viewing the claim significantly increased the percentage of smokers who perceived General Snus as lower in risk than cigarettes. So starting from the left-hand side of the slide you can see that without the claim

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

around half of smokers perceived General Snus as lower in respiratory risk compared to cigarettes. For heart disease and stroke, this is below 40% without the claim. For mouth cancer and gum disease, it's down below 20% without the claim.

However, when the claim was provided in the video ad, the percentages of smokers who perceived General Snus as lower in risk were substantially higher. In fact, for some of the health effects, the claim doubled or even tripled the percentages of smokers who perceived General Snus as lower in risk than cigarettes.

Here we see smokeless tobacco users' perceptions of risks from General Snus compared to cigarettes. This is only for four of the health effects, which you can see on the x-axis.

As we saw for smokers, the proposed claim significantly increased the percentages of smokeless tobacco users who perceived General Snus as lower in health risks than cigarettes. For example, for serious health problems, without the claim, a little over 40% of smokeless tobacco users perceived General Snus as presenting a lower risk compared to smoking cigarettes. With the claim, a little over 70% perceived General Snus as presenting a lower risk compared to smoking cigarettes.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Now let's look at how smokeless tobacco users perceived General Snus compared to other smokeless tobacco. On this slide, the top figure shows the percentages of smokeless tobacco users who perceived General Snus as lower in risk than moist snuff, and the bottom figure shows the percentages who perceived General Snus as lower in risk than other snus brands. For all of the health effects, adding the claim to the video ad significantly increased the percentages of smokeless users who perceived General Snus as lower in risk than moist snuff and other snus brands.

Without the claim, if you look at the light blue bars, around 15 to 30% perceived General Snus as lower in risk than moist snus and other snus brands across the different health effects. When the claim was added to the video, this significantly increased for all health effects to around 35 to 50% across the various health effects.

Here we see perceptions of absolute health risks among all six tobacco user groups. These are from the study condition with the proposed claim. The figure shows the percentages in each tobacco user group who perceived daily General Snus use as creating a moderate, high, or very high chance of either of the health effects.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

There were differences across user groups and across health effects. Starting on the left side of the figure, all groups perceived substantial risk of gum disease and mouth cancer. Perceptions were somewhat lower for the respiratory diseases, including lung cancer, chronic bronchitis, and emphysema. And perceptions were moderate for the cardiovascular effects, heart disease and stroke. For all of the health effects, young adult never tobacco users perceived the highest risks, there shown in the red bars. For the respiratory and cardiovascular effects, the user group with the next highest perceptions was older adult never tobacco users, which are shown in the gray bars.

Now let's look at results on intentions. Participants reported their intentions to buy General Snus on a scale from 0 to 10, and here we see the mean estimates in each tobacco user group. The dark blue bars show intentions without the claim and the light blue bars show intentions with the claim.

With or without the claim, intentions were much higher among cigarette smokers and smokeless tobacco users compared to the other groups. Intentions were low among former smokers and never tobacco users. For cigarette smokers and smokeless tobacco users, mean intentions were also on the lower part of

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the scale; however, for these groups, the claim appeared to increase intentions to buy, although this effect only reached statistical significance among older adult smokers.

I also did want to note that for smokeless users, Dr. Warner brought up the lack of the significant effect, I'd note that the sample size is a bit lower for the smokeless tobacco users.

And also it's worth noting that participants in the study were only shown flavored General Snus products. There was no attempt to match the flavor that the smokeless tobacco users preferred with the study stimuli. And about half of -- I believe it's around half of U.S. adult smokeless users prefer flavored products.

Among consumers who intended to buy General Snus, the PBI study did not assess how they intended to use it, such as whether they would try to use it as a complete substitute for cigarettes. However, the PBI study did assess perceptions of risk from using General Snus exclusively compared to dual-using it with cigarettes.

This figure shows the percentages of smokers and smokeless tobacco users who perceived exclusive General Snus use to present lower risk than dual-using it with cigarettes. As

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

shown, the proposed claim significantly increased these percentages for all health effects assessed and for all three tobacco user groups.

For example, for smokeless tobacco users, if you look at the right-hand panel, without the claim, about half perceived a lower risk of serious health problems from exclusive General Snus use compared to dual use with cigarettes. But when the claim was added to the video, about two-thirds of smokeless users perceived a lower risk from exclusive use.

Thus, the claim appeared to help smokeless tobacco users and smokers understand that exclusively using General Snus would be less harmful to their health than dual-using it with cigarettes. Note that between a third and a half of current U.S. adult smokeless tobacco users also smoke cigarettes.

The PBI study also assessed smokers' understanding of the health risks of partial switching. The study asked smokers, "For General Snus to put you at a lower risk of disease, how many cigarettes can you smoke on a day when you also use General Snus?"

This slide shows responses among young adult smokers on the left and older adult smokers on the right. The response options are shown on the x-axis of each figure. Swedish Match

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

defined the correct answer as zero cigarettes. The y-axis shows the percentage of smokers who chose each option.

As shown, adding the claim to the video significantly increased the percentages of smokers who correctly responded zero cigarettes. At the same time, adding the claim did not increase the percentages responding with the dual-use options up to five, up to 20, or as many as you want. However, it did leave about 20 to 30% responding "don't know."

Overall, these findings provide some support that the claim would not mislead consumers to believe that they could benefit their health by partially switching to General Snus.

Youth and young adults who don't use tobacco products are a potentially vulnerable group, given that young people are more likely than older people to initiate tobacco use. Swedish Match didn't submit any information about the potential effects of its claim on youth.

However, the PBI study did evaluate the claim's effects on young adult never tobacco users. It found that young adult never tobacco users' perceptions of risk were somewhat higher than those observed among older adults. Also, young adult never tobacco users' intentions to buy the product were a little higher than those among older adults, though still very

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

low.

The effects of the claim on young adults were also similar to those observed among older adults.

We note that snus use is currently low among U.S. youth. 2014 is the most recent year for which published analyses of the National Youth Tobacco Survey data reported estimates separately for snus and other smokeless tobacco products.

On this slide, the figure on the left shows snus and other smokeless tobacco use among middle school students. Estimated past 30-day use of any snus product was 0.5% among middle school students. The figure on the right shows the estimated rates among high school studies. Past 30-day use of any snus product was 1.9% among high school students. Also, we note that some high school students are 18 years old.

A more recent analysis by Wang and her colleagues, which is not shown here, estimated current use of any smokeless tobacco among youth in 2017. Wang found that past 30-day use of any smokeless tobacco in 2017 was 1.9% among middle school students and 5.5% among high school students. This suggests that the overall rates of smokeless tobacco use among youth either stayed about constant or went down a little between 2014 and 2017.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

So, to summarize, Swedish Match proposes to market its eight General Snus products by disseminating a revised modified risk claim to consumers in its advertising. This would include advertising in channels such as its website, direct mail, email, at consumer events, on social media and in print. It does not propose to add the claim to its product labels or to remove any of the warning labels.

The PBI study found results that appear to support the potential benefits of disseminating the claim to consumers. When smokers and smokeless tobacco users were not provided with the claim, many did not perceive General Snus to be lower in health risks than cigarettes. Most also did not perceive General Snus as lower in risk than moist snuff or other snus brands.

Providing the proposed claim appeared to help smokers and smokeless tobacco users to better understand the risk difference between these General Snus products and other tobacco products while not appearing to mislead consumers to think that the products are risk free.

Providing the claim also increased intentions to buy these General Snus products among older adult cigarette smokers.

Although the PBI study did not assess the claim's effects

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

on intentions to switch completely, it did suggest that the claim improved consumers' understanding that dual use with cigarettes presents higher risks than exclusive General Snus use.

All together, FDA's preliminary assessment of the PBI study is that it addresses the deficiencies in the consumer perception research in Swedish Match's original 2014 submission.

In terms of the study's results, it provides evidence suggesting that the claim would improve U.S. consumers' understanding of the product's health risks, including relative to cigarettes, other smokeless tobacco, and dual use of the products with cigarettes.

The claim also increased intentions to buy General Snus among adult tobacco consumers who could benefit their health by completely switching.

The claim did not significantly increase intentions to buy General Snus among current nonusers of tobacco, although we do expect some level of potential increase as a downstream consequence of changes in risk perceptions. Thus, it would still be important for Swedish Match to target the modified risk claim toward adults who already use tobacco or who may

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

already be interested in using tobacco.

Thank you. And I'll now turn it back over to Dr. Mermelstein for the clarifying questions.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: Are we asking clarifying questions of FDA?

DR. MERMELSTEIN: Yes.

DR. THRASHER: Yeah, okay.

(Off microphone comment.)

DR. THRASHER: Yeah. You mentioned how the presentation of the modified risk claim included the warning labels. Have you done any secondary analyses to look at the extent to which the claim may be reducing the effect of the warnings themselves, particularly the warnings that mention health outcomes that are also mentioned in the claim, like mouth cancer?

DR. PERSOSKIE: No, the Applicant didn't submit analyses that were stratified by warning label. We also didn't conduct any follow-up analyses on our own of that issue. But you're right, so could I -- just to clarify. So in the study, people were randomized to view the ad with one of the four and so it's sort of an externally valid way of looking at the effects of a single-claim exposure because they'll see one of the four.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. THRASHER: But it would be possible to do an analysis where you just look at those --

DR. PERSOSKIE: Yeah.

DR. THRASHER: -- who were exposed to the --

DR. PERSOSKIE: Yeah.

DR. THRASHER: -- mouth cancer one and see whether the effect is any different for that group or --

DR. PERSOSKIE: Sure.

DR. THRASHER: Okay, thank you.

DR. KING: Thanks for the presentation, very comprehensive and polished as always from you. My question is related to your Slide 24 and the study specifically on perceptions related to lower health risks from exclusive General Snus use and I'm going to focus on that word "exclusive."

So can you clarify for me, in the exact question that was asked among the survey participants, was the word "exclusive" used or was it "switched completely" or was it "snus instead of cigarettes," like the Applicant is proposing in their messaging? What exactly were these people asked?

DR. PERSOSKIE: Yeah, they were asked if someone uses General Snus every day and uses no other tobacco or nicotine products. I believe that's the -- I don't have the exact

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

wording in front of me, but I believe that is the wording.

DR. KING: Okay.

DR. PERSOSKIE: And the other version -- so compared to someone who uses both General Snus and smokes cigarettes every day. Perhaps the Applicant can --

DR. MERMELSTEIN: While we wait for that -- are you pulling that up? Okay. So why don't we wait for that.

MR. SEIFERHELD: So with questions that asked about relative risk, they were phrased as follows: "Compared to the daily use" --

(Microphone feedback.)

MR. SEIFERHELD: That's not very polite of you. "Compared to the daily use of both cigarettes and General Snus, the daily use of only General Snus has," and then the scale reads, "a much lower chance, lower chance, same, higher, much higher," etc., and then concludes by saying "of causing stated condition." As you can imagine, consumers looped through a variety of these questions. So in this particular example, let's say, of causing heart disease or causing high bronchitis.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Yeah, I also had some questions about the particular questions that were used and that identifying -- so

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

it becomes important, I think, to assess the extent to which the consumers would grasp that they need to switch completely because the evidence that's available, if I'm understanding this correctly, is for complete switching to snus or exclusive use of snus.

I have some concerns about the questions that were asked, so one question is for General Snus to put you at lower risk for a disease, how many cigarettes can you smoke on a day when you also use General Snus?

Survey methodology is one of my areas and I think that's a misleading question given the intent of it, misleading to people asking -- or responding to the questions, and also misleading to when the results are presented because that implies that it's on a day when you also -- when you use, when you also use General Snus. So the "also" implies that you're smoking and using General Snus, but also it implies that there are some days that you could smoke and not use snus and you would still accrue these same benefits and that's not -- there's not an evidence base for that.

The question that you just cited, "Compared to daily use of both cigarettes and General Snus, the daily use of only General Snus has a much lower chance, a lower chance, the same

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

chance" and I think that's the question that you cited, is that -- did I get that one correct? I'm not sure that that quite captures it, in that lower chance or much lower chance, there's not -- I haven't seen any data on the threshold of how much you can smoke along with snus and still accrue health benefits.

So, in some ways, if you're doing both versus just one that has these new purported health claims, it seems like that's sort of stacked in the direction of saying a much lower chance but, in fact, we don't -- I'm not sure that that's even the right answer because we don't know that there are health benefits associated or we've not seen health benefits associated with switching or with using -- with dual use versus complete switching.

So this is implying you have a lower chance but you're not -- we don't know whether or the extent to which you're actually better off. So the question here really is which one gives you the demonstrated health benefits and that question wasn't asked. So I have some concerns about the questions that are used to assess what's, I think, pretty important messaging here in that, given the wording, which is using General Snus instead of cigarettes rather than something like switching

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

entirely to General Snus, are questions --

DR. MERMELSTEIN: Dr. Ossip, let me just interrupt a second. Is there a specific clarifying question or is this part of our discussion for later that you're asking? Your expressing of concerns may be part of our discussion, but --

DR. OSSIP: Yeah, sorry, I think it's a little bit of both. Yeah, thank you.

DR. MERMELSTEIN: So if there's no question for the Applicant --

DR. OSSIP: If there was a particular rationale for using these specific questions to assess the outcome of understanding the need for exclusive switching.

DR. MERMELSTEIN: So that's a clarifying question --
(Crosstalk.)

DR. OSSIP: That's a clarifying question.

DR. MERMELSTEIN: Okay. So I think we'll move to just general clarifying questions at this point, if you wanted to --

DR. PERSOSKIE: Could I just mention one thing about the last question? So there are two aspects of understanding that, I think, were looked at in the study and at least that FDA would be concerned about and that is the first one of those is do people understand the risks of exclusively using General

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Snus compared to dual-using it with cigarettes?

And then the second one is -- and that's what this slide gets at, do people understand that if you also smoke when you use this that will present a higher health risk than if you just use General Snus?

This other question gets at a different issue, which is partial switching compared to exclusive smoking. So do people mistakenly believe that there's a benefit to partially switching and not completely switching? Two different issues. And I believe this -- I believe this is a question you were asking the Applicant to clarify, is that --

DR. OSSIP: Actually, both because I wasn't clear that either really got at the issue of do they clearly understand that the evidence shows that to accrue the health benefits one needs to switch exclusively.

DR. MERMELSTEIN: Okay, so I'm just going to ask, is there a specific question that you have to clarify, that you want the Applicant to? Ask as opposed to your expressing some -- you know, what the intent is.

DR. OSSIP: Yeah, I guess if there was a rationale, is there something I'm not understanding about the questions? So is there a rationale for those specific two questions to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

address that issue?

DR. PERSOSKIE: Yeah, I think it's interesting because I think they could have asked this -- they could have got at this second issue, this partial switching compared to exclusive smoking with a risk perception item similar to the one that they used here.

They could have just asked people what would be the risk for someone who, you know, used General Snus to cut down on their smoking versus someone who just keeps smoking the same amount. But instead of doing that, they asked this kind of multiple choice item about how many cigarettes they could smoke per day and still get the risk reduction and they did find that, you know, providing the claim made it more likely that smokers would respond zero cigarettes, so that gets at kind of per day, on a day when they also smoke. I guess the question it leaves open is do people think that they can still smoke some days.

DR. OSSIP: Okay.

DR. PERSOSKIE: I don't know if I would have -- if I would hypothesize that that would go in a different direction than we're seeing here for the cigarettes per day, though. But I would be interested to hear you guys, you all discuss --

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. MERMELSTEIN: Okay, so we're going to hold that. He'd be interested to hear for our discussion about it. And, again, I just want to focus on other clarifying questions now for the Applicant or for the FDA.

Dr. McKinney, you had a question that I cut you short for before?

DR. McKINNEY: No.

DR. MERMELSTEIN: You're okay?

Dr. King.

DR. KING: Just one very quick one just to clarify for the record. So the actual products that were tested in terms of this particular exercise was only two specific products. What were they again? And then how many products were not tested out of the ones that the Applicant now wants to enter the market with.

DR. PERSOSKIE: So there's eight products in the MRTPAs. Five are currently on the market, three are not. This tested two of those, so -- and they were 24-counts of pouch snus that were either mint or wintergreen flavor.

DR. KING: Okay. And so the two are two of the three that are not currently on the market; is that correct?

(Off microphone comment.)

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. PERSOSKIE: Sure.

MR. SEIFERHELD: The two products that were included in the study are the mint and wintergreen flavor. They were chosen because they represent the majority of our product sales, 70% of our sales in the U.S. are the mint or the wintergreen SKU. So they are currently available.

And we, you know, in early conversations with FDA discussed the need to include, say, all flavors versus our presentation and our understanding was that including a representation of our products would be sufficient to then explain the remaining volume, if you will. So by choosing the two SKUs that were accountable for the majority of our sales, we felt that we were presenting a pretty comprehensive story.

DR. KING: Okay. So there's no reason for you to believe there would be any differential impact if the study were to be conducted separately on other products, you believe those two are representative of the entire portfolio?

MR. SEIFERHELD: We do, yes.

DR. KING: Okay, thank you.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: This is for FDA again. Sorry, I know you want to get out of there, but one last question. So for Slide

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

19, you know, this is where you start to show some of the compelling results around people's perceptions of the different health outcomes that are mentioned in the claim.

One of the things that occurs to me is that gum disease is not included in the actual claim and yet it's used here as evidence for the effectiveness of the message. So I'm wondering, do you have any problems with that? And I can tell you my impression or maybe save that for the discussion, but can you help me understand why gum disease is used here as evidence for the effectiveness of the claim when that information is not included in the claim?

DR. PERSOSKIE: We presented results for all the health effects that were assessed and I also have views on whether that would be accurate, an accurate claim versus not, you know -- or an accurate perception or not that the gum disease risk is lower for the General Snus products compared to cigarettes.

But I think that would be an issue we would like to hear from you on. We want to hear from you about whether you think this claim is going to -- this evidence suggests that the claim could create misperceptions or whether, overall, it would be helpful for consumers.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. MERMELSTEIN: Other -- yes, go ahead, Dr. Bailey.

DR. BAILEY: I've just got a question for the Applicant. I was wondering about on these, on General Snus, what types of tobacco are used in General Snus and whether it's sourced. And also, you showed that huge reduction in the HPHCs, about 2,000. That might relate back to the GothiaTek method issues to make Swedish snus and kind of what the methodology is and that drastic decrease in HPHCs in these products.

MR. PEYRON: In terms of the tobacco, we are sourcing tobacco from a number of different countries and we pick the tobacco based on low nitrosamine levels. And there is also -- and when it comes to benzopyrene, we have moved out of fire-cured tobacco and into air-cured tobacco to have lower benzopyrene levels. Is that the answer you were looking for?

DR. BAILEY: Yeah. And perhaps the reasoning behind the big decrease in HPHCs that you saw, about 2,000, is that when you moved away from fire-cured tobacco in the products?

MR. PEYRON: That was when we reduced the benzopyrene dramatically, yes.

MS. HERNDON: I have a question for you. Stay there, please. In the previous presentation, the video noted that the product is chilled.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

MR. PEYRON: Yes.

MS. HERNDON: Is it sold chilled in Sweden? Is it sold chilled in the United States? And if not, is there a difference in the product when it is not chilled?

MR. PEYRON: It's sold chilled in both Sweden and the U.S.

DR. MERMELSTEIN: Any other clarifying questions?

(No response.)

DR. MERMELSTEIN: Okay, we're slightly ahead of schedule, but I think we're going to take a 15-minute break now and when we come back, we will have public comments.

Committee members, please remember no discussion of the meeting topic either among yourselves or with the press or any member of the audience. Lots of other good things we can talk about today.

So we will be back promptly in 15 minutes, thank you.

(Off the record at 10:04 a.m.)

(On the record at 10:19 a.m.)

DR. MERMELSTEIN: We're now going to move to our Open Public Hearing section, and we're going to start with Matt Myers from Campaign for Tobacco-Free Kids.

MR. MYERS: Thank you, first of all, for the opportunity. In 4 minutes I've just a few things I'd like to do. We filed

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

written comments and upon hearing the oral presentation this morning, I would urge you all to take a look at our written comments. I have a couple of critical points I would like to make. One is if FDA is going to -- is seriously considering granting this, it is important to understand that this will set a precedent. And so the fact that there's a history of young people not using this product should not lull this Committee or FDA into complacency about what is required to get a proposal granted forward. Of particular concern is the fact that there is no information in front of this Committee to allow you to make an accurate assessment of the impact of what's being requested on youth use.

It is a frivolous comment to say that surveying adults tells you about youth use. It is a frivolous comment to say the fact that adults tell you that they won't switch or that the "never starters" won't switch tells you anything about youth use because of the age at which young people make these decisions in this country.

So you may not be concerned about widespread use of General Snus, but you're going to have other applications in front of you from IQOS to others at a time when we have an epidemic of e-cigarette use among youth. And if you allow this

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

to go forward without requiring the right kind of evidence as a matter of precedent, you're opening the barn door to something that we will all regret further on down the line.

The same applies, I think, to an important issue that you've all been raising and that is whether or not this particular claim focuses exclusively on smokers. It does not. It is a notice to the general public as opposed to smokers, if you switch completely, this is what will happen. Again, that becomes a very important precedent for other products down the line and therefore complacency about the specific wording here, and the targeting of the specific wording here, has the tendency to open the door to things that we will regret later on, even if we don't with this particular one whatsoever.

The third question that I think is important is one you're already talked about and that is the phrasing here "instead of" is sloppy and it is not precise, it does not communicate adequately or effectively that only complete switching provides you whatever health benefits that you receive. I think that is something that you need to be very precise about. We can't get into lazy wording that can be interpreted in multiple different ways because the implications down the line for other products, as well as for this product as it moves forward, I think, are

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

particularly important for all of us as we go here.

Fourth, I do think it's important to remember that this Committee previously voted on the relevance of experience in Sweden and found both that it was not relevant for how it would impact nonsmokers and it was not relevant for switchers. We need to have new information if you really want to make a cross-comparison here. Again, you may not be as worried because this product is not as attractive to a wide audience, but you are setting a precedent for the type of information that you're going to require moving forward going from here.

And I think it is important because one of the answers that you didn't get accurately this morning was is this product the same product that is being sold in Sweden? The answer is no, it is not. It does not meet current standards for selling this product in Sweden and I think that is a very important thing, the products that Swedish Match sells here are not consistent with the products. It may be true historically, but it isn't true today.

Thank you.

DR. MERMELSTEIN: The next speaker is Gregory Conley.

MR. CONLEY: Good morning, my name is Gregory Conley, and I currently serve as the president of a nonprofit health

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

advocacy organization called the American Vaping Association which advocates for sane and sensible policies towards vapor products and other low-risk smoke-free alternatives with the end goal of getting as many smokers to voluntarily switch to less hazardous products as possible.

As I was preparing for this comment, which is to urge the Committee to recommend approval of both General Snus' MRTP by Swedish Match as well as Altria's MRTP for Copenhagen, I was reminded of a quote by Dr. Gene Kim: "To tell the truth is an act of love. To withhold the truth is an act of hate. Or worse, apathy."

Unquestionably, hatred has been associated with the war on tobacco for decades. It allowed scientists, for years, to rely upon data on inhaled snuff to say that all smokeless tobacco must carry the risks found in those studies of the Appalachian people.

And in the 1980s, novel products like Skoal Bandit led to hundreds, if not thousands, of news stories, all with the intent of driving the message that smokeless tobacco is just as, if not more, hazardous than smoking. But since the 1990s, when the data from Sweden became increasingly clear and the data from America became even more clear that all modern

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokeless tobacco products are far less hazardous than smoking and yet we end up in a place where seemingly less than 10% of Americans understand that a smoker who switches to smokeless tobacco is improving their health.

And, sadly, this is where the apathy came in. For nearly 3 decades apathy has infected the tobacco control community in addition to the previously mentioned hatred. All while adult smokers have continued to smoke and die, there has been little or no attempt to truthfully inform smokers that if they switch, they can improve their health. Even the American Cancer Society and their long-term population health studies, they have great data on smokeless tobacco and whether or not it's actually led to deaths, but it's largely kept under lock and key. Why is that?

Let's be clear. Every claim being sought by the applicants is true. Every claim is truthful. The decades of epidemiological evidence supports it and these apps should be -- applications should be promptly approved, recommended for approval and hopefully one day, before I pass in my nineties, we'll see IQOS and Camel Snus have their applications approved by the FDA. It has been more than a year for IQOS, by the way.

One day, hopefully soon, the court system will recognize the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

absurdity of this process where you not only have to show that your claim is truthful, but that population-level health will benefit from you being permitted, as a manufacturer, to tell the truth.

That is wrong, but even within the confines of this absurd system, both these applications show that smokers and the public at large will benefit from the truth being told to them about the reduced risks associated with both the products before the Committee today.

So right now you are the gatekeepers of truth, so let's open those gates and not only improve public health but act in an ethical manner, as well, because all adults deserve access to truthful information. Please do not keep adults from becoming aware of the truth about these products. Thank you.

DR. MERMELSTEIN: Our next speaker is Alex Clark.

MR. CLARK: Good morning, my name is Alex Clark. I'm the CEO of the Consumer Advocates for Smoke-Free Alternatives Association. We're a 501(c)(4) grassroots advocacy group promoting tobacco harm reduction as a necessary strategy to reducing the early death and disease attributed to smoking. Thank you for the opportunity to speak with you this morning.

By way of disclosures, CASAA accepts unrestricted
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

donations from various sources, including consumer and industry stakeholders. My salary and travel expenses are authorized by an all-volunteer board of directors.

We are here on behalf of our more than 230,000 members to express support for the MRTP application from Swedish Match and urge the TPSAC Committee and the FDA to expeditiously approve the proposal to market General Snus as a low-risk alternative to smoking.

While we're supportive of Swedish Match's marketing plan involving age-restricted social media and print media, we are concerned about the proposal for earned media, which relies on a media that is predominantly hostile to innovative low-risk tobacco and nicotine products. We're concerned that this will have a limited reach beyond the current population of people who use smokeless tobacco and ideally, awareness of low risk -- of the low risk associated with using snus and other smokeless tobacco products will reach people who smoke, who struggle with traditional cessation strategies. We believe that in order for any marketing campaign intended to communicate the relative risks of smoke-free tobacco products to succeed, the FDA and CDC must take immediate action to correct misperceptions about nicotine and smokeless tobacco among consumers and health

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

professionals.

We're not suggesting that FDA devote resources to promoting any one specific modified risk tobacco product. Instead, we are urging the Agency to do more by way of developing and promoting appropriate balancing statements that bring consumer perception regarding the risks associated with smokeless tobacco more in line with available evidence.

We'd also like to take this opportunity to echo recent statements by Senator Richard Burr of North Carolina regarding the apparent deficiencies in the MRTP and PMTA process. After 9 years of having authority over tobacco products, the FDA has yet to give its blessing to new low-risk tobacco products or modified risk marketing statements. While it is correct to say that a relationship exists between a lack of MRTP and PMTA applications and a lack of approvals, it is even more clear that the burden and expense of the process is a significant barrier to participation. Maximizing public health benefit of low-risk tobacco and nicotine products is contingent upon consumers choosing to use safer products that they enjoy. Providing clear guidance and stream-lining the approval process is vital to promoting diversity and innovation in the marketplace.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

People who use combustible tobacco products deserve honest communication about the availability of demonstrably lower-risk tobacco and nicotine products. But it is clear that recalcitrant ideology and fear continue to be bottlenecks to the process of approving new products or allowing companies to tell the truth about relative risk, all to the detriment of public health.

And I would like to take just a moment to draw your attention to our written comments regarding the wording chosen in Swedish Match's marketing claim, "using General Snus instead of." I would note that we actually feel that this is very deliberate and much in keeping with meeting people where they're at. It is more encouraging people to use these products rather than demanding that they switch completely. We believe that this will have a much more positive outcome. So again, thank you for your time this morning and we respectfully urge you to favorably recommend this application for approval.

Thank you.

DR. MERMELSTEIN: Thank you.

Our next speaker is Carrie Wade.

MS. WADE: Good morning, my name is Carrie Wade, and I'm the Director of Harm Reduction Policy at the R Street

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Institute, which is a Washington, D.C.-based think tank.

Before I begin, I'd like to thank the Committee for affording me the opportunity to present written or oral testimony, which I've submitted to you.

Within the harm reduction policy program, our main areas of focus are sexual health, opioid, and tobacco harm reduction. Exploring the ways that tobacco harm reduction strategies can improve the lives of smokers has been a major focus of our research and advocacy.

Considering the staggering number of tobacco-related illnesses and deaths that occur yearly, I think that tobacco harm reduction through utilization of reduced-risk products has potential to have the most impact on the health and welfare of our populace. I think that because just by 30 years of intensive public health campaigns warning us about the dangers of smoking, smoking continues to kill nearly half a million Americans a year. Clearly, an abstinence-only approach to smoking isn't working and a harm reduction approach to smoking could mitigate many of the consequences for smokers who can or who cannot or choose not to quit.

The good news is that the FDA has recognized this with the development of the modified risk tobacco product pathway as a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

public health strategy to reduce the negative health consequences associated with smoking. However, for this to work, it is vital to finally demonstrate that the MRTP pathway works.

I believe that General Snus is an ideal product to be awarded the first MRTP. It's a traditional, extremely well-studied product with proven population health benefits in areas that widely adopt the use of snus and individual health benefits for those that switch.

Both independent research and scientific studies provided by Swedish Match indicates that snus compares favorably to combustible cigarettes in chemical composition and adverse health outcomes. Analysis of tobacco concentrations in snus products uniformly demonstrate a reduction in concentrations of harmful chemicals compared to cigarettes and an improvement in health outcomes for those who switch to combustible -- from combustible cigarettes. I apologize for that.

Unfortunately, in this country, smokers might not have a chance to make an informed decision about the risks that they take. In 2013, 89% of U.S. adults wrongly believed that smokeless tobacco is as harmful as combustible cigarettes.

Labels have the record, have the ability to set the record

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

straight on this. Product labels, especially with regard to health, are a vital source of information and have the potential to reduce disparities in access to knowledge.

Several studies have evaluated the effects of the relative risks, risk labels of snus products, with consistent results. Proposed labels of snus products describing the decreased risk, the decreased relative risk, I'm sorry, compared with combustible cigarettes increase the likelihood and motivation to buy and try snus among current smokers with little effect on never or former smokers. Consistent with the study are findings that labels describing the reduced risk of snus compared to combustible cigarettes better inform users of relative harm but have no effect on the perception of the absolute risk of snus. In this quest to improve the welfare of smokers and encourage innovation within the tobacco industry, the FDA has set rigorous standards for successful MRTP applications.

Swedish Match should be commended for its willingness to serve as the industry trailblazer and the FDA should be equally applauded for its role in this collaborative process that will benefit the scientific and public health communities, as well as future applicants.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Finally, it is my hope that the TPSAC recognizes the potential for the MRTPA framework to benefit public health and considers this an achievement in partnership between the FDA's Center for Tobacco Products and the industry that it guides.

Thank you.

DR. MERMELSTEIN: Thank you.

And our final presenter, Michael Ogden.

DR. OGDEN: Good morning, I'm Mike Ogden, Senior Vice President of Scientific and Regulatory Affairs at RAI Services Company. My comments this morning are on behalf of RAI Services and also on behalf of R.J. Reynolds Tobacco Company and American Snuff Company. It is encouraging that several companies have made the attempt to seek modified risk marketing orders for several noncombustible products and we look forward to FDA's treatment of these applications in due course.

Without belaboring the point, it's clear that the modified risk application process is time and resource intensive with no set timetable for review and clearance. Hopefully, as more applications come before the Agency, the speed and certainty of how best to obtain a clearance will emerge.

However, even if that were to occur, the MRTP process was specifically set up to address a certain claim regarding a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

certain product or products and not the whole category. Thus, incremental change in adult tobacco consumers' behavior will be slow if left solely to this process.

Thankfully, it need not be slow. We have the science in the form of epidemiology that demonstrates that smokeless tobacco products used exclusively present less risk of death and disease than smoking. The question is why hasn't FDA, and public health more broadly, undertaken the effort to communicate this information to the 40 million Americans who continue to smoke and have not quit? FDA in general, and Commissioner Gottlieb and Director Zeller in particular, have routinely embraced the existence of a continuum of risk that applies to tobacco products with combustibles at the high end and noncombustible tobacco products at the low end.

If FDA were to fully embrace its mantra that the Agency will follow science and that moving smokers away from cigarettes is its highest priority, then surely FDA would provide adult smokers with this information early and often. Indeed, as compared to the other regulatory efforts that FDA is considering taking, providing the scientific truth is the fastest way to make the biggest impact on public health.

There's a tremendous misunderstanding among smokers as
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

well as the public at large with respect to the relative risk of smokeless tobacco products as compared to cigarettes. The most recent and comprehensive study of individuals' perceptions of risk associated with tobacco product use was based on responses from a representative sample of over 32,000 U.S. adults participating in the PATH Study. This study found that only 9% of adults believed smokeless tobacco was less harmful than smoking while 64% believed it was as harmful and 28% believed it was more harmful. Other studies confirm that virtually no segment of the population understands that smokeless tobacco is safer than cigarettes. For example, studies have reached the same conclusion when studying high school seniors, college students, young adults, university faculty, health professionals, tobacco control professionals, and current and former smokers.

In addition to affecting people's behavior, telling consumers the whole truth about non-combustible tobacco products would respect their right to be fully and accurately informed about information that affects their health. We believe that individuals have a right to make their own health choices.

But individuals cannot make autonomous informed choices

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

about their lives without pertinent and accurate information. Thus, individuals have a corresponding right to information that affects their ability to make choices about their health. FDA should tell consumers the whole truth about smokeless tobacco products and it should do so now. Candid communication by the Agency would likely persuade millions of smokers to switch.

Thank you.

DR. MERMELSTEIN: Thank you.

That's the end of our Open Public Hearing. We're now going to move to Committee discussion of the topic at hand, whereas again our job here is to discuss the questions that we may have about the consumer perception study and implications of overall population health of different populations. So this is a time for the Committee to express concerns or bring up topics.

Go ahead, Dr. O'Connor.

DR. O'CONNOR: So the first question I have, which goes to the marketing strategy and how this claim will be disseminated, which I think is almost as important as how the claim is phrased, is why is it not on the package or the label? Why is it only in video and media?

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

And we know from years of research on warning labels that one of the important ways that warning labels work is by providing a constant reinforcement of the message. And so I'm interested in the underlying thinking of why it is only in advertising and not on the package.

DR. MERMELSTEIN: Is that a question you'd like the Applicant to answer?

DR. O'CONNOR: Yes.

DR. MERMELSTEIN: Okay.

MR. ROERTY: Thank you, that's a great question. And my name is Gerry Roerty, and I'm the general counsel for Swedish Match in the U.S., and my group is actually responsible for providing the amendments. And I would refer you to our January 30th, 2019 amendment which describes both our efforts to ensure that youth do not see these advertisements. We actually use age-gated environments which are third-party verified. It's not a click, are you 21 or not. We actually make people go through the process, go through driver's license verification, and our direct mail is much the same.

The reason we went away from the label is because, in the first application, we thought that the label was the way to go to correct the health warnings that we perceived to be

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

misleading and unfortunately, we were not successful. And so the idea wasn't -- in speaking with the CTP and the FDA about this, we concluded that the direct advertising of General Snus, which, by the way, does include the health warning at the bottom, was the best way to go. So we're actually trying to be very targeted. This is a relatively low-incident product. It's about 0.04% of the moist snuff market, to give you some perspective. And so we have a very limited number of consumers at this point and we felt like rather than go broad, let's go direct and so that's why we decided to go with the way we did.

DR. MERMELSTEIN: Dr. Thrasher, did you have a follow-up to that or -- no? I mean, Dr. O'Connor, did you have a follow-up to that?

DR. O'CONNOR: Well, just a somewhat related question, which is so your measure of intention to use is a Juster scale, so it goes from 0 to 10, but your mean scores are in the 1 to 2 range. So I'm assuming that that means that the distribution of these is highly skewed towards zero.

So when thinking about population impact and how much this messaging, however it's delivered in this case, it's a one-shot in the video, so it's going to be limited in terms of how much it can move the needle at all, have you looked into the extent

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

to which the likelihood of future uptake in a context where this message is sort of just barely moving the needle among current cigarette smokers? And so what is the projected population impact in terms of how much this might boost switching overall in the population?

MR. PEYRON: I think we have been most concerned about moving the needle in the right direction and we see that from the study that we're moving it in the right direction. How big the impact will be is, of course, very relevant but it's most relevant that it's impacting in the right direction. And when it comes to the marketing, I would agree with you that we are taking a very cautious approach, but that is -- we think that is prudent.

Thank you.

DR. MERMELSTEIN: Dr. Kozlowski?

DR. KOZLOWSKI: This is Lynn Kozlowski. Could I make a comment?

DR. MERMELSTEIN: Go ahead, Lynn. Thank you.

DR. KOZLOWSKI: This isn't related to Dr. -- in relation to Dr. O'Connor's question. My understanding was that the FDA's review in December 2016 pretty much requested that they didn't want to see a change in the warning label, that they

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

wanted something placed outside the health warning. And so I view the FDA's feedback as being influential on why a proposal didn't come forward to put something on a warning label.

DR. MERMELSTEIN: Dr. Apfelberg.

DR. APELBERG: This is Ben. Just to clarify, you know, the issue of changing the warnings obviously was a really important issue in the review, I mean, it came up at TPSAC, but it wasn't so much that you couldn't propose to modify them. The concern was that -- one of the concerns was that the way the -- you know, that change was tested, it was -- really wasn't adequate to understand not only the impact of that claim, but also how putting in the context of a warning might impact how people perceive the message.

So, yeah, I mean for sure, that was a part of the discussion and a part of the assessment, but there weren't specific directions to the company in terms of what they could or couldn't do. It was really laying out the deficiencies as we saw them at the time.

DR. MERMELSTEIN: Thank you.

Dr. Wackowski.

DR. WACKOWSKI: Yeah, I also had a comment and maybe a question about the channels and particularly with respect to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the design of the study. So that experiment tested the claims using the video format and in a way, I think that was probably a smart decision because we probably would expect that the differences in risk perceptions might be greater in that channel than the other channels since it's probably the most engaging of the formats. But at the same time I suspect that the video channel might be the one that consumers are least exposed to because where are they going to see it, maybe on the website, but they have to first get to the website and click in and click on the link to the video.

So I guess from an external validity kind of a perspective, we don't necessarily know the effects of the claim on maybe the other channels that people might be more likely to be exposed to and I'm wondering if any other testing was done or consideration to that was given.

Thank you.

MR. SEIFERHELD: It's a good question. It's a question that was brought up in conversation with FDA as we were designing the study, and ultimately, we concluded, based on our own thoughts and FDA comments, that choosing one channel would be appropriate for this study with an understanding that content would need to be similar moving forward in market. On

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

that same point I would remind people, as well, that the purpose of postmarket surveillance is to ensure that enacting our MRTP strategy, should we be granted it, accomplishes what we have set out to do. So to your point, we tested it in video and then, moving forward, we would explore other channels and use other channels, maintaining the consistency of content and message and be evaluating for effect in a postmarket setting.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: So my question is for the Applicant and it's a variation on the question that I asked during your presentation and it builds on the Campaign for Tobacco-Free Kids' statement. I remain befuddled why there's no information about youth perceptions of snus and especially in the context of what we've seen with e-cigarettes and Juul. Is there a concern that altering this messaging could encourage young people to uptake a nicotine delivery system that can be addicting?

MR. ROERTY: You know, again, as a company, I hope you can appreciate that even doing research with young people would be proceeding the wrong way. And so I don't want it looked at as an excuse for us, as a company, but could you imagine a tobacco company recruiting a bunch of 14- and 15-year-olds and doing

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

research with them? We don't do that. We don't want to be accused of indirectly marketing to them by engaging in consumer research. What I can tell you is that we do what we can to control youth seeing these messages and again, I would please encourage you to go look at our recent amendment so you can see all of the steps that we go to, to make sure that doesn't happen.

As for what impacts, you know, youth behavior, we understand that by and large it's influencers and it's influencers in their life. And so I share your frustration that we, as an applicant, can't go about doing that.

That said, one of the things we would do if you gave us an order would be to work directly with the CTP as part of a postmarket surveillance program to ensure that that happens. And, again, what Mr. Myers said is correct, just because it's low now doesn't mean it will always be low, but it's a good place to start and it gives you the assurance, together with the efforts that we make to target just adult tobacco users, that it won't happen.

I would also point you all, you have -- the good news is you have the benefit of the PMTA technical lead report. This product was granted a PMTA order. The FDA concluded that it

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

was in the interest of the public health that this product be sold, so you start there. It's in the interest of the public health that it be on the market. They further concluded that the flavors that we do use, wintergreen, mint, in a slight citrus tone to a natural tobacco flavor is not likely to appeal to youth.

And so we start there and all we're asking is to be given the opportunity to put the product out there, advertise it with the claim, and allow us to work with the FDA to come up with a postmarket program so we can study these issues much like you are getting those answers.

DR. WEITZMAN: I think this question is to the FDA. And we hear about postmarketing surveillance. Let's assume, for a moment, that we do see increased youth uptake postmarketing, what would be the response or what's the range of possible responses?

DR. APELBERG: Well, what we'd be able to do in a postmarket setting is to evaluate, like you're saying, what's happening at the population level and if the -- you know, it's clear that based on the patterns of use or whatever other data might come up that the product, with its claim, no longer benefits the population as a whole, there are actions that FDA

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

could take, including withdrawing the order, you know, for an MRTTP or withdrawing the order for the product to be in the market at all. You know, so I mean there are options depending on what that evidence looks like and how that impacts the assessments, you know, the same kind of assessment that we have to make in determining whether to authorize, is it still true, is it still the case based on what we're seeing in the real world.

DR. MERMELSTEIN: Dr. Ossip.

(Off microphone comment.)

DR. WEITZMAN: So I still remain concerned about the surveillance because we've just heard that the Applicant believes that it would be imprudent to try and survey youth about a specific product. We have multiple national surveys tracking youth tobacco use. Wouldn't it be possible to add the question specific to snus, going forward?

DR. APELBERG: Yeah, and then I guess I'll say that there are plenty of studies, surveys and nationally representative studies, that do collect data on snus. I mean, in this case, as you can imagine, one of the challenges is we're talking about a specific product, right, we're not talking about a whole category of products and, you know, if we would move

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

towards authorization we'd want to make sure that there is a plan in place where data would be collected that would address, you know, whatever these critical concerns are. And so I think that you all having this discussion is informative to us, obviously, to know what are the particular concerns if it moves in a positive direction, you know, and what I'm hearing from you is that obviously, being able to assess potential uptake in youth is critical and we would agree that that's critical.

But I think one of the challenges to keep in mind in the postmarket setting is this idea of really drilling down to the product itself rather than just -- I mean, it's informative, too, to understand what's happening in the general marketplace, but I think one of the unique challenges is really about studying the uptake of the product, perceptions, behaviors related to the product itself.

DR. MERMELSTEIN: Just as a quick follow-up, Dr. Weitzman, certainly current surveys ask about specific products, too, so that's not -- if that's what you're asking about, I think the question is who's doing the asking? But the ability to ask about a specific product is always there. I mean, that does happen in current surveys, so their preferences are asked.

DR. WEITZMAN: So I know that, I just wanted -- it's a
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

rhetorical question. We really should, if we're going to move forward with this, make sure that we do monitor whether or not this alters behavior in a direction that none of us would want.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: I think we've seen some compelling evidence both from the data presented at the last TPSAC and from just the history of this particular product. And so what we're asked about really here is the modified wording.

So I have concerns about two aspects of that wording because I think the wording and the specifics of the wording really is important. One I raised before, so I'll do it very briefly now, is the use of "instead of cigarettes," which I think is vague and potentially a misleading survey -- wording.

And I'm concerned that the survey items, broad as they are in the single kind of setting in which they're done, granted, that would happen with any item, but I think those particular items don't really give us a sense of what the perception would be of that wording, if it's clearly understood that the evidence base is around complete switching. The second concern I have is the wording "puts you at a lower risk of" and then it lists the diseases and we've seen some general data presented.

We don't know -- I think maybe Dr. Bierut had asked the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

question about what about women, so we don't have data by various groups or do we see differences by age, do we see differences by gender, do we see differences by populations with particular conditions?

When we look at the risks for -- the relative risks for like fatal MIs and for whether the confidence intervals overlap one, it may have been a small sample, but the high end of the confidence interval was potentially of concern.

So I think that "puts you at a lower risk," you know, does -- is there an obligation to be accurate to the public, if I am thinking of switching or I'm thinking of starting with snus, to get a sense of what is my risk, is it lowering my risk, does it lower my risk in a meaningful way? So I'm a little concerned that that component may be a bit broad based on the items that we've seen. I think both of these are addressable issues, but I am concerned about those in the context of what we're looking at right now.

DR. THRASHER: So while we're talking about the messaging, you know, I certainly appreciate the comments by Tobacco-Free Kids around how this is really going to establish a precedent for how it is that FDA and the companies who are filing similar applications are going to show the evidence around the impact

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

of messages on consumer perceptions. And so I worry about the sloppiness of some of the wording here.

But another issue that concerns me is this kind of litany of diseases that are listed in the statement and how it is that people could interpret that as meaning okay, that's kind of all risks, and we see evidence of that when we look at the slide that I pointed attention to earlier where people being exposed to this message also see gum disease going down when that's not even mentioned as one of the disease outcomes in this message.

And so the impression that I get is that people see this litany and then they think that it applies to everything. So I worry a little bit about the litany versus maybe shorter statements that may be more intelligible, particularly to people with low literacy, which is my other concern, and I don't know whether the Applicant looked at the message effects for people at different levels of literacy, especially given that we know that, you know, most smoking is concentrated amongst more disadvantaged groups where health illiteracy is higher than amongst nonsmokers.

So can you speak to that issue both in terms of is this message kind of causing people to generalize the potential benefits of switching across all disease outcomes, as well as

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

whether people who have low health literacy are going to be responding in similar ways to people with higher health literacy?

MR. SEIFERHELD: So in reverse order, we did not include any cohorts based on health literacy. It's just something not addressed in our study. With regard to the concept of the list of conditions, as was mentioned earlier, we actually tested three claims in our study and our rationale for focusing in on the claim that's being discussed today is that it was the most impactful, in a real-world setting, in getting people to make that switch from cigarettes. The other two conditions were more general, were more broad based and talked about things like tobacco-related diseases. So in fact, while we hear your concern, our choice was driven by the ability to most powerfully impact people into making a switch that's better for them combined with demonstrated understanding of the risks and especially dual risk of the products.

DR. THRASHER: So then are you not concerned that the message is also having an effect on people's perceptions of things that aren't mentioned in the message, like gum disease?

MR. ROERTY: In answering that question, and since I'm the non-research person here, I think it's important that I say

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

this, which is, first of all, I take -- I do take some offense at the characterization that this is sloppy. Let me explain.

The idea here was to make sure that the claim was understandable at a fairly low reader level, eighth grade level, and so we started with certain wording that was much more sophisticated and in the end, what we had to do is -- and we put this through qualitative work as well, which, by the way, is also included within our amendments and if you're interested in that process, it's detailed both in the September amendment as well as certain of our other amendments. It was a long, drawn out qualitative process to get at the exact words. And we talked about "exclusive" and "exclusive" to some people meant this is a really cool thing, this is a hip -- you know, this is the thing to do, and "instead of" made sense. So it wasn't sloppy or loose in any way, shape or form and we were really encouraged by the fact that what people basically said was -- you know, even when people misunderstood, their intentions that were expressed were if I'm a nonuser, I'm not going to use the product.

If I want to quit, I'm not going to cease my effort to quit to use this product. If I'm a former user, I'm not going to use this product. So even if people misunderstood certain

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

things, their behavioral intention is so very encouraging. And what I would say to you is that as far as the reading level, we were very sensitive to that and we thought about that.

When it came to this issue about, you know, only using General Snus, we were very sensitive to that, as well, and we knew how important that was. But the good news is that even if there are people who do dual use, the good news is from a population modeling effect when you get people who were smoking to move over to General, the net population benefit is a positive and I think that's the thing we wanted to leave you with, is that this was a very deliberate process and we arrived at the claim through a very tortured qualitative process followed by a quantitative review. So I hope that answers your question. I don't know if it does.

DR. THRASHER: It doesn't, necessarily, but I appreciate your comments. But I mean, it's interesting that the other case that we'll be reading about later today mentions how when they were doing their qualitative research, they opted not to use the phrase "instead of" because it didn't convey the notion of completely switching over.

So I'm also registering a little bit of other research that's being done by other industries there. So I'm just

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

saying that there's vagueness in the terminology that doesn't seem to communicate clearly what it is that I would expect in methods like this to communicate.

Thanks.

MR. ROERTY: I see.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Yeah, I'm going to follow up on that. I respect your approach to try to make sure that this was understandable to your target population or to a very broad population, but I think the details do matter and I think it matters that they need to not only understand it but they need to understand the correct message. And I can understand how "exclusive" may have been misleading for some populations for the reasons that you mentioned, but there are other ways to say it that convey complete switching, switching entirely only using -- you know, there are other words that could convey and I remain concerned about that, that "instead of" may be understandable, but they may be understanding the incorrect message.

And, again, I am concerned about "puts you at a lower risk of." Unless we're pretty confident that anyone who's reading it, when it says "puts you at a lower risk," it's referring to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

them, they're included in that broad statement. And, again, I think both of these are reparable issues.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: So, you know, one of the things that we're trying to do here is thread the needle with the idea of -- I'm focusing on population health with the idea of I think we would all agree that getting people who smoke combustible cigarettes off combustible cigarettes is a great thing and we would like them all to quit completely, but if they can't quit, could they switch. It leaves the question of how much switching is involved and with that, we also have to worry about adolescents and new initiation. So we're trying to kind of go between all of these different things with public health.

So one of the things that I'm struck with is the small market share that really snus has at this point, it was a very small percentage of the population and I'm wondering if you could tell me who those people are, are they people who actually have more money or less money? Do you know who your customers are already and -- because it gives us an idea of who you'll be growing, then.

MR. SEIFERHELD: I can. And as a matter of fact, last year we conducted research that was meant to understand our

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

users and recruited those people through a package sticker. So literally, they bought the package and there was a little sticker on it that invited them to come take the survey, following the same procedures outlined by Gerry earlier, that they would come to a website, be age verified and measured from there. I want to underscore that if anyone identifying themselves as being under 21, they were excluded from the research because they have no business -- you know, this is too close for comfort and they have -- you know, youth, as we have said before, have no business using this product. I can tell you that the snus user skews -- first of all, heavily male. Well, 90%-plus male. They are about a median age of about 35. Half the group was ages 21 to 34 and the other half was age 35 and up.

They tend to be fairly well educated comparatively to smokeless tobacco users and slightly more affluent. I use the word affluent carefully, I'm not suggesting rich, just a little higher up on the income scale. They skew substantially Caucasian in the ballpark of 90%. They tend to also display, again, a fairly sound education of the smokeless market.

And in our case, our research demonstrates that people who use General Snus, the majority of those people were mono-users;

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

in other words, they only used General Snus and that was probably -- it was definitely the majority, I want to say about 60%. I do not have the data in front of me. I can tell you, compared to category tracking studies we have done, that is higher than other brands. Hopefully, that gives you a general flavor.

DR. BIERUT: Can I ask, did you know the educational attainment of this population?

MR. SEIFERHELD: They skew heavier towards a college degree. I don't have the exact number in front of me, but they would be a little higher educated than the typical smokeless user.

DR. BIERUT: So what I think you're saying is the group that we're thinking of as generally the lower-risk group for the tobacco products. So you're telling me they're higher educated, they're more white and overall have more resources economically, they are the snus users than the general smoking population.

MR. SEIFERHELD: Yes, this is among our brand, yes.

DR. BIERUT: Among your brand, so -- which is generally what I think of this group that hangs at that lower risk for anything.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Okay, thank you.

DR. MERMELSTEIN: Dr. Warner.

DR. WARNER: First of all, I appreciate my colleagues' questions and I think that the details are important. I'm worried a little bit about losing sight of the forest for the trees here, in the following sense. We've heard earlier, and I think everybody knows that U.S. consumers' ignorance about the relative health consequences of smokeless tobacco, particularly low nitrosamine smokeless tobacco, compared to cigarettes is truly appalling. This proposed label, everybody agrees, is accurate and it doesn't appear to be significantly misleading. I would contrast that with the warning labels that the company and all snus and smokeless manufacturers have to put on their containers that are misleading, the warning label about cancer and so on.

That's probably not accurate when it comes to a product like snus and it's certainly misleading because it leads to this perception that smokeless products are even more dangerous in some instances than cigarettes.

So I want to take that as a starting point and mention -- by the way, I'm new to the Committee, but obviously I've been following what it has been doing, what FDA has been doing since

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

its inception, and I'm really concerned about the precautionary principle running amok. The precautionary principle says, basically, you don't do anything until you're basically a hundred percent sure that this is going to be safe and an improvement. I would turn that on its head a bit and say we have a seventh of the U.S. population that are currently smokers at an extraordinarily high risk of dying. If they transition to a product like snus, they will be at a dramatically lower risk of dying. I have to keep that in mind because I think a precautionary principle says let's not forget what's important here and I think Dr. Bierut was alluding to that earlier on.

I think the low use of snus in this country, at this point, means that in all likelihood this is not terribly important in the grand scheme of things for the effects on health overall, although if this worked and they ended up selling a lot of product to people who were smokers and they decided to quit smoking and try the product, that does have a population health benefit. I think the risk here to population health is very small. The benefit, I think, is considerably larger. Both of them are potential, the risk and the benefit.

Matt Myers said that this, if it is approved by FDA, will
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

set a precedent and I think he's absolutely right about that, but I want to ask FDA to consider if it is not approved, what precedent are they setting? It suggests to me, to be very candid about it, that there is little point to the MRTPA process because it is an onerous and expensive process. I think it is a necessary one, but my concern is that if for a product like snus, where I think the health risks are really clear compared to smoking, much more so than with any other of the smokeless products, if this one -- and the study, I did not personally think that the study was perfectly done, but I think it's convincing that the risks are relatively low here and there's some potential benefit.

And my sense is that if this were not approved that it might be the death knell of the process because it basically would be saying you can't get anything through this process. And if that's true, I don't know what the point of the concern about the continuum of risk is. I don't know what the point is about FDA trying to evaluate the relative risk's population implications of different products.

It just strikes me, if this case can't get through, probably nothing can. On the other side of that, when Matt said it would set a precedent, I think that for me it's not a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

precedent of, oh gee, we've approved one, therefore there's going to be this flood of subsequent approvals. I think each one has to be reviewed on its merits and compared to what has come before. I'm just very concerned about, as I say, losing sight of the forest for the trees. We're trying to figure out how to improve population health here.

DR. MCKINNEY: I'd just like to tweak some of those statements just a little bit. When we talk about approve, this product has been approved with a PMTA, so it's appropriate for the protection of public health. I think really what we're talking about here is accurate communication to the consumer and approving that communication to the consumer. But other than that, thank you for your comments.

DR. MERMELSTEIN: Dr. King.

DR. KING: Yeah. So I have two comments and the first comment really focuses on this issue of dual use. And so, you know, in the end, I fully acknowledge that there is a continuum of risk. I think that there's relatively broad consensus across the scientific community that if someone were to switch completely, there would be a net benefit. But it's a big "if," it's theoretical, and if you actually look at the preponderance of the science, we don't necessarily have a robust body that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

shows that people will actually switch. That being said, theoretically, yes, if some were to switch completely there would be a benefit and that's why I'm very concerned about the language and getting it right and I fully acknowledge that, you know, what is said is accurate but is it the most accurate as possible, and the answer to that, to me, is no.

And I don't understand, it seems very simple to me that you could carefully craft something along the lines of what Dr. Ossip was saying, that switching completely or switching entirely, it's just a semantics issue, it could be done right and it could be easily. And as we've already heard, a lot of the target demographic, anyway, is more educated people, so the eighth grade standard, you know, may not necessarily, you know, be warranted here.

You know, that being said, I think that this whole notion of making sure that the statement is accurately relayed to the public is a critical one and right now I'm not convinced that the current language does that for a variety of reasons and it seems like a pretty straightforward and simple thing that could be hammered out. That being said, I also continue to have concerns about this youth issue and I completely reject the notion that just because something is low now we have to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

completely dismiss what the relevance could be in the future. I mean, my response to that is one word, Juul. You know, at one point Juul was not all that popular either, but you're going to have a machine behind this where it's heavily advertised, including by social media in the Applicant's own proposed plan. And so just basing the notion that if nothing is happening now and smokeless use is relatively low, you know, I dismiss that as well.

We've got 1 in 20 kids in this country using smokeless products and half of those are snus already, so -- and that's absent a heavy mass media campaign or any other promotion. And so we really have to consider this population impact, which is what Congress has told FDA they need to consider in these plans.

And so this continued notion of the absence of any youth data is preposterous to me. I think it's perfectly possible to collect data on youth, you could do it in a tactful and independent way through other entities, but this continued reliance on applicant after applicant to this Committee saying that we don't collect data on youth and so we can't tell you anything is just absurd to me. And it could be done and it could fit within the purview of the FDA.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

And on the same line, I'm very concerned about this notion of let's just wait until postmarket to see what happens. And you know, I adore my sister agency, the FDA, but you're not exactly pillars of expediency and it takes a long time to do things right. And so how long are we going to wait if something does happen? Can you immediately pull something on the market?

And is it going to be a situation like Juul, where now we have a horrendous problem on our hands that we're not going to be cleaning up for years because we allowed a product to enter the market that didn't have a media campaign behind it and then it was heavily promoted and now we have a problem. And so just some considerations for us in this Committee moving forward.

You know, the dual use issue and also this youth issue are something that are going to repeatedly come up, and I think that it could be done and it could be science based, it could be evidence based. I'm not adverse to a continuum of risk and the fact that switching completely could benefit individuals, but it's got to be done right and it's got to be science based and we can't continue to flagrantly dismiss these issues meeting after meeting, applicant after applicant, because as Matt Myers said, this sets a precedent and we've got to get it

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

right, folks.

(Off microphone comment.)

DR. DUFFY: Oh, I'm sorry. I just wanted to pick up a little bit on what Ken said, as I've been listening to all of the comments, and I think that I guess I'm coming from the position that I'm loosening up a little bit as well. I think that this is a company, Swedish Match, that I've known for years and listened to a presentation way back in the '80s. They've been a company that has been looking at harm reduction before it was very popular.

I remember them talking about, in the '80s, not wanting to kill off their buyers and I give them a lot of credit for that, I think. And they're also a company that, at least as far as I know of, have never marketed to youth.

And so that makes me trust them a little bit, anyway, that they haven't done that in the past and they -- I don't think they intend to. And there is something to be said for intention. I think that I agree with the wording issue, but I think it's a semantics thing and I think it could be easily fixed, the "completely" thing.

And I think the harm reduction thing is something that we need to do, I think the public needs to be informed to some

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

degree, and if we can fix it with a little bit of wording -- and I think they've tried very hard to respond to the FDA's concerns from 2015 and I wasn't here then, but from what I can see. And I like the fact that, you know, it's not in the box warning, it's next to the box warning, there's still a warning there in place. So those are the reasons that I think that we should consider it.

DR. MERMELSTEIN: Dr. Stepanov.

DR. STEPANOV: Yeah, I also was thinking about potentially, you know, revising maybe the statement. So I'm concerned about the accuracy of understanding the message. So a few points have been raised that -- is extrapolated or projected to other health risks such as gum disease.

Also, I have a concern about personal risk perception, so it is not necessarily accurate to claim that the individual user switching to this product completely or substantially reduces their risk for, let's say, mouth cancer. But another one is it seems like they also perceive that this particular product will be less harmful than other snus products. So I think there is a concern there because, first of all, it's not accurate, probably, that other snus brands, even including Swedish snus brands, could be more harmful than snus -- than

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

General Snus. We don't know -- we do know that smokers don't really like snus too much, at least in the U.S., from studies, switching studies. Smokers don't care as much about this product.

So what if the understanding is that it's General Snus that reduces risk but not other snus products and a smoker intends to try, they buy, they don't like it, so they could potentially benefit from switching to snus in general, but they will not try other snus brands because they think that they are more risky than this one.

So it's more like a general comment and maybe question to you, to the Applicant, if you have any comments on this particular outcome that General Snus is perceived -- or other snus products are perceived as more risky than General Snus.

MR. PEYRON: No, not really. I mean, that is how the process is set up. An alternative would be to have a standard to allow claims related to all products have met that standard. I think that would have been a good process, but that's not how it's done. So this is where we are and how we had to proceed.

DR. MERMELSTEIN: Dr. Kozlowski, you're on the phone, did you have a question?

DR. KOZLOWSKI: Yes, I had a comment. I do want to offer
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

support for the general comments that Dr. Warner made. I think it's the case that there's a profound misunderstanding on the part of the American public about the risks of snus and that if you consider the PATH survey, you -- they asked a question in quite a limited way, they only asked do you think is snus less harmful.

They didn't have an option of "much less harmful" and in fact, I think the evidence shows that overall it's much less harmful. And so I think there's an opportunity here to make a contribution to correcting a profound misunderstanding that consumers have about an important material fact linked to this product.

DR. MERMELSTEIN: Dr. Warner.

DR. WARNER: Thank you.

First of all, I want to agree very strongly with Lynn and I want to go back to a point that I made earlier and then actually follow up on Dr. Stepanov's comment, which I thought was very important. The warning labels, which even in the marketing that we saw that they're going to use their new label, the warning label is big, bold, and certainly far more visible, and it is clearly misleading, it is factually misleading. This is a small corrective to that.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

I mean, I just think we're putting such incredible standards on a proposed statement that is accurate when the basic warning labels that FDA requires quite possibly are not accurate in the case of snus and under -- unequivocally misleading. There's no question that the FDA warning labels are maybe wrong and certainly misleading and we've seen the evidence of that.

I thought your question is one that was very good and it occurred to me when I was reading through the materials and I actually would like to ask FDA for a response to this. If the effects of the label were to get other users of other snus products to switch to General Snus, I think we can probably agree the public health consequences of that are negligible in any direction. If it got them to switch from a higher nitrosamine smokeless tobacco product to General Snus, there could be some public health benefits to it.

But the basic question is a really important one. Suppose we take a product that is intermediate between snus and cigarettes, that's somewhere in that continuum of risk. So let's say there's a smokeless tobacco that is higher in nitrosamines and therefore would probably, all other things being equal, be adjudged to be more risky than snus.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Would you get them the modified risk claim because it's clearly better than smoking, but it might get people who were snus users to switch over to that other product because it has the health message on it, basically, the -- you know, the corrective, if you will.

So I'm inclined to agree with what I just heard here about this being FDA's process, but it is troublesome because it applies individual product by individual product and I'm just curious what FDA's thinking is about this and how are we, as a committee, supposed to respond to a message for a product that isn't like snus, which is at the bottom of the tobacco product risk spectrum?

DR. APELBERG: Yeah, it's a good question. You know, we have the statutory requirements and we have the standard that has to be met and it is related to both individual risk and the impact on the population as a whole. So in that case, the example that you just gave, I mean, what we wanted to do is to lay those potential impacts, you know, so you're communicating something, there might be a benefit if -- you know, if smokers switch completely how likely is that to happen and what's the impact there.

And then if there is the potential for impacts due to
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

other groups changing their behavior, whether it's, you know, users of less -- potentially less harmful smokeless products, that needs to be weighed into our overall assessment. Of course, the challenge is that it's hard to anticipate, you know, with precision, you know, what all those patterns of -- you know, of impact might be, but those are things that we would have to grapple with.

I mean, that would be part of -- the overall assessment of the potential impact on the population is not just what is the individual risk profile of somebody that moves to this product, depending on where they started, but then also how likely are those -- how big are those groups and how likely -- how big is the behavioral impact among them? You know, so it's a complicated set of questions, but that's ultimately what has to be weighed much in the same way we're weighing what's the potential impact on youth and how does that, you know, impact our overall assessment of the health impact to the population. And I would just say, in terms of this process by which we look at individual products and make a determination about modified risk for labeling and advertising, we recognize the limitations that have been stated this morning by many folks and we agree with them.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Unfortunately, that is the way the law is written and so we have to work within that and right now the tool we have is a modified risk tobacco product application for an individual product and so we have to use that tool.

I mean, we think it's important that if we do identify products, individual products that should in fact, you know, allow to label and advertise with modified risk, that we use that tool for the benefit of public health. And so the tool might not be the tool that everyone would want us to have, but it's the one written in the law and we want to use it to the best of our ability to advance our public health mission.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: So I want to just, you know, make it clear that I am very much in favor of kind of moving forward with this type of, you know, process because I think that, again, we're balancing the risks, which -- and the known risks of combustible cigarettes.

I'm actually fascinated by the idea that the people who are using snus now, to me, are sounding higher educated, more resources, and white, with the idea that those are the groups I think have a high level of literacy, have -- are looking for these products to kind of switch and may be able to mitigate

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

these issues about the misperception of the harm of snus.

And, you know, I think that one of our jobs is to make sure that this information is freely available to all of our population. I think that that's really an important aspect, especially given the misperception.

I am also interested by Dr. Stepanov's question, too, because as I recall from our last meeting, that these products don't have the same amount of harmful and potentially harmful carcinogens in them. And though snus is a wonderful example of bringing it down, as I recall with some of the presentations, that depending on the process, it does differ and we do have to -- the FDA will be kind of confronted with, you know, what type of leak-over there is to other types of products in this sense and how is that risk managed.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: I mean, I guess since others are also kind of sharing their perspective on the continuum of risk and how we need to be thinking about that, I certainly agree with that and certainly see lots of potential for this kind of a product.

As I saw, our mandate for this session right now was about how this particular statement influences consumer understanding and that's where I was having issues because I share with a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

number of people here that I think there are ways that you can craft the message that will communicate these concepts more clearly to a variety of different audiences, particularly to the audience of dual users, and I think that that's certainly something that needs to be focused on in the next round of testing, if there is one.

And I also know that with these kinds of online panels that are used for these messaging testing studies, it's not that difficult to do and it can happen really quickly.

And so I wouldn't expect that this would be the kind of thing where it would reconvene TPSAC to look at the final wording, it's more saying these are some of the issues that we're identifying here. We or I would recommend that you try to address them and then FDA, you can have some sort of a discussion that maybe leads to the approval.

DR. MERMELSTEIN: Dr. Wanke.

DR. WANKE: I'd have to say I agree with you, Dr. Thrasher, and it's one of things I'm hoping that FDA can address, is that it seems that the process to come up with an optimal message might be very straightforward and simple, especially if it's done in collaboration with communications experts in the public health community or other investigators.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

But it seems like the process is set up to discourage that kind of collaborative effort and that I'm struck by the fact that the original TPSAC hearing was in 2015, am I correct, and now we're here at 2019 when that process could have happened during that time. Is there a way within the way that the allowable process and the way that the act is written to have that kind of back-and-forth to have that done or would it require sending the company back to the drawing board, having them do their own research without it being transparent to the community and that there isn't, you know, an announcement of these are the variety of messages that are being considered, the public health community can also do research and provide feedback on what optimal phrasing would be or what the impact would be, independent of what the industry is doing?

DR. HOLMAN: So this is really up to the applicant. I mean, the applicant certainly can engage with any stakeholders they choose and this isn't an applicant-driven process. I mean, we get an application and we evaluate it. At the end of the day, what the applicant does with our feedback is up to them and so they could go by any method they want.

I will say a lot of people brought up a concern about labeling and I certainly hear those concerns and agree with a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

lot of the points being made, but I guess I want to point out another piece of the process which is, if we were to issue an order allowing the labeling as proposed and advertising as proposed, it doesn't mean that labeling or advertising needs to be locked in. I mean, the applicant has the ability, for example, to do additional studies and further refine that labeling and advertising to hit the target messages that they want to hit. And I guess sort of another point is, you know, labeling is really tricky. I mean, I've been at the Agency for almost 20 years and in that entire time, first, I worked on over-the-counter drug products, now I work on tobacco products, labeling is extremely challenging.

You're looking at a very diverse population and you're trying to get that diverse population all to come to the same exact understanding and that's just impossible, right? And so one of the things that we look at from the FDA perspective is "but is it good enough?" Like, is it likely to have the impact we want, looking at particular subpopulations that may be more vulnerable, of course. And you know, it often is an iterative process to really get the exact labeling, you know, determined.

And so, again, it's trying to balance, I guess from our perspective, like whether we think what's been proposed and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

what that data shows in terms of comprehension is adequate enough to allow that to be marketed but again, it doesn't preclude later refining that to further improve it. Hopefully that helped address your concerns.

DR. BIERUT: So I want to address this issue also of kind of the assessment of adolescents and youth. So I understand the position of the industry of not wanting to touch that, that that's, you know, a third rail and not wanting to touch it. But on the other hand, you know, from our end, that's really important and there are surveys already that are going out, but those surveys are locked in and really not necessarily very quick and easy to change and really address some of these problems.

So I think that we'd also have to think of is there a process to kind of bridge this issue between requiring the tobacco industry, you know, the industry to do these studies but, you know, kind of helping develop some type of firewall or other procedures.

I know this occurs with the opioids and had something to do with the FDA many years ago because I have some colleagues who are in some type of process with that and we really need that because I don't want us to be sitting here again asking

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the question what about youth and understanding industry's component of we don't want to touch youth.

DR. MERMELSTEIN: There's a rapid pilot response mechanism within some of the TCORs which could be used that way. Okay, just to go around and then I'll get you on the left.

Kay -- Dr. Wanke.

DR. WANKE: I wanted to thank you, Dr. Holman, for your answer and ask a clarifying question. When the message is -- let's say a message is approved, isn't it for a certain number of years? And will you remind me, does that then require re-approval of the specific message or is it -- like, does the industry come back asking for a re-approval or is FDA just reconsidering it? Is that the opportunity to consider alterations of the terminology?

DR. HOLMAN: So I think one of the strengths of this process -- we talked about some of the limitations. One of the strengths is that we do have a lot of ability to monitor that product and the labeling and advertising after it goes on the market, in conjunction and in collaboration with the applicant.

And so Ben alluded to it earlier, I mean, we will -- when we issue marketing orders under this pathway, we will include postmarketing commitments of some sort with the Applicant and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

we will be doing some surveillance so that we can monitor it as real time as possible, which means we may make adjustments before the expiration date, if warranted. But if not, we would be collecting data, of course, across numerous years and then at the end of that period, we'd sort of assess, like, do we extend this or do we cease. And so it isn't -- you know, again, I think one of the strengths is that FDA has a lot of authority to really go back and reevaluate our decision if we, in fact, allow a product on the market and I think that's very clear in the statute. And so that's, again, one of the strengths here that I think we certainly will be relying on as we move forward with, you know, marketing orders under this pathway.

DR. MERMELSTEIN: Dr. O'Connor.

DR. O'CONNOR: Yeah. So I'm resonating to something Dr. Warner -- Dr. Kozlowski said, which is that, you know, we are somewhat in the deep, deep weeds here of really trying to wordsmith and I worry sometimes that the perfect is becoming the enemy of the good and that, you know, there's a -- there's no perfect study that will give us the answer. The only way we're really ever going to know is by having the thing live and getting a sense of what the response in the population is.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Aside from that, we could go back and forth for years with different study designs and this one has these advantages, this one has this advantage, this wording attracts this group, this wording attracts another group and you would -- none of the studies would ever really give you the answer that you really want and I think that's -- the concern here is, you know, as Dr. Warner said, if a product is sort of constantly a loop of trying to get to the perfect study, then it can never happen.

DR. McKINNEY: One of the advantages of this Committee is its diversity. The issues that we discuss are very complex and it's very nice to hear and we have government, academia, industry here and we have a lot of discussions and there are some venues outside of this Committee that allow us to do that as well.

But when it comes to actually working together, which was suggested that we should talk to each other and try to come up with studies to solve the problem, it gets more difficult. And just an example, given policies at some universities, people can lose their funding if they even talk to the tobacco industry. So I just want to raise that as we -- I think, Kay, you put that forth that we work to think -- to work together to try to come up with solutions and it's very difficult outside

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

of this environment.

DR. OSSIP: I want to get back to what Dr. King had said because I think he made points very articulately and when we're talking about potential changes in the wording, I think what we're hearing around the table from people who are expressing that view is that there's some pretty simple changes that I don't think require complex research designs around them to make the difference, but they change from something that's vague to something that's accurate, that accurately reflects the state of the data right now and that's around complete switching, for example.

And so, actually, a point of clarification from the FDA because I'm not sure that I heard that answer and understood it. If there were to be a position that clarifying wording needs to be substituted for what's there, is there a fast track through the FDA or, in fact, is that a lengthy process for approval? I think maybe it was Dr. Thrasher who said is that something that could be done internally by the FDA or would it need to come back through TPSAC or what would happen from there?

DR. APELBERG: Yeah. I guess just I'll get to that question, but to take a step back, I mean, I think in general,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

when we're talking about language and comprehension and understanding, you know, ideally we'd like it to be evidence based and that's why we put a lot of value in the studies that are done to evaluate comprehension and understanding and what those show us. And so to your question specifically around can we work with the Applicant to change the language, yes, I mean, we can, you know, if there's -- if we feel that it would improve the communication and benefit the population as a whole.

But I guess I wanted to actually throw a question back to the Committee, you know, for those who are raising the concerns about some of the specific language, like, are there particular issues with the findings of the consumer perception study that sort of leads you to be concerned about what it's communicating and what people are taking away or is it more of a question of, you know, you're not quite sure about whether some of the measures are appropriate or there might be some way to communicate this that would have an even better impact on -- you know, on understanding? It would be useful for us to sort of understand, you know, sort of where the concerns are coming from or are they more just sort of like gut feelings about kind of what people will take away from this message.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. OSSIP: I wanted you to just clarify, but I wasn't suggesting that the wording changes be made without some research around it, but as Dr. Thrasher pointed out, with online surveys, that could be mounted pretty quickly.

DR. APELBERG: Yeah.

(Crosstalk.)

DR. APELBERG: Yeah, got you.

DR. OSSIP: -- evidence base on it. And you know, I think in some ways it's both, I think the statement itself does not -- I think, does not accurately convey the state of the literature. Even just that "instead of," I think "switching" is really -- "switching completely" accurately conveys.

There may be different ways to say it. I respect the industry's concern about the use of "exclusive" based on their qualitative research. I think there's some validity to that. At least their process. But I think also there are concerns about the questions that were used and if those same questions were to be used even with revised wording, those concerns would remain.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: I mean, I think I've expressed some of my concerns, but one -- another example would be, you know, the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

comprehension question that's used, you know, people have discussed and public comments that were submitted also discussed how it doesn't necessarily communicate the idea of completely switching because people could be smoking on one day and using snus on the other day, so you all have all that information.

Even so, the correct response, as they've indicated, you know, it's 37 to 54% of the population that is correct in their response, which is you have to smoke zero cigarettes in order to get any benefits. Yeah, I'm not saying that it needs to be 90%, but you know, 37% seems pretty low to me if that's really what it is.

And then there's also the issue kind of the confusing wording, which I think is something that Dr. Ossip has also raised.

I mean, I guess I would also be concerned about -- I raised the issue about people generalizing the potential benefits across the board, beyond the list of diseases. Often, in communications research, what we do is we include what we call bogus items in the response options that register content that's not included in the message and the expectation is that that item will not be influenced by whether people are exposed

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

to the claim or not. And that also provides a little bit of evidence around the specificity of the effect, which I think is something that we want to show some evidence of. And where we saw the gum disease results, which is an outcome that's not included in the message, it behaves very similarly to what it is that you see for the other outcomes that are in the message and so the question is, is it being -- is the effect generalized across a bunch of health outcomes?

And maybe that's appropriate, but there are certainly methodologies that they could be using that would enhance the validity of the conclusions and the phrasing of the actual claim could be improved, I think, based on the data that were presented here and the issues that people raised in the public comments and in the briefing documents.

I do wonder also whether it would be useful to break these up into smaller claims where you're maybe just mentioning one health outcome at a time and distributing those across advertising materials. That may have much a bigger effect and bigger intended effect. So there are a number of things that I could imagine and one could do if one was testing messages and trying to enhance its effectiveness that wouldn't be resource intensive, could be done relatively quickly, and that could

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

address some of the other concerns around needing to have sizable enough populations of key groups like dual users and also, you know, potentially youth.

MS. HERNDON: As someone who works day to day in the field in state government and local government on tobacco prevention and control, I just want to note that I'm still not really clear about product generalizability in this discussion.

I wasn't a member of this group when the previous discussion went on and I'm not sure if Swedish snus is the same product as all other snus and if Swedish snus is the same product as what is sold in America under General Snus.

I also have a question about an idea that came up, to kind of wrestle with some of the finer points here, and that is how can the TCOR's rapid response mechanism be used to sort through some of the issues that we're bringing up today? And then I'll bring up one more that hasn't been mentioned. I do agree with a lot of Dr. King's concerns as somebody who works day to day in the field, understanding how youth risk behavior can go awry when there is something as addictive as these products are, as well as how smokers' intentions to quit and use evidence-based methods can go awry. I'd love to see us do more to restrict some of the kinds of messaging, if this goes forward, to places

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

where it's really only seen by current smokers and not through social media, which is something that the youth have easy and generalized access to.

And then for smokers who are really trying to quit, and this is aside from the process, I'd really like to see us do more to promote evidence-based approved methodology that combines counseling and FDA-approved medications used at the correct dose or used in combination. There's a lot of data on standard of care treatment now that we're really not getting out to physicians and social workers and clinicians across the country that I think could really --

DR. MERMELSTEIN: All good points, but I think just to focus us back and I think, perhaps, start to bring some summary to where we are at. And I think there's a fair amount of consensus, even though a range of opinions, and I think that there is consensus that the importance of providing accurate information about relative harms and that there is a harm continuum and so that the goal of getting people off combustibles and on to less harmful, if they can't quit, is certainly a laudatory one and whatever we can do to promote that and this is one potential path. I think there's a good amount of consensus about that. I think, as we've discussed,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the challenge is finding a sweet spot of the message and that's where most of our discussions have been in terms of the tweaking of it.

And as Dr. Holman said, the labeling is by far a huge challenge and we are presented with one message and yet we're requiring, I think, the Applicant to show what we know doesn't actually ever work, that one message fits every subpopulation and every -- you know, every element and we're asking for these things.

So I think it is, again, what's a starting place and what's a reasonable sweet spot to start with and that may be where we're at because, as you said, every -- you know, we could tweak a word here and tweak a word in one subpopulation versus another subpopulation. There won't be one perfect message, but we want the message that does the right balance. And I think that it's a dynamic marketplace. The message now may not be the message in 5 years and how people respond. So we might want to be more responsive and facile in getting things out and allowing some good rigorous postmarket surveillance. I think their study was a reasonable one. It may not have asked every possible question and comparison and we'll always have alternatives, but the approach and analysis

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

and the design were straightforward and I don't think we're questioning those results.

Everyone wants -- everyone, this is us, we're academics and we're others, we always want something more, we want more data, but at some point is this a reasonable balance and that's, I think, for the FDA to make their best bet. Do you know whether it's going to be "instead of" or "complete switching"? I have a project where I'm trying to get people to switch from one product to another and they interpret switch as alternating.

I mean, we'll never get it perfect. You know, "complete switch" doesn't mean the same thing to everyone and it means, like, today I'm doing this but tomorrow I'm doing completely -- I switched. I mean, there's lots of ways of interpreting it. I don't know which one is better, so I don't think that's our role to say this is better than that. We're looking at the evidence and there may be multiple ways of conveying the message. So I think we've had a fruitful discussion and I think we've pretty much brought up all the points in great questions.

DR. KOZLOWSKI: Robin, can I make a point?

DR. MERMELSTEIN: Yes.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. KOZLOWSKI: This is Lynn.

DR. MERMELSTEIN: Yes, thanks. Go ahead, Lynn.

DR. KOZLOWSKI: I think in some of our thinking about youth use of these products, we, of course, are biased to want no youth to use any of these products. But the PATH survey's Monitoring the Future shows that there are youth users of smokeless tobacco products and cigarettes and vaping products and so on and that if information like this spilled over to youth who were dual users of cigarettes, and there are some, and smokeless, this could be constructive for them.

I'm making the point that what's been mentioned is oh, this could simply be bad for youth and it's more complicated than that because despite our best efforts, there are youth users of these products and they misunderstand the differential risks as well as adults do.

DR. MERMELSTEIN: That's all true and I think, you know, getting accurate information out there is helpful and it starts the conversation and that's helpful, too. So hopefully you've gotten what you need today in terms of a lot of points made.

DR. APELBERG: Yeah. And I do just want to take a moment to just really thank you all. I mean, we feel like this is a really thoughtful engagement and discussion. We really

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

appreciate the points that have been raised.

There's quite a number of important points and I wanted to make sure you all understood that we take this feedback really seriously and we will -- our, you know, plan now is to take this back and incorporate it into, you know, our final evaluation of the submission.

So, once again, just thanks for the -- you know, for sort of being so willing to engage and to really not be shy in expressing your perspectives on this particular application. Anything else?

DR. MERMELSTEIN: A quick process question.

DR. KING: Yeah, I was just wondering why there wasn't any type of vote, specifically. Is that intentional or why in the past we've had, I think, votes which allows for the broad spectrum of opinions across the Committee to be heard in a more quantitative manner.

DR. APELBERG: Yeah. So, you know, typically, we've had voting questions that have really been focused on the scientific accuracy of the claim, not the sort of overall, you know, assessment of whether a product should be authorized or not.

In this case, because, you know, this was an amendment to
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the original application, we felt what would be most useful was to really just have the qualitative discussion so we can make sure that we hear the points that -- you know, that are concerning or, you know, the points that Committee members have in support of the amendments or, you know, the application.

So my feeling has always been that the -- you know, it's the richness of discussion that's really the most useful and informative to us, you know, in terms of making -- helping to inform our decision.

DR. MERMELSTEIN: Great, thank you.

Okay, we're going to take a lunch break now, a little less than an hour. We can come back at 1:00 and get things rolling again. I want to remind the Committee that for this next hour we will not be discussing any of the applicants or the discussion here, so feel free to engage in other discussions besides this, and we will reconvene at 1:00. Thank you.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

DR. MERMELSTEIN: Good afternoon. Thank you all for coming back promptly. I know that some of you were not here for the morning session, so I'm going to just repeat a short introduction. I'm Robin Mermelstein, Chair of the Tobacco Product Scientific Advisory Committee. I'm going to make a few statements, and then again we're going to go around and introduce everyone in the Committee.

So for those of you who didn't hear it this morning, for topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by me, as the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks.

Thank you.

MS. COHEN: The Center for Tobacco Products of the Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the Authority of the Federal Advisory Committee Act of 1972 and the Family Smoking Prevention and Tobacco Control Act of 2009.

The Committee is composed of scientists, healthcare professionals, a representative of a state government, a representative of the general public, ex-officio participants from other agencies, and three industry representatives. With the exception of the industry representatives, all Committee members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with applicable federal conflict of interest law and regulations is being provided to participants

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

in today's meeting and to the public.

The purpose of this second session of the meeting is to discuss the modified risk tobacco product applications submitted by Altria Client Services LLC on behalf of U.S. Smokeless Tobacco Company LLC for the smokeless product Copenhagen Snuff Fine Cut.

Accordingly, this session of the meeting is categorized as one involving a particular matter involving specific parties.

Based on the categorization of this meeting and the matters to be considered by the Committee, all meeting participants, with the exception of the three industry representatives, have been screened for potential conflicts of interest. FDA has determined that the screened participants are in compliance with applicable federal conflict of interest laws and regulations.

With respect to the Committee's industry representatives, we would like to disclose that Drs. William Andy Bailey, David Johnson, and Willie McKinney are participating in this meeting as nonvoting representatives. Dr. Bailey is representing the tobacco growers; Dr. Johnson is representing the small business tobacco manufacturing industry; and Dr. McKinney is representing the tobacco manufacturing industry. Their role at

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

this meeting is to represent these industries in general and not any particular company.

Dr. Bailey is employed by the University of Kentucky, Dr. Johnson is employed by National Tobacco Company, and Dr. McKinney is employed by Altria Client Services.

Although Dr. McKinney's employer, Altria Client Services, submitted the application we are discussing today, 21 C.F.R. 1486(c)(4) allows that a nonvoting industry representative may participate in a meeting in which the matter before the Committee directly or indirectly affects the company employing that industry representative; however, the industry representative, in this case Dr. McKinney, may not discuss the company's position as such but may discuss any matter in general terms.

DR. MERMELSTEIN: Thank you.

Just as a reminder that the meeting is recorded, so for the Committee, when you speak up, speak up into your microphone. And we're just going to go around and introduce -- Sally, we'll start this side.

MS. HERNDON: I'm Sally Herndon. I'm the Government Representative from the North Carolina Division of Public Health.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. WARNER: Ken Warner, University of Michigan School of Public Health.

DR. BIERUT: Laura Bierut, Washington University in St. Louis.

DR. KING: Brian King, U.S. Centers for Disease Control and Prevention.

DR. WANKE: Kay Wanke, National Institutes of Health.

DR. BAILEY: Andy Bailey, University of Kentucky.

DR. JOHNSON: David Johnson representing the small tobacco manufacturers.

DR. MCKINNEY: Willie McKinney, Altria Client Services, representing the tobacco manufacturing industry.

MR. ZELLER: Mitch Zeller, Director, FDA Center for Tobacco Products.

MR. HOLMAN: Matt Holman, Director of Office of Science, CTP/FDA.

DR. APELBERG: Ben Apelberg, Director of the Division of Population Health Science, CTP's Office of Science.

DR. STEPANOV: Irina Stepanov, University of Minnesota.

DR. WACKOWSKI: Olivia Wackowski, Rutgers University School of Public Health.

DR. DUFFY: Sonia Duffy, Ohio State University.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. THRASHER: Jim Thrasher, Arnold School of Public Health, University of South Carolina.

DR. OSSIP: Deborah Ossip, University of Rochester Medical Center.

DR. WEITZMAN: Michael Weitzman, NYU School of Medicine.

DR. O'CONNOR: Richard O'Connor, Roswell Park Comprehensive Cancer Center.

DR. MERMELSTEIN: And just again, I'm Robin Mermelstein from the University of Illinois at Chicago.

DR. KOZLOWSKI: Lynn Kozlowski, University of Buffalo School of Public Health.

DR. MERMELSTEIN: Thank you, Lynn.

Okay, we're going to start with Dr. Apelberg.

DR. APELBERG: Okay, great.

Good afternoon, everyone. Once again, my name is Dr. Benjamin Apelberg. I am the Director of the Division of Population Health Science at the Center for Tobacco Products' Office of Science, and today, right now, I'm going to give an overview of the U.S. Smokeless Tobacco Company LLC modified risk tobacco product application currently under review.

Once again, this is the FDA disclaimer.

Okay. So I'm going to start with just a summary of the
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

U.S. Smokeless Tobacco Company's application under review, including the modified risk request submitted and how FDA evaluates modified risk tobacco product applications. I'll then walk through, briefly, the lines of evidence submitted by the Applicant to support their application and the questions we are posing to the Committee today.

Okay, on March 20th, 2018, FDA received a modified risk tobacco product application from U.S. Smokeless Tobacco Company which states that the Applicant is seeking an order under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act for its Copenhagen Snuff Fine Cut tobacco product, which is a loose, fine cut moist snuff.

As a reminder, the Federal Food, Drug, and Cosmetic Act defines a modified risk tobacco product as a tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. This includes products whose label, labeling or advertising represents that the product is less harmful or presents a lower risk of tobacco-related disease than other commercially marketed tobacco products, or that the product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain or is free of a substance.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

And just as a reminder, the MRTP pathway is not a pathway to market a product. Copenhagen Snuff Fine Cut was commercially marketed in the U.S. as of February 15th, 2007 and has been designated as a grandfathered product by the FDA. Thus, this meeting is not about whether the product should be marketed, but rather the focus is on marketing it with the specific modified risk claim being proposed.

So FDA is currently evaluating the scientific information submitted in the MRTPA to determine whether the statutory requirements for authorization provided in Section 911 have been met. In addition to the evidence presented by the Applicant, we will consider recommendations made by the Committee, public comments, and any other scientific evidence or information that is available to the Agency.

So the Applicant is requesting the modified risk claim, "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."

When determining whether to issue an order under Section 911(g)(1), FDA must assess not only whether the proposed modified risk claim is scientifically accurate and consumers understand it, but also whether the product, as it is actually used, will reduce the risk to individual tobacco users of the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

product and benefit the population as a whole, taking into account both tobacco users and nonusers.

FDA's evaluation of an MRTPA can be thought of in terms of a few key overarching questions. Each of these involves the evaluation of many specific questions which draws from multiple scientific disciplines. In evaluating an MRTPA, FDA has to consider the product with the proposed modified risk information. So these questions include:

- 1) Is the proposed modified risk claim scientifically accurate?
- 2) What are the health risks of the MRTP to individual tobacco users?
- 3) How do consumers perceive and understand the modified risk claim? And
- 4) What are the potential benefits and harms to the health of the population as a whole?

Based on the questions relevant to our evaluation, today we are asking the Committee to focus on a few key areas.

First, we will assess the evidence related to the health risks of the candidate product and the proposed modified risk claim. I'll begin by describing the harmful and potentially harmful constituents, or HPHCs, in the candidate product and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the nonclinical and clinical evidence related to disease risk, and then will present the epidemiological evidence used to assess the relative risks of the product and the scientific accuracy of the proposed claim. TPSAC will be asked to discuss the accuracy of the proposed modified risk claim.

Next, we will present sample labels and advertisements submitted by the Applicant and results from their Claim Comprehension and Intentions Study, or CCI Study. The Committee will be asked to discuss potential implications of the study's findings.

And then, lastly, we'll present data from observational studies and the Applicant's clinical and CCI studies which are used by the Applicant to assess the potential use of the product. I will also briefly discuss the company's population model used to estimate the potential population health impact. TPSAC will be asked to discuss the potential users and use behaviors with respect to the proposed modified risk tobacco product.

So now here are the three specific questions we're posing to the Committee.

First, the Applicant proposed the following modified risk claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

this product from cigarettes reduces risk of lung cancer."

Discuss the available scientific evidence and vote on the whether the proposed modified risk claim is scientifically accurate. Here, the options are yes, no, or abstain.

Question 2: In addition to evaluating the proposed modified risk claim for scientific accuracy, FDA also evaluates consumer understanding and perception of the modified risk information.

Discuss the potential implications of the proposed modified risk information on consumer understanding and perceptions.

And then Question 3: Discuss the potential users of the proposed MRTP. And here there are two sub-questions:

- 1) What is the likelihood that cigarette smokers will switch completely to Copenhagen Snuff Fine Cut?
- 2) Considering the health risks from the use of Copenhagen Snuff Fine Cut and those who may be likely to use the product, what are the groups of potential concern, for example, users of smokeless tobacco products with lower HPHC levels or youth are just two example.

So those are the questions we're bringing for the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Committee and with that, I'll turn it back over to the Chair.

DR. MERMELSTEIN: Thank you, Dr. Apelberg.

We'll move to Applicant presentations.

MR. MURILLO: Thank you and good afternoon, Madam Chair, members of the Committee, members of FDA, and everyone joining us today. My name is Joe Murillo. I'm the Senior Vice President of Regulatory Affairs for Altria Client Services. We're here today to discuss the modified risk tobacco product application submitted by U.S. Smokeless Tobacco Company. I will moderate the presentation, joined by several colleagues whom I will introduce shortly. And on behalf of all of us, thank you for the opportunity to provide this overview and following this presentation, to answer your questions.

We're here today because we're seeking FDA authorization to market Copenhagen Snuff Fine Cut with a modified risk claim. The proposed claim is, "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer."

Copenhagen Fine Cut is a type of smokeless tobacco called moist smokeless tobacco, which is often called MST. It isn't a new product; in fact, this product has been on the market since 1822. During today's presentation, we will refer to the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

product as Copenhagen Snuff and to the manufacturer of the product as UST.

Copenhagen Snuff presents both a dilemma and an opportunity. The dilemma is this: products like Copenhagen Snuff are not risk free, but they are substantially less hazardous than cigarettes, specifically as it relates to lung cancer. This is the overwhelming consensus of the scientific, medical, and public health communities. It is a scientific fact. But adult smokers don't understand that fact. In survey after survey, most adult smokers get it wrong, even backwards. One example of this comes from FDA's Population Assessment of Tobacco and Health, or PATH, survey. In PATH, more than 90% of smokers said that smokeless tobacco products are just as harmful as cigarettes or even more harmful.

Here's the opportunity. Our evidence shows that providing adult smokers with the correct information would have a net benefit in population health. With sustained exposure to this information over time, the real-world impact could be much larger.

Dual users, that is adult smokers who also use smokeless tobacco, are one population that could benefit. There are about 2.3 million adult dual users, according to PATH, so dual

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

users present a logical harm reduction opportunity. They have already made the choice to use smokeless tobacco. Given that, they may be more open to using it exclusively and giving up cigarettes completely.

There is an even bigger group that could benefit from the facts. About 128,000 smokers die from lung cancer every year, according to the Centers for Disease Control. The 23 million adult smokers who, according to PATH, are likely to use a tobacco product marketed with a claim, if they believed it, offered a reduced risk of harm. But these 23 million adult smokers, more than half of all adult smokers, don't know that MST is an option. Within that dilemma lies the opportunity to give these millions of adult smokers a reason to transition from cigarettes to MST products. We can do that by providing them with the facts about the relative disease risks of these products. That's why we're seeking a risk modification order for Copenhagen Snuff.

Under Section 911(g) of the Tobacco Control Act, the FDA is required to authorize a modified risk claim when the product, as actually used by consumers, meets two requirements. First, it significantly reduces risk to individual users and second, it benefits the health of the population as a whole.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

The information we present to consumers must be accurate, not misleading, and supported by scientific evidence. We believe that our application meets each of these criteria and satisfies the statutory requirements for a modified risk claim.

Now, let's turn to our agenda. I'll take a few more minutes to describe the claim, our marketing plan, and the product itself. Then you will hear from Mohamadi Sarkar, who is a clinical pharmacologist and the architect of our application. He will talk about the published scientific literature that substantiates our proposed claim, with a focus on evidence related to health risk.

Next, Gary Harvey, who is an outside consultant and statistician, will describe our evaluation of two public, nationally representative datasets linked to CDC mortality data. These analyses provide epidemiological evidence about the health risks of cigarettes and smokeless tobacco. They also include unique comparisons not typically reported in the published scientific literature.

Stephanie Plunkett will take the floor after Gary. She is a behavioral neuroscientist and a psychologist and will describe how we developed and tested the claim. She will discuss adult consumers' understanding of the claim and its

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

impact on risk perception and behavioral intentions.

Finally, Ryan Black, a clinical psychologist and statistician, will tie it all together with a discussion of the population impact of the proposed claim. He will discuss the potential for unintended impacts on youth and other nonusers, our plans for postmarket surveillance, and the net benefit to the population as a whole.

We believe that authorizing our proposed claim is a step in the right direction. Under FDA's oversight, providing adult smokers with this information will complement, not compete with, prevention and cessation. Adult smokers can't be expected to switch to less harmful products if they aren't told about them. They need information to make informed decisions. They have a right to receive it and this claim will empower them to choose a less harmful product lower on the continuum of risk.

FDA has already determined, as a matter of science, that there is a continuum of risk among tobacco and nicotine products. FDA has also determined, as a matter of policy, that efforts should be made to move addicted smokers down that continuum of risk to less harmful products.

Conventional combustible cigarettes are at the top of this

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

continuum. Burning tobacco and inhaling the smoke is the most harmful form of tobacco use. Noncombustible tobacco products are lower on the continuum of risk. These products, like Copenhagen Snuff, are far less risky than cigarettes and FDA-approved medicinal nicotine is at the lowest end. And, of course, the best way to reduce the risk of tobacco use is to quit.

So now I'd like to take a moment to focus more closely on our proposed claim and provide some background about the product.

Again, the claim we propose is this: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." We'll hear more later today about how we chose the language of this claim. For now, I'd like to highlight three aspects.

First, it starts with the headline, "IF YOU SMOKE, CONSIDER THIS," in all capital letters. That's because we wanted to draw the attention of adult smokers.

Second, the claim focuses on a single disease, lung cancer. It is a risk reduction claim. The claim doesn't say and does not imply that the product is safe.

Third, it specifies a single desired use behavior, that is

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

switching completely from smoking to this product.

So there's no confusion, I want to be a hundred percent clear about the intended audience for the claim, adult smokers. We can't eliminate the possibility that others might encounter the claim. It's worth noting that in our testing, adult never users did not show any increased interest in this product. Neither did adult smokers who were planning to quit. Seeing the claim didn't change that. But we'll take steps to minimize its reach to unintended audiences, which brings me to our communications plan.

Misperceptions about Copenhagen Snuff and lung cancer risk are deeply entrenched. Correcting these misperceptions will take time and sustained communication. Accordingly, we plan a comprehensive campaign to communicate the claim to adult smokers. This campaign will rely on marketing tools that best reach adult smokers while minimizing reach to unintended audiences, especially kids.

Let me give you a sense of how this approach might look in practice along with some of the safeguards we will employ.

We'll use tools such as print advertising, direct mail, and the Copenhagen branded website. Through direct mail, for example, we can communicate the claim to more than 10 million

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

adult smokers. Other possible tools include point-of-sale materials and labels on the bottom of the can. Any tool we use will be responsibly used.

Print ads will include the required rotating warnings and we place print ads only in publications with predominantly adult readership following FDA's definition.

We also limit the reach of one-to-one marketing communications, like branded websites, brand marketing events, and direct mail. To receive these communications, adult tobacco consumers must satisfy two requirements. First, we verify that they are 21 years of age or older and second, they certify that they are a smoker, smokeless tobacco user or both.

At retail, our trade programs have multiple safeguards to prevent underage access to tobacco products. For example, we limit display of our products to non-self service location. We help train store personnel to verify age prior to sale, we require retailers to post signs that prohibit underage sales, and we also require them to post signs that tell adults not to buy tobacco products for kids.

Now let's turn to the product itself. Copenhagen Snuff has a long history of use in the U.S. For decades, Copenhagen Snuff has been one of the most popular smokeless tobacco

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

products on the market and it remains so today. It's made by blending 100% finely cut American-grown tobacco from Kentucky and Tennessee with water, salt, and flavors. We can document the historical product formulas from as early as 1905. But the overall process for making Copenhagen Snuff has been largely the same over time.

Over the last decades, we've refined our manufacturing process to reduce the formation of tobacco-specific nitrosamines or TSNAs. As described in our submission, these refinements have reduced TSNAs in our MST products by up to 90% relative to historical levels.

Copenhagen Snuff also has a well-established adult consumer base and stable use patterns. Consumers use this product by placing a small amount, or pinch, of the product in their mouth between the lip or cheek and gum. They hold it there for approximately 30 to 40 minutes before removing it.

Most consumers use the product daily and on average, they consume about half a can a day. Typically, they expectorate or spit out the excess saliva that builds up in their mouth while they are using it and so for this and other reasons Copenhagen Snuff is not for everyone. It's appeal is limited. Consumers of Copenhagen Snuff are, by and large, adult white males who

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

are 35 years of age and older. We recognize that no single product or category of products will appeal to all adult smokers who are looking for reduced risk alternatives. That is why we believe there must be a portfolio of products with FDA-authorized modified risk claims. We're starting with Copenhagen Snuff.

We believe this claim for this product is supported by compelling scientific evidence and meets the applicable statutory requirements. Authorizing this claim would be an important first step towards solving the dilemma faced by adult smokers. We can give them a reason to switch, we can help them make decisions informed by fact. We hope that you'll agree and that your discussions and recommendations will support authorization of our proposed claim.

With that, I'll pass the microphone to Mohamadi.

DR. SARKAR: Thank you, Joe. And good afternoon, everybody. I'm going to talk about the scientific evidence we gathered from the published literature which has strongly grounded our application and has informed our analysis at all points along the way.

We conducted a comprehensive search of the existing peer-reviewed literature using a protocol with inclusion and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

exclusion criteria, as shown on the slide, which were based on best practices as described by the Institute of Medicine and other sources.

Our research identified over 6500 publications on topics related to this application and based on our inclusion and exclusion criteria, we narrowed the final list to about a thousand publications which dated back to as early as 1950 and also included many recent ones as well.

Now, we limited these publications to original research and reports from authoritative bodies. We focused our analysis on U.S. products and did not filter based on favorable or unfavorable results.

The publications we cite cover a range of health-related topics such as epidemiological, or epi, studies; clinical and nonclinical; and mechanistic studies. The nonclinical studies used tobacco, tobacco extracts, or individual constituents. In this hierarchy of evidence, we assigned significant weight to the epidemiological studies and we did this for three main reasons.

First, they reflect real-world use conditions in the U.S. population.

Second, the epi studies track health outcomes from long-

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

term product use.

And, third, they report risks in a diverse range of populations, such as never and former users, as well as current users including switchers and dual users.

Now, we recognize that epi studies often do not capture the specific brands of tobacco products used; however, we are confident that we can use the existing epi to assess the health risk of Copenhagen Snuff and here's why. Let's look at the -- let's look at how Copenhagen Snuff use fits in relation to the timing of the epi studies.

This chart shows the prevalence of MST in chewing tobacco and the smokeless tobacco marketplace between 1972 and 2011. As shown in the dark blue shaded region, MST products are the predominant form of smokeless tobacco and have been so for many years.

In 1972, shown at the far left of this chart, MST products already accounted for really half of the smokeless tobacco market. By the late 1980s onwards, around the midpoint of this chart, the market share of MST grew rapidly to become the major form of tobacco consumed in the U.S.

Now, let's overlay on this chart the timing of some of the major U.S. epi studies. One such example is the CPS II study,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

which is a prospective mortality study that began in 1982 with follow-up through 2000. Another example is the NHEFS survey which began in 1971 with a follow-up through 1992. Results from these surveys have been published and we included them in our analysis.

But to add to these studies, we also analyzed, through recent nationally representative studies, the National Health Interview Survey, or NHIS, and the National Longitudinal Mortality Study, or NLMS. These surveys began in 1987 and 1993 and have been linked with mortality information through 2011. As shown here, the rise in MST's market share within the category coincides with the timing of the epi studies and this is especially true for the NHIS and NLMS data.

UST products accounted for almost 90% of the total MST market share through the late 1980s and about 55 to 70% thereafter. Specifically during this time, Copenhagen Snuff was one of the major smokeless tobacco products consumed during the time period of the epi studies and accounted for approximately 40% of the total MST market. That is why we can be confident that the epi data reflects the health risk of Copenhagen Snuff.

In addition to the epidemiology, we reviewed other lines
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

of evidence in the published scientific literature. These included evidence from human studies, reporting biomarkers of potential harm, and biomarkers of exposure, as well as nonclinical evidence like HPHC comparisons, in vitro studies, and animal studies.

And taken together and as described in detail in our submission, the totality of the evidence from the published literature further supports the conclusion that the use of smokeless tobacco is far less risky than cigarettes. And we are not the only ones to arrive at this conclusion based on the published scientific literature. This is now the consensus of public health as well. Here are just a few examples.

In a similar publication describing the strategic dialogue on harm reduction, many leading scientists and researchers have reached the consensus that noncombustible tobacco products are more likely to reduce harm than combustible products. Another example is the advice to consumers by the American Cancer Society which states on its website that spit or smokeless tobacco is a less lethal but still unsafe alternative to smoking. Additionally, the WHO, through its study group on tobacco product regulation, concluded that users of smokeless tobacco products generally have lower risks of tobacco-related

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

morbidity and mortality than users of combustible products such as cigarettes.

Thank you for your attention, and now let me turn the microphone over to Gary to further discuss the details of our analysis which augment the epi findings from the literature.

MR. HARVEY: Thank you, Mohamadi.

There are two main questions I will be addressing today based on our analyses of the linked mortality datasets in prior published epidemiological studies.

First, do smokeless tobacco users have the same or lower lung cancer risks compared to current smokers? And second, do smokeless tobacco users have the same or lower all-cause and all-cancer mortality risk compared to current smokers?

Our linked mortality analyses are based on two nationally representative databases which include information on the individual's tobacco use, sociodemographic characteristics, and detailed causes of death. One is called the National Health Interview Survey, which I will call the NHIS; the second is called the National Longitudinal Mortality Study, which I will refer to as the NLMS.

The NHIS includes 154,000 individuals with about 3,000 current smokeless tobacco users. The NLMS includes 210,000

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

individuals with about 3,500 current smokeless tobacco users.

I'd like to start our discussion with our lung cancer mortality analysis for men and women. The bars on this chart compare the risk of death of lung cancer in a population of never tobacco users, current smokeless tobacco users, and current cigarette smokers.

We performed Cox proportional hazard regression analyses using SAS survey read procedure controlling for age, sex, race, income, education, body mass index, self-reported health status, current smoking, and current smokeless tobacco use. The vertical axis shows the hazard ratio, which is approximately equivalent to a relative risk or odds ratio.

This chart shows two completely independent analyses where the left set of bars uses the NHIS data and the right set of bars uses the NLMS data. Showing these two independent analyses side by side demonstrates the robustness and the consistency in the estimates.

The left-most blue bar shows the baseline risk of the never smokeless tobacco users and never smokers. This baseline risk is shown as a one. The striped bars show the risk for current smokeless tobacco users relative to never smokeless users. The red bar shows the risk for the current smokers

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

relative to the never smokers.

The results of the lung cancer mortality analysis are striking. Let's start with the tall red bar showing the current smokers lung cancer risk in the NHIS analysis.

The whiskers or the error bars surrounding the 18.06 hazard ratio show the uncertainty surrounding the estimate as 95% confidence intervals. The error bars show that the current smokers' risks in the red bars are statistically significantly larger than the baseline risks in the solid blue bars. The same is true in the NLMS analysis. The increased lung cancer risk seen here, 18-fold or 12-fold respectively, are consistent with the published epidemiology.

Let's next look at the current smokeless tobacco users' risks in the blue striped bars. The error bars go both above and below the baseline risk of the never tobacco users shown in the solid blue bars. This demonstrates that the lung cancer mortality risk for smokeless tobacco users are not statistically significantly different from the baseline risks in the solid blue bars in either of these two independent analyses.

Another take-away from this chart, which is particularly relevant in light of the proposed claim, is that current

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokers have significantly higher lung cancer risks compared to smokeless tobacco users.

Next, I would like to review estimates from prior published epidemiological studies. On the left side of this chart we see five orange bars showing published lung cancer risk estimates for smokeless tobacco users compared to never smokers -- or compared to never smokeless tobacco users shown in the first blue bar on the left.

The first two bars are based on Henley 2005 which analyzes lung cancer deaths in CPS I and CPS II data for male current smokeless tobacco users. These two studies include a 12-year and 18-year follow-up respectively.

The next bar, Lee 2009, is a meta-analysis of four studies, including the two estimates from CPS I and CPS II on the left and two other studies which include ever smokeless users.

The next bar, Andreotti 2016, analyzes lung cancer deaths and incidents among ever smokeless tobacco users from a cohort of participants in Iowa and North Carolina.

The next bar, Wynder 1977, analyzes lung cancer deaths and incidents from a cohort study of participants in 20 hospitals across eight U.S. cities.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Collectively, the smokeless tobacco risk shown in the orange bars show that there is either no increased risk of lung cancer or if there is some increased risk of lung cancer, it is below the current smokers' lung cancer risk in the red bar as reported in the 1989 Surgeon General report. The difference in the lung cancer risk between the smokeless users and the current smokers is striking.

This next chart shows the same five orange bars you saw on the last chart plus our risk estimate shown in the striped bars. The striped bars show lung cancer risk estimates for men and women who are current smokeless tobacco users relative to never tobacco users. Our first striped bar shows the NHIS analysis and the next bar shows the NLMS analysis.

On the far right of this chart in the red bars we show the risk estimates for current smokers. Our smokeless risk estimates shown on this chart are consistent with the prior published epidemiology. The conclusion from this chart is clear and robust. When we look across our analyses and the published literature, we see that they all show that the lung cancer risk of smokeless tobacco use is significantly lower than the lung cancer risk of current smoking.

In this next chart we compare the lung cancer risks of
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

former smokers who are currently using smokeless tobacco to the lung cancer risks of former smokers who have never used smokeless tobacco. This chart shows risk estimates from the published literature as well as our analysis.

Our baseline risk for the former smokers who never used smokeless tobacco is shown in the green bar on the left. The orange bar shows a Henley 2007 analysis of the CPS II data which compares lung cancer risks of male smokeless tobacco users who are former smokers versus former smokers who have never used smokeless tobacco.

The next set of four bars do a parallel analysis, except these estimates are derived from the NHIS and the NLMS data. These bars show the lung cancer risks for men only and for men and women combined. These smokeless tobacco risk estimates are consistent with the literature.

The red bars on the right show the lung cancer risk reported in a Thun 2013 publication based on men and women in CPS II. The first red bar show the risk of current smokers relative to former smokers who quit before the age of 40. The second bar shows the risks for current smokers relative to former smokers who quit between the ages of 40 and 49.

Smoking cigarettes increases lung cancer risks. Quitting

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smoking dramatically lowers these risks. Considering all of the analyses we have so far discussed today, they all point in one clear and consistent direction. If smokers quit smoking and switch to smokeless tobacco, then their risks of lung cancer are dramatically reduced.

We would now like to examine whether smokeless tobacco users also have lower all-cause mortality compared to current smokers. This chart is the same type of analysis I showed you in my first chart except this analysis includes all causes of death. The results of this all-cause mortality analysis are, again, striking.

Let's focus on the current smokers risks in the red bars. These current smoker risks of death are about double the risks of both never tobacco users and the smokeless tobacco users. These differences are statistically significant. This doubling of the current smokers' risk compared to the baseline risk is right in line with the published literature.

To test the robustness and consistency of our results, we performed hundreds of sensitivity analyses. The analyses include men and women combined, but also men and women analyzed separately. The prior analyses include all races, but we also limited our analyses to the white population. And for that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

matter, we analyzed the white male subpopulation because white males are the primary users of smokeless tobacco.

We also analyzed other causes of death beyond lung cancer, all causes, and all cancer. We also performed sensitivity analyses of the statistical model by changing the model specification and by changing control variables. None of these hundreds of sensitivity analyses importantly impacted the conclusions that I'm sharing with you today.

As another test of the robustness and consistency of our all-cause mortality estimates, we compared our various all-cause mortality risk estimates with the published literature. This is the same type of chart I showed you for lung cancer but now this chart shows the risks for all-cause mortality.

The first two sets of bars are based on the same Henley 2005 studies in CPS I and CPS II we discussed earlier. The Accortt 2002 article analyzes all-cause mortality from the NHANES I follow-up study. The Timberlake 2017 article analyzes current smokeless tobacco users in the NLMS data. This is the same dataset we included in our NLMS analysis, but the Timberlake analysis includes a longer follow-up period than we used in our analysis.

The striped blue bars show the smokeless tobacco risk

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

estimates relative to the baseline risk. These four bars show the all-cause mortality risks for men only and for men and women combined in both the NHIS and the NLMS data. These risks are clear and compelling. The risk of dying is significantly less in smokeless tobacco users as compared to current smokers.

This brings us to our third linked mortality analysis. Here we do the same analyses and same sensitivity checks we did for our all-cause mortality analysis, but we limit the causes of death to all cancer. These results of this analysis are completely consistent with our prior analyses.

Here we see that the current smokers die from cancer at about three times the rate compared to smokeless tobacco users. This tripling of the cancer mortality risk for current smokers compared to smokeless tobacco users is statistically significant.

As another test of the robustness and consistency of our all-cancer mortality estimates, we compared our various all-cancer risk estimates with the published literature.

This is the same type of chart I showed you during our discussion of lung cancer and all-cancer mortality, but now this chart shows the risks of all-cancer mortality. The six orange bars on the left of this chart are based on all-cancer

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

analyses and articles that we have already discussed including Henley 2005, Andreotti, Lee, Accortt, and Timberlake. The Andreotti and Lee articles include both cancer deaths and cancer instance.

The blue striped bar shows smokeless tobacco risk estimates. The red bar on the right shows the current smokers' cancer risks are roughly three times larger than the smokeless tobacco users' risks as shown in the estimates from NHIS, NLMS, and the published literature on the left.

These risk estimates, taken as a whole, are again clear and compelling. The risk of dying from cancer is significantly lower in smokeless tobacco users as compared to cigarette smokers. Overall, smokeless tobacco users have lower lung cancer, all-cause mortality, and all-cancer mortality risks compared to the current smokers.

Looking at the big picture, what do we know? We know cigarette smoking dramatically increases the risk of lung cancer, all-cause mortality, and all cancer. We know if current smokers quit, their risks are dramatically reduced. And we know that our linked mortality analyses and the epidemiological literature point in one clear and consistent direction. The lung cancer risk among smokeless tobacco users

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

are far lower than current smokers.

I'd like to thank you for the opportunity to share these analyses. I'll now turn over the floor to Stephanie.

DR. PLUNKETT: Thank you, Gary.

I'll be addressing the development and testing of the proposed claim. My presentation will focus on four topics. I'll start with behavioral theory, underlying how conversion from cigarettes to Copenhagen Snuff may occur. After that, I'll talk about how we chose the claim we are discussing today followed by the results of claims comprehension and risk perception assessments, and finally, the impact of the claim on behavioral intentions.

Earlier today, Joe spoke about the dilemma and the opportunity presented by Copenhagen Snuff. Compared to cigarettes, this is a lower-risk product. But adult smokers don't know that it is lower risk. The opportunity is to motivate them to switch by giving them the information they need to make correct decisions. Behavioral science informs how we can achieve this objective.

Well-established behavioral models, like the theory of planned behavior, provide a framework for understanding how switching may occur. These models focus on how perceptions

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

lead to intentions and how intentions lead to behaviors. The theory of planned behavior identifies three constructs thought to influence intentions. First, attitudes about the behavior in terms of the positive or negative evaluation of its outcome.

Second, subjective norms such as perceived social pressure to perform or not perform the behavior.

And, third, self-efficacy in relation to the behavior, also known as personal control.

It is important to reiterate here the desired outcome of the claim is to completely switch to Copenhagen Snuff and no longer smoke cigarettes.

The theory of planned behavior tells us that this conversion is a process and this process depends on multiple interacting factors. These factors include preexisting beliefs about the product, beliefs about the consequences of switching to the product, social pressures of using the product balanced against social pressures of continuing to smoke, and whether they believe they can successfully switch if they try.

Misperceptions about the risks of smokeless tobacco are a barrier to the conversion process. Adult smokers have preexisting misperceptions about the relative health risks of smokeless tobacco products compared to cigarettes. That fact

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

is evident. Our research, FDA's research, and more than a dozen published studies establish that adult tobacco users believe that smokeless tobacco products are equally harmful as cigarettes or even more harmful. These misperceptions are so deeply entrenched that they influence the believability of the claim which impacts its ability to change perceptions, intentions, and behaviors.

But over time, adult smokers will internalize the positive reduced risk message and take the first step towards conversion. Communicating accurate risk information is important and necessary to bring about these changes.

Let's turn to our claim. We developed this claim in a two-phased research program. In Phase 1, we developed the specific language of the claim and this involved identifying language to ensure that (1) consumers knew they needed to stop smoking in order to reduce lung cancer risk, which is what led us to the phrase "switching completely," and (2) consumers understood that there is risk with the use of Copenhagen Snuff.

This claim language also had to be understandable to adult tobacco consumers when presented to them in an advertisement with product imagery and required federal warnings. We conducted a series of qualitative research studies on potential

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

phrasing options to identify claim language that met these objectives and the final claim satisfied all of these criteria.

During Phase 2, we assessed the understanding and implications of the claim in a quantitative study called the Claim Comprehension and Intentions Study, or CCI study for short. We designed the CCI study to answer three fundamental questions.

The first question is whether participants would correctly understand the claim. The second question is whether participants would correctly understand that this product still poses risk to health. And, finally, we determined whether there were changes in behavioral intentions due to claim exposure.

The CCI study used a quasi-randomized control study design. It involved 5,871 adult tobacco users and nonusers from across the U.S. To reflect the general population, we matched participants to the U.S. population using major demographic variables based on quotas from the PATH Study. We met with FDA to discuss the design of the study and oversampled the legal age to 24-year-old population. We divided participants in two subgroups. Group 1 consisted of current adult tobacco users and this included adult smokers planning to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

quit, adult smokers not planning to quit, MST users, and dual users. And Group 2 represented adult nonusers, which included former users and never users.

To assess the effect of the claim on risk perceptions and intentions, we randomly assigned participants into a test condition and control condition and the only difference between these conditions is the presence or absence of the claim. Participants in the test condition saw an advertisement with the claim and participants in the control condition saw the same advertisement without a claim. And we rotated the federally mandated warnings throughout these advertisements.

Both the test and control conditions included a within-subject comparison. This allowed us to compare risk perceptions and intentions before and after viewing the advertisement. And this comparison is important and that's because consumers have preexisting beliefs and use intentions about smokeless products like Copenhagen Snuff. And our findings about participants' incoming beliefs are consistent with the literature and provide context for interpreting our results.

To assess claim comprehension, we showed participants an advertisement containing the claim which remained available to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

them throughout the study and we asked them to select one of four responses to the following question: Based only on the information shown on this ad, smokers who switch completely from cigarettes to Copenhagen Snuff increase the risk of lung cancer, reduce the risk of lung cancer, eliminate the risk of lung cancer, or don't know.

Of total participants, 61% selected the correct response, that is, reduces the risk of lung cancer. Looking closer, a majority of all user and nonuser subgroups selected the correct response ranging from 55% to 70%.

We also asked study participants, both pre- and post-exposure, how harmful do you think using Copenhagen Snuff is to a person's health? Very harmful, moderately harmful or not at all harmful. And we asked this question to make sure that the claim does not mislead users or nonusers about the general harmfulness of the product. And our data show that it does not. After seeing the claim, 89 to 99% of participants associated some level of harm, either moderately or very harmful, with using this product. Furthermore, the claim did not increase the perception that Copenhagen Snuff is not at all harmful in any subgroup.

Additionally, we asked participants, on a zero

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

percent/extremely unlikely to a hundred percent/extremely likely scale how likely is it that these things will happen to a person who only uses Copenhagen Snuff daily, and participants selected a response for each of the negative outcomes listed here. Looking at the responses, both before and after exposure to the claim, we see no differences.

For example, let's focus on mouth cancer. The average among adult smokers planning to quit, before exposure to the claim, is 76 as represented in the dark blue bar compared to the light blue bar directly below it, which shows an average of 77 after seeing the claim.

Note that the claim did not have an impact on any of the responses shown here. This suggests that participants still associate risk with the use of Copenhagen Snuff for mouth cancer, heart disease and heart attack, nicotine addiction, and discolored teeth or decay even after viewing the claim.

Now, to tie this back to our claim which states a reduced risk for lung cancer when switching completely from cigarettes to Copenhagen Snuff. The goal of this claim is to provide consumers accurate information about the relative risks of lung cancer.

We evaluated participants' relative perception of risk of

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

lung cancer by asking them to rate the likelihood of lung cancer for both cigarettes and Copenhagen Snuff before and after seeing the advertisement. We used the same zero percent to a hundred percent scale I showed previously.

This chart shows the percent of individuals rating Copenhagen Snuff as either higher risk of lung cancer compared to cigarettes, and that's shown in the gray bars; the percent stating equal risk, which is the white bars; and the percent stating less risk shown in the blue bars.

Let's focus on the gray bars, which represent the misperceptions of lung cancer risk, and that is the belief that there is higher risk of lung cancer with Copenhagen Snuff compared to cigarettes. I'll discuss adult smokers not planning to quit, which is an audience of interest for this claim and in this subgroup, we observed that there is a four percentage point decrease in the misperception after viewing the claim.

Now still looking at the subgroup, but focusing on the blue bars, which reflects the message of the claim, that is the belief of less risk for lung cancer, we observed that there is a two percentage point increase in this accurate perception after viewing the claim. This suggests that the claim is

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

helping to correct the misperceptions of lung cancer risk in adult smokers not planning to quit.

So how do we interpret these findings? The bottom line is the results aren't altogether surprising. We developed the claim to be clear and expected that participants would understand it and they did understand it, and we saw no indication that it was misleading.

Finally, we observed that the claim shows potential to help correct misperceptions of lung cancer risk in adult smokers not planning to quit.

Still, while participants clearly understood the language of the claim, their preexisting misperceptions about the relative risks of smokeless tobacco products and cigarettes were apparent. It is evident that the beliefs don't match the science and that perceived lung cancer risk far exceeds actual lung cancer risk. The claim is the first step to correct these misperceptions.

Now I'd like to turn to the assessment of behavioral intentions. Similar to the assessment of risk perceptions, we wanted to isolate the affect of the claim on behavioral intentions. Let me show you the study design slide again to recall how we collected the data.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

We determined the behavioral intentions before and after showing the advertisement with the modified risk claim in the test condition, and the advertisement without the modified risk claim in the control condition for all the different subgroups.

The CCI study assessed behavioral intentions using validated scales. We assessed behavioral intentions of try, use, dual use, and switch.

To assess the impact of the claim on cessation, we included a measure from published literature on quitting smoking and quitting all tobacco, and we also included a measure of purchase intent.

Here's an example of one of the behavioral intention measures. This is the intention to use measure which includes four items that are rated on a scale from one/strongly disagree to six/strongly agree. From these four items a composite score is calculated and then compared between test and control.

The CCI study showed that the proposed modified risk claim did not significantly affect behavioral intentions with the exception of a statistically significant difference in intentions to use among adult smokers not planning to quit. That said, we note that the effect size is small. The CCI study did not find any other statistically significant

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

differences in behavioral intentions between the test and the control conditions.

We recognize that intentions alone might not reflect an accurate assessment of real-world likely behavior. Despite their best efforts, it's difficult for the respondents to predict future behavior with certainty. For that reason, we established a likelihood of future behavior measure and this measure is based on a combination of positive behavioral intentions and purchase intent, and we included purchase intent for a reason. The literature shows that incorporating a demand measure like willingness to spend money to purchase Copenhagen Snuff right now leads to a stronger assessment of likely future behavior.

Here, the likelihood of behavior metric was based on a composite score of greater than 3.5 and the response of yes to the question regarding intent to purchase Copenhagen Snuff right now. We used this combination of positive behavioral intent and purchase intention to identify participants likely to try, use, dual use, and switch to Copenhagen Snuff for both adult tobacco users and nonusers in the various subgroups.

We recognize that the following analyses are not as robust as the primary analyses on intention measures, yet the trends

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

are still indicative of a potential positive benefit to the population. We used this likelihood of behavior metric to compute a relative impact factor based on the pre/post change between test to control that is analogous to an odds ratio.

Let's first look at the impact factor of the claim on cigarette smokers' likelihood of switching to Copenhagen Snuff. In the CCI study we found that the impact factor was 1.21; that is, for cigarette smokers exposed to the claim, they are 1.21 times more likely to switch to Copenhagen Snuff than those exposed to the ad without the claim. In addition, we observed that cigarette smokers were 1.16 times more likely to transition to dual use and dual users were slightly more likely to transition to exclusive use of Copenhagen Snuff.

The claim did not change former smokeless tobacco users' likelihood to relapse with Copenhagen Snuff. We found no difference between the test and control, which leads to an impact of one. Finally, we found that never tobacco users were less likely to initiate after exposure to the claim.

In summary, our findings suggest that even after exposure to the claim, consumers understand that using Copenhagen Snuff poses risks to health and are not misled.

In addition, our results demonstrate a favorable response

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

for adult smokers not planning to quit in both the perceptions of risk for lung cancer and in intentions to use.

Taken together, these result trends -- these results trend towards a positive impact of the claim. It will take time and repeated reinforcement of this message to motivate adult smokers to switch completely to Copenhagen Snuff. With more than half of adult smokers open to using a tobacco product they believe is lower risk, our claim advertisement can help correct inaccurate beliefs about the lung cancer risk of Copenhagen Snuff and provide adult smokers a reason to switch completely to this product.

Now I'll pass the microphone to my colleague, Ryan Black.

DR. BLACK: Thank you, Stephanie.

I'll be speaking about the potential impact of authorizing the proposed claim on the health of the population as a whole and we'll discuss the following topics: gateway, youth use, population modeling, and our approach for postmarket surveillance. I'll start with the gateway effect.

This term refers to behavioral concern involving both initiation and subsequent transition to a more harmful product. Specifically, a nonuser initiates use with a less hazardous tobacco product like Copenhagen Snuff and later switches to a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

more harmful tobacco product like cigarettes.

To begin to understand this potential effect, we looked at the impact of reduced risk messaging on initiation among never tobacco users in our study. In our CCI study, the vast majority of adult never users showed no interest in using Copenhagen Snuff either before or after viewing the proposed claim. And when we looked specifically at never users who are legal age to 24, we again saw the vast majority showed no interest in using Copenhagen Snuff. Simply put, the claim did not encourage adult never users to start using this product in the first place.

Our data do not suggest that marketing Copenhagen Snuff with a claim is likely to increase initiation among never users, the first step necessary to generate a gateway effect.

The second step is a potential for Copenhagen Snuff users to subsequently move to cigarette smoking. The language of the proposed claim should, if anything, discourage this transition. We don't want anyone to switch to more harmful products. The purpose of our claim is to transition adult smokers away from cigarettes, not to them. That's why our postmarket surveillance program will monitor initiation and subsequent transitions.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Next, I'll address another concern: youth tobacco use. We do not want youth to use any tobacco product and we certainly do not want the claim to influence youth to use Copenhagen Snuff or any other tobacco product. In the claim testing we conducted, we did not include those under legal purchase age. We do not include youth in our research studies and we did not do so here. Instead, we relied on government data and published literature. Based on our view, we believe the claim is unlikely to change youth smokeless tobacco use beyond currently observed rates. The overall prevalence of smokeless tobacco use among youth has been low and relatively stable to declining in recent years. Data from the National Survey on Drug Use and Health illustrate this point.

This figure tracks the percentages of different age groups who used smokeless tobacco within the past month from 2002 through 2017. The line at the bottom shows that smokeless tobacco use among 12- to 17-year-olds peaked at 2.5% in 2007. Since that time it has slowly declined. Other national surveys show similar trends.

Also, use of Copenhagen Snuff by youth is very low. Based on our analyses of PATH data, only 0.02% of all 12- to 17-year-olds report using Copenhagen Snuff. The literature shows that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

a wide range of factors have been associated with smokeless tobacco use among youth, including risk perceptions. This raises a concern that lower risk perceptions may influence smokeless tobacco initiation.

That said, a recent experimental study directly evaluated the impact of modified risk messaging on risk perceptions and susceptibility to use among youth. Specifically, Dr. El-Toukhy and colleagues found no difference in susceptibility to use among youth exposed to lower-risk messaging compared to those exposed to same-risk messaging.

These results would suggest that the claim is unlikely to impact youth initiation of use. We plan to monitor youth initiation in postmarket surveillance using national surveys and published research.

Now I'd like to talk about our population model which we use to demonstrate a benefit to the population as a whole taking into account users and nonusers of the product.

Population models predict outcomes within a population under changing conditions. Models rely, in part, on empirical data. They also rely on assumptions informed to the extent possible by science and evidence. Population models can shed light on expected trends but they are estimates, at best. They

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

are not intended to predict future outcomes with numerical precision. We developed and validated a cohort model to evaluate the impact of the authorized claim on the health of the population. We built this model using best modeling practices which are described by the Institute of Medicine, ISPOR, the leading professional society of health economics and outcomes research, and the Society for Medical Decision Making.

Broadly speaking, two factors predict the claim's impact on population health: first, the reduced risk of exclusively using smokeless tobacco compared to smoking; second, the change in consumer behavior with the introduction of the claim. Our model pulls these together to predict the impact on the population.

We used a time-staggered multiple cohort population model to estimate the net benefit of preventing premature deaths within the U.S. male population. We focused on males because the vast majority of smokeless tobacco consumers are male. We used census data and published literature to define the U.S. male population and to inform the tobacco use patterns used in our model. We used our linked mortality analyses to estimate the risk of exclusive smokeless tobacco use.

We compared two scenarios to estimate the net benefit.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

The first scenario represents the world as is today. Changes in consumer behavior, what I'll refer to as transitions, are a key component of our model. The model included many potential transitions among various states including never tobacco use, cigarette smoking, smokeless tobacco use, and dual use. These are shown by the arrows in the diagram.

A rate is associated with each of these transitions. We used reliable published sources including a systematic literature review from Tam and colleagues to inform both the transitions and transition rates for the world as is today scenario.

The second scenario represents a hypothetical future world in which FDA has authorized our claim. For the hypothetical future scenario, we modified several key transitions such as initiation, switching, and dual use based on the relative percent difference from the likelihood of behavior measures from the CCI study that Stephanie presented. The modified transitions are represented by the arrows in blue.

These are the five transitions highlighted with the blue arrows on the previous slide. In this table, ST represents exclusive smokeless tobacco use. The second column shows the base case transition rates from the published literature. The

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

base case rates were adjusted using the findings from the CCI study to determine the modified case transitions. While the findings from the CCI study were not statistically significant, nearly all findings were trending in a favorable direction to a public health benefit. The modified case transitions are shown in the far right column and were used in the future world scenario.

As an illustration, the first row shows current smokers switching to exclusive smokeless tobacco use. The transition rate in the base case was 1.4%. While not statistically significant, we observed a 21% increase in switching likelihood among male cigarette smokers in our CCI study. This 21% increase translates to a 1.7% rate for the modified case.

We included two additional transitions which others, including some FDA researchers, have incorporated in similar population models. The first transition, in the dotted blue line, includes never tobacco users who would have otherwise smoked cigarettes but instead use smokeless tobacco. Similar to other models, this transition produced a population benefit. While the claim is not directed to never tobacco users, we included this transition in our analysis for consistency with other population models.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

The second transition includes cigarette smokers who would've otherwise quit but instead use smokeless tobacco. Similar to other models, this transition was not beneficial.

The difference in mortality between these two scenarios represents the net benefit. We observed a net benefit of approximately 93,000 premature deaths prevented over the 60 years following authorization of our claim. As we all know, models are driven by inputs. As I've shown today, taking into account all of the inputs, we did not see anything that would outweigh the benefit of authorizing the claim.

We confirmed the robustness of our findings through numerous sensitivity analyses. This chart illustrates one of them. The white dot represents the population benefit or specifically, the premature deaths prevented following authorization of the claim. In this sensitivity analysis, we varied two key transition rates over a wide range. The first, along the horizontal x-axis, is never tobacco users who initiate with smokeless tobacco. Increasing the transition rate for initiation would negatively impact population health. The second, along the y-axis, is cigarette smokers who completely switch to smokeless tobacco. Increasing the transition rate for switching would benefit population health.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

The label BC represents the base case, which is the world as is today scenario. We varied the transition -- the initiation rate from negative 40% to positive 100% and we varied the switching rate by plus or minus 40%. As shown by the orange area labeled risk, these rates would have to move to relatively extreme levels to outweigh the net benefit.

Finally, our plans for postmarket surveillance. We plan to conduct appropriate postmarket studies such as cross-sectional and cohort studies to evaluate the impact of the proposed modified risk claim on product use and perceptions. We will consult with FDA on the design of these studies. We will use data from these studies to keep our population model robust and current.

We also plan to use information from internal and external sources to prepare adverse event reports. These reports will capture adverse events associated with the use of, or exposure to, Copenhagen Snuff. We will periodically provide these reports to FDA.

We will also perform comprehensive literature reviews to gather information on health effects, risk perceptions, patterns of use, and misuse of Copenhagen Snuff.

Finally, we will monitor and analyze data collected in
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

national surveys, specifically, we will monitor changes in tobacco consumption, risk perceptions, and self-reported health measures over time and share findings with the FDA.

Thank you for your attention. I'll hand it off to Joe.

MR. MURILLO: So just a few final remarks from me as we bring our presentation to a close. Our application provides a lot of scientific evidence about this product, enough we believe to merit authorization. Today we've demonstrated that the proposed claim is truthful, accurate, and substantiated by the scientific evidence.

Copenhagen Snuff is significantly less harmful than cigarettes. Switching completely from cigarettes to Copenhagen Snuff reduces the risk of lung cancer. Tobacco users and nonusers understood that Copenhagen Snuff is not risk free and we demonstrated benefit to the population as a whole taking into account users and nonusers with authorization of this claim.

Earlier today I described the dilemma and the opportunity presented by Copenhagen Snuff. The evidence presented today has brought the contours of this situation into even sharper relief.

Some 2.3 million adult smokers -- and I'm sorry, some 23

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

million adult smokers, over half of all the adult smokers in the U.S., are looking for a reduced risk alternative to cigarettes. More than two million adult smokers who already use smokeless tobacco are a logical audience as well.

Yet, despite overwhelming scientific evidence to the contrary, a vast majority of them still believe that smokeless tobacco is at least as hazardous as cigarettes if not more so. With this claim and supporting campaign, we can begin to correct this staggering misperception.

We hope that the Committee will support FDA authorization of our application and we respectfully urge you to do so. Thank you so much for your attention and consideration and we stand ready to assist your deliberations and look forward to your questions. Thanks.

DR. MERMELSTEIN: Thank you for your time and presentations. We have some time left in your allocated time, so why don't we do just clarifying questions, not discussion but clarifying questions now, if there are any, to the Applicant while it's fresh in people's minds.

MS. HERNDON: A simple clarifying question of the report that you gave in terms of the differences in -- on cancer mortality, all-cause mortality, and all-cancer mortality, was

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the age endpoint the same in all those studies? And remind me, if so, what it was.

MR. MURILLO: Gary, would you mind taking that, please?

MR. HARVEY: The age endpoint did vary between the different studies. Can we see Slide Number one, please?

(Pause.)

MR. HARVEY: So in our analyses of the NHIS and the NLMS data, we are combining the representative samples of the U.S. population and then the smokeless tobacco users. The follow-up time varies from 5 years and then we did a sensitivity analysis looking at 6, 10 and a full follow-up period which would include more than 20 years of follow-up time. Various follow-up time in the orange bars. So we're looking at the adults, smokeless tobacco user population, various ages, typically 40, 50, 60 is what's influencing this analysis.

DR. MERMELSTEIN: Dr. O'Connor.

DR. O'CONNOR: Clarifying on the -- from population modeling with -- so you gave a figure of 93,000 deaths averted. Is that per year or is that over the modeling window?

MR. MURILLO: Over the window.

DR. O'CONNOR: And how long was the window?

MR. MURILLO: Sixty years.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. O'CONNOR: Sixty years. Thank you.

DR. WEITZMAN: So the slide that was just up and the related slides, that looked at smokeless tobacco use, not specifically at Copenhagen; is that correct?

MR. MURILLO: That's correct. But Copenhagen is well represented, as Dr. Sarkar described, about 40% market share during the relevant time period.

DR. WEITZMAN: Thank you.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Thank you for a systematic and thorough presentation.

MR. MURILLO: Thank you.

DR. OSSIP: If you could look at CC-49 and these are your sensitivity analyses, I think, for -- is it all-cause mortality risk? But they apply, I think, to all of your analyses. I guess, first, just as a lead-in to that, remind me, how was current smokeless tobacco use defined?

MR. MURILLO: Gary, why don't you take these, as well? I think it will be more efficient.

MR. HARVEY: So within the surveys they asked if they used chew or snuff, so current smokeless tobacco use is defined as currently using chew or snuff. We also looked at a sensitivity

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

analysis looking only at snuff, excluding the chew users, also.

DR. OSSIP: And the questions were generally currently using?

MR. HARVEY: Yes, the ones --

DR. OSSIP: Okay.

MR. HARVEY: Everything you saw from our analyses looked at people currently using smokeless tobacco.

DR. OSSIP: Okay. And I wondered if you had looked at the data at all by -- and you may not have had this by amount of use or by length of time using in that, if you had, you know, populations who were using occasionally or had just started using, you might have a different time course for all mortality and that the patterns of smokeless use may vary from the patterns of cigarette use.

MR. HARVEY: Sure. In the surveys that we used, they did not distinguish how much they're using on a daily basis, but we did analyze the use of smokeless tobacco in terms of initiation and so the vast majority of people who are current users of smokeless tobacco initiated before their early twenties. So when we're looking at people, say 60, then on average we're looking at more than 40 years of smokeless tobacco use among the current smokeless users.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. MERMELSTEIN: Okay, Dr. Duffy.

DR. DUFFY: Did you have a follow-up to her question or any -- I'm looking at CC-77, it's on page 39 in the book. And it's the chart that looks at the pre/post on exposure to the message and the second group, the ASNP, the not planning to quit group, are you saying that after exposure you got only a 2% change? That's not --

MR. MURILLO: So we got -- yes, we got a 2% change on -- in terms of the Copenhagen is less risky as to lung cancer pre and post.

DR. DUFFY: So that's not much of a change, just eight people converted?

MR. MURILLO: I don't have the mathematics --

(Crosstalk.)

DR. DUFFY: I figured it out roughly, but --

MR. MURILLO: Yeah. That's the change.

DR. DUFFY: It's not much, really.

MR. MURILLO: That's correct.

DR. DUFFY: Not many people got it.

MR. MURILLO: Well, not many people changed the risk and --

DR. DUFFY: Their risk perception.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

MR. MURILLO: Correct. What Dr. Plunkett was pointing out is that the 16 to 12% is also encouraging because we start to start seeing some movement which also she described is not surprising given the decades of misperception that is embedded in their preload.

DR. DUFFY: Right. And then the next group is the dual users, which is the group that you think you might want to convert, right?

MR. MURILLO: Yes.

DR. DUFFY: Because they're already using it and they're actually going the opposite direction.

MR. MURILLO: Yes, that's what that shows.

DR. DUFFY: So they didn't get it at all. I'm just trying to clarify that I'm reading this correctly.

MR. MURILLO: It's not that they didn't understand the claim, it's that it did not move them as to their view of lung cancer. I think, as Dr. Plunkett described, people understood the claim fairly well. The question is, is it changing their deep seated misunderstanding of the lung cancer relative risk and those are the results as to that point.

DR. DUFFY: Okay.

DR. MERMELSTEIN: Dr. Warner has a quick follow-up to that
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

question.

DR. WARNER: You may think it's going to be quick.

(Laughter.)

DR. WARNER: But it is a direct follow-up on the question and I will apologize to you, I think I will speak facing this way so I can look.

MR. MURILLO: No problem. I'd love to hear you.

DR. WARNER: I had the exact same reaction that Dr. Duffy is having and I'm sure most of us did. One of the things that struck me, and I'll mention the couple of following slides in addition to that one, is that there's no indication of 95% confidence intervals or any measures of statistical significance.

DR. DUFFY: Right.

DR. WARNER: So on this one, my reading is that there was basically no effect, you can tell me if I'm wrong. If you then go to Slide 83 on page 42, we're told there's a significant difference in intention to use among adult smokers not planning to quit, but maybe I missed it, was there data that was not given for that? So that's a second question.

And then the final one, in the same context, is Slide 86 on page 43, once again, no indication of statistical

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

significance. If I'm reading this correctly and if we were to think that there is statistical significance here, it appears that the biggest impact in relative terms would be cigarette smokers transitioning to dual use and then you get a small incremental impact on that of cigarette smokers switching to Copenhagen Snuff, but again there's no indication of statistical significance. So when I was reading this material at home and now hearing the presentation, I still hear no evidence that anything happened in terms of behavioral intentions.

MR. MURILLO: Well, there's a difference between statistical significance and no evidence that anything happened. I'm not going to debate you. I was about to call Stephanie to go deeper, but there is no statistical significance in the finding except as described with respect to another finding.

The point here is that we saw some measures, particularly with respect to the adult smokers not planning to quit, which is a fairly important audience, that seemed to be trending in the right direction. But there is no statistical significance here.

DR. WARNER: Because when I look at the data on -- from
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

studies like this, I look for two things. One, obviously, is statistical significance and another is size. So sometimes you just don't have a large enough sample to get a good statistical significance but you got a big difference in terms of relative risk or what have you. I'm not seeing either of those here and I'm just trying to understand how one can make a lot of sense out of this, then going to your model, and I do population modeling, I understand that stuff, and I know how that can be manipulated. I'm not suggesting you've done that here, I just understand it. I'm wanting to be persuaded that there is some real meat to this, and I guess I just don't see it yet.

MR. MURILLO: So let me show you -- Slide 3 up, please. So here we see, as I think was pointed out, this idea of ASNPQ, the adult smokers not planning to quit, showing an increase in intentions and all likelihood metrics, try, use, dual, and switch. Again, not saying it's significant, it's saying it's something.

Then we go to 25, CM-25, if I could have that, that's Slide 1 up. Oh, there it is. Where we see a small but statistically significant increase in intention to use, right? And then most other intention measures are trending in the right direction, which is 118, if I could have Slide 3 up. So

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

that's what we see here with -- that's what we mean about the converging trend with respect to adult smokers not planning to quit.

Now, as Stephanie pointed out, what we have here is a situation where we have decades of misperception that is ingrained in people and they come to this -- they come to this with great skepticism and whether it's the theory of planned behavior or one of the other theories, I don't think it is at all surprising that in a controlled study with limited exposure to this thing we're going to be able to move the needle.

We have 90% of smokers assuming that this thing is as harmful or more harmful. It's not going to be that easy to move this needle and yet, we have to take some step in the right direction. The longer we wait to tell them the truth about this, the more we're going to let it go. And I'm not going to debate with you that we have statistical significance where we don't, right, we will concede that. We see some trending in a useful direction which we used for the modeling, but we have to take a first step.

DR. WACKOWSKI: I had a comment and a question. I, too, was surprised to not see any difference, really, in the risk perception for lung cancer, especially from the previous

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

application, we did see a difference there for long-risk perception. And then I wondered if potentially one of the reasons for that in this case is because of the pretest/post-test design rather than just a post-test only design, I think, because as I understood it, you asked them all these risk perception questions, intentions questions, showed them the ad for about a minute and then asked them the same questions again in a very close time proximity. And so just that kind of setup could sort of predispose people to stay consistent with their original answers, so that could be one reason.

My other question was about the rationale for proposing this claim for the Fine Cut, specifically, and not for the other Copenhagen styles or the category or the Copenhagen brand more broadly, especially since my understanding is that the Fine Cut style is a bit more challenging to use for a new user and for a smoker and that the pouch style is something that I think has been marketed to smokers in the past more specifically, so if anybody could clarify about that.

MR. MURILLO: Right, so there's a couple of questions there. Let me start from the back end and deal with the Fine Cut. And Stephanie, I'm going to ask you to comment on the design and so if you could get ready for that. Copenhagen

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Snuff is the fourth most popular MST product in the United States and as we demonstrated in terms of the relevance of the epi, it is really the overwhelming popular choice during the time period that is relevant in the epi, in fact, for many, many years it was the only style of Copenhagen that was sold. So we wanted to pick an SKU, a product, a sub-product that is well represented in the epidemiology.

The second thing I would say, and if I could have Slide 1 up, please, Copenhagen Snuff is highly relevant to adult smokers. There is about 460,000 Copenhagen Snuff uses, this is all according to PATH data, 380,000 are exclusive users. Of those, 140,000 are adult smokers, 80,000 are dual users. So it is a product that has shown the possibility, as demonstrated in these data, of converting smokers to that product.

Finally, I would say, while Stephanie is coming up to discuss the study design, that the MRTPA process is product by product. For this particular product, we picked a product that was well represented in the epidemiology which anchors our submission for other products, we might bridge to it, we might pick other things to focus on, but we think this product, with this claim, based on its proven track record of ability to convert and it's representation in the epidemiology was a good

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

choice. So I'll ask Stephanie to comment on the study design for a second.

DR. PLUNKETT: One of the reasons for the pre/post design is we knew that individuals would be coming into the study with preexisting beliefs and the challenge of balancing those beliefs between the test and control, and we wanted to really isolate the effect of the claim and look at those test and control differences.

And just to give an example, some of these preexisting beliefs that came in, if I could have Slide 2, please. We looked at individuals' believability in the ad and what you see in the red boxes here, what's surrounded, is that we had a large majority of participants who did not believe in the ad, they either said strongly disagree or disagree, those individuals were -- believed that lung cancer risk was a hundred percent likely on that zero to hundred percent scale. So we saw that individuals were coming in with these really heavy preloads that we were confronted with, which is why we chose that design.

DR. MERMELSTEIN: Dr. O'Connor, you had --

(Off microphone comment.)

DR. MERMELSTEIN: Okay, so Dr. Thrasher.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. THRASHER: A follow-up on that. So can you help me understand why you didn't do, like, a randomized design and what would the advantages of doing this quasi-experimental design that basically forced you to do this pretest evaluation to ensure that groups were equivalent, as well, I assume.

DR. PLUNKETT: Yes, it's one was of a logistical nature. So in order to get participants in that fulfilled, the sample size that we needed for current users, nonusers, and former users, we had a 3-month enrollment period. And so when individuals -- so for the most part, people were randomized but once the quota was filled, then we had to move on to the other cells, so it led to just a few individuals that would not have been randomized, but for the majority of the population, they were randomized.

DR. THRASHER: Just as a follow-up, then. So the groups were comparable in the end on important characteristics and aside from the sociodemographics that you used to kind of create the quotas?

DR. PLUNKETT: Some of the pre-measures you could see were different. If we could get a slide to show maybe an example of that. And we ended up using pre as a covariate in some of our analyses. Let me see if I can show you an example of --

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

(Off microphone comment.)

DR. PLUNKETT: Just looking for some pre measures that -- which show the difference between the test and control coming in. Perhaps if we can't get that at the ready now, I could show you later, but it wasn't exactly equal except for what we matched on.

DR. MERMELSTEIN: Just two more and then we're going to take a break. We will have time for additional questions afterward.

Dr. Bierut.

DR. BIERUT: So I'm looking at Slide CC-52 on all-cancer mortality, and I know that the claim that you're looking at is very specifically on lung cancer, but do you think that this product causes oral cancer? And the reason I'm asking is because you show nothing here with your all-cause mortality.

MR. MURILLO: Let me ask Gary to come and comment on the oral cancer analysis within this, which we did do. Let me ask -- answer your question directly. Clearly, Copenhagen Snuff is not risk free.

DR. BIERUT: Um-hum.

MR. MURILLO: And there is a Surgeon General's warning on that topic and we believe the public needs to be guided by

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

those messages. I will refer to Gary because we did do a review of oral cancer specifically.

MR. HARVEY: So you are correct, on the CC-52 chart we're looking at all cancers. Oral cancer is included in that analysis on all the bars you see here. In our NLMS analysis there were no oral cancer deaths among the smokeless tobacco users, as a group, so 3,500 of them as compared to, say, lung cancer where there were a lot more deaths.

In the NHIS analysis we did look, but we had to go look at the restricted data for that and there were less than five, I think there were two or three oral cancer deaths, so we can't publish that particular analysis because it's less than what's required.

We did put together a literature review. If you could show Slide 2, please. So here's an analysis of the literature showing the estimated usually relative risks or odds ratios for oral cancer and comparing it to various current smoker oral cancer risk on the right. And so in some cases the risks are elevated, in some cases they're not. In all cases they are less than the current smokers' risks for oral cancer.

DR. BIERUT: So I just want to make a comment that this brings up the important point of what's -- you need to know

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

about the risk and the prevalence --

MR. HARVEY: Um-hum.

DR. BIERUT: -- to really make a judgment here and so it sounds like since the prevalence was so low you were not seeing enough of this.

MR. HARVEY: That's correct. And so going back to the chart we had up just a moment ago. When including oral cancer, it just isn't moving the needle here because it's relatively infrequent among the smokeless tobacco users and this is what you see. So the oral cancers are in the current smokers, on the right, smokeless on the left. There's still a large difference.

DR. MERMELSTEIN: Dr. King, did you have one last clarifying -- we'll have time later as well.

DR. KING: Yeah, just quickly. So I have a commendation, a quick question and a comment. So the commendation, I thought this was a nice presentation. Frequently I attend these meetings and I wonder is there anyone alive out there listening to the comments from the Committee and the people who come after and improve upon that. And so there was a lot of points that you addressed in your presentation I think have been raised previously, including the issue of youth and the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

framing, you know, specifically around certain outcomes such as lung cancer and elsewhere and so I thought, you know, it was noticed.

MR. MURILLO: Thank you.

DR. KING: In terms of the question, could you tell me the level of NNN in your product? Micrograms per gram of tobacco is just fine.

MR. MURILLO: Okay. Tim? I'll ask Dr. Danielson, one of our product chemists, to come up and answer that.

DR. DANIELSON: Good afternoon. I'm Tim Danielson, Senior Principal Scientist with Altria Client Services. In regards to NNN, correct?

DR. KING: Yeah.

DR. DANIELSON: If you can please pull up Slide 2. The levels of NNN in Copenhagen Snuff are approximately 1700 and that is the data we provided in our application, and you can see that that level is well within the marketplace range that was conducted in 2014 and 2015. And you can see, as well, partially those Copenhagen Snuff values that were collected during that time frame, are still well within that range.

DR. KING: So a follow-up to that. So the FDA has publicly announced that they intend to potentially implement a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

standard to reduce the level of NNN in products, which I believe is about 1.0, and according to your application it looks like your product exceeded that. And so I'm just wondering is what are your plans, if the product is no longer going to be allowed to be on the marketplace, what's the intent of submitting this application?

MR. MURILLO: So FDA has proposed a standard and that is an open matter with the FDA. They have the authority to propose any number of standards. We have the ability to comment on that, we commented extensively including as to what the impact on the marketplace could be if such a standard were adopted.

Our views as to whether that, as a standard, is appropriate for the protection of public health and also some technical issues with respect to what the process would be to come into compliance with such a standard. So such a standard is not in place today. If it were in place at some point in the future, we would deal with it then.

DR. KING: But your product currently exceeds the potential standard that --

(Crosstalk.)

MR. MURILLO: I think every -- pretty much every product
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

on the market exceeds the standard that was proposed in that rulemaking.

DR. KING: Yes. Yes, okay. And you're the first applying that we address. And then, finally, just a comment. I really would encourage you to be mindful of the data sources you use among youth. Your population-based modeling didn't appear to account for youth, but you're using household-based surveys and there's generally broad consensus in the scientific community that household-based surveys underestimate youth use of the products and that goes for smokeless as well.

So you're looking at PATH and you're looking at NISDUH, which are not school-based surveys and so your estimates of 1.4% smokeless use are considerable underestimates. And so NYTS, the National Youth Tobacco Survey, as well as Monitoring the Future, show higher rates, about fourfold higher. And so as you do, you know, postmarket surveillance or other work, I'd really encourage you to look at the more robust and defensible evidence-based sources for youth and right now that's school-based, because when a kid is sitting in their living room with their parent in the next room, they're highly unlikely to actually report an illicit behavior, whereas when they're in school and using, you know, surveys to answer we generally see

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

markedly higher rates. And so for NYTS it's actually 5% and contrary to what's asserted, it's actually not going down. It stayed the same since about 2013-14 where we've seen no change.

So moving forward in terms of your youth estimates, I'd really encourage you to use the evidence-based measures that we know are most robust and right now, most of the surveys you're using are traditionally underestimating use among kids.

MR. MURILLO: So thank you for that. If I may just comment on two specific points. One is we do show it, we do have it available from NYTS, that would be Slide 3 up, please, and I'll take your point but note that it would appear that the trend is going in a better direction. I would prefer to see no use, frankly. And then if you look at Slide 2 up, please, we did look at it from the perspective of YRBS and Monitoring the Future. We take your point completely. We chose to focus on PATH in part because it does get down to the brand level and we wanted to see whether there was any Copenhagen Snuff in there and in fact, we learned, as you saw in the slide, that there was next to no youth reported use of Copenhagen Snuff in that particular survey.

DR. KING: Great. So in the past 5 years there's been no change and just to confirm, your population modeling did not

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

include youth, correct?

MR. MURILLO: It did include youth.

DR. KING: And you used what survey?

MR. MURILLO: That's a Moore (ph.) study.

DR. KING: And what's the source?

MR. MURILLO: I'm going to confirm and get back to you after the break, if that's --

DR. MERMELSTEIN: We'll have time for more questions later.

DR. KING: Okay, thank you.

MR. MURILLO: Yes.

DR. MERMELSTEIN: Thank you for, really, a complete presentation. We're going to take a 15-minute break now. We'll come back and we will have time for more questions later this afternoon. Thank you. So we'll be back at 3:10.

(Off the record at 2:55 p.m.)

(On the record at 3:10 p.m.)

DR. MERMELSTEIN: Okay, we're going to start up again and we're going to start with Dr. Apelberg's presentation, and then we will have an opportunity for more questions.

DR. APELBERG: Okay. Hello, again. Good afternoon, I'm Dr. Benjamin Apelberg. So now I'm going to present FDA's

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

preliminary evaluation of the application, and I want to make it clear that this presentation reflects a preliminary review of the scientific evidence conducted by members of FDA's MRTPA Review Team. I'm just going to be up here presenting it for ease of presentation.

And so the MRTPA Review Team comprises scientists from multiple scientific disciplines in our Office of Science and the individuals that contributed to the scientific review and presentation of the material that I'm going to go over today are listed on this slide. So although I'm presenting on behalf of the review team, the team will be available for -- to address clarifying questions, if there are any, at the end of the presentation.

Once again, the FDA disclaimer.

Okay, so first I'm going to start by presenting levels of HPHCs in the candidate product compared to cigarettes and other smokeless tobacco products. I'll then walk through the nonclinical, clinical, and epidemiological evidence used to describe the relative health risks and to inform the assessment of the scientific accuracy of the proposed modified risk claim. Much of this, the focus of this part of the presentation will be on lung cancer, because that is the specific claim that's

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

being proposed.

So, in 2012, FDA published a list of HPHCs in tobacco and tobacco smoke, nine of which are present in smokeless tobacco and have well-established analytical methods. The Applicant reported levels of these nine HPHCs in the candidate product as well as the pH and total moisture of the product.

The Applicant didn't directly compare HPHC levels in the candidate product with a comparator cigarette. In FDA's backgrounder, to facilitate this comparison, we performed a comparative evaluation of high-end use levels of the candidate product provided by the Applicant and mainstream smoke data from U.S. domestic cigarette brands. To allow for comparison of a non-portioned product to a portioned product, we used a potential daily intake of one tin per day, or 34.02 grams, and one pack per day, or 20 cigarettes. So when comparing HPHC levels of the candidate product to those in cigarettes, we found there were relative increases in the potential daily intake of some HPHCs, including arsenic, B[a]P, cadmium, NNK, NNN, and total nicotine and relative decreases in others, including acetaldehyde and formaldehyde.

It is important to note, however, that differences in a number of factors, including portal of entry, extraction rates,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

metabolism, and toxicant absorption, can affect the toxicity of HPHCs introduced through different routes of exposure.

Therefore, it's unclear how relative differences in HPHC intake levels between Copenhagen Snuff Fine Cut and cigarette smoke will translate into differences in exposure levels and ultimately, disease risk.

We also compared HPHCs from the Applicant's MRTPA to data from the published literature on moist snuff and as a point of comparison, to general snus from Swedish Match's 2014 MRTPA, and so we wanted to look at the HPHC levels across these various categories. So HPHCs vary across smokeless tobacco products due to types of tobacco used, manufacturing and storage methods and other factors.

So what this table shows is that compared to other moist snuff tobacco products, the candidate product has, on average, 90% higher B[a]P, 46% higher cadmium, and 4% higher total nicotine. The most notable difference in HPHC levels is between the candidate product and General Snus, a brand of Swedish snus. Swedish snus has been found to have lower levels of TSNAs than moist snuff or other smokeless tobacco products.

So, in particular, the candidate product contains, on average, a difference of 165% higher cadmium, 427% higher NNN,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

349% higher NNK, and 44% higher total nicotine and higher levels of arsenic and B[a]P than General Snus.

Although not shown in the table, when compared to dry snuff and loose leaf smokeless tobacco products, HPHC levels of some constituents are higher in the candidate product, such as B[a]P, arsenic and free nicotine. It's important to note that oral intake of chemicals such as B[a]P, cadmium, NNN, and NNK can cause a number of health effects including lung and other cancers.

The Applicant submitted nonclinical, clinical, and epidemiological evidence to describe the relative health risks of Copenhagen Snuff to individuals, including the risk of lung cancer. And as you heard previously, and you will hear in some of the subsequent slides, some of the evidence submitted is specific to the candidate product but most of the evidence submitted relies on data from the product category of moist snuff or smokeless tobacco more generally. Most of the nonclinical, clinical, and epidemiological evidence submitted is from the published literature.

In addition, as you heard earlier, the Applicant conducted original analyses of federal datasets to draw inferences regarding the risk for tobacco-related diseases.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

I'll also discuss, briefly, the Applicant's short-term clinical study on abuse liability later in the presentation.

In terms of the nonclinical evidence, the Applicant didn't provide any nonclinical studies assessing the potential of the candidate product specifically to induce toxicities.

Comparison of the daily intake of HPHCs, as I mentioned, between the candidate product and other products showed an increase in some constituents such as arsenic, B[a]P, and nitrosamines, all of which have been associated with lung and other cancers in animal studies. Therefore, depending on a number of factors, there may be an increase in daily intake of potential lung carcinogens with the use of the candidate product as compared to other products. But as mentioned previously, a variety of factors may affect the net exposure levels and therefore confound the estimate of comparative lung cancer risk between the candidate product and cigarettes. Because of that, I'll turn to the clinical and the epidemiological evidence for additional information.

In terms of clinical evidence, the Applicant did assess plasma nicotine following brief exposure to the product but didn't assess any other biomarkers of exposure in Copenhagen users, specifically. However, evidence from the published

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

literature suggests that smokeless tobacco users do have higher levels of some biomarkers of exposure, but not others.

For example, exclusive users of smokeless tobacco have higher concentrations of serum cotinine and NNAL than exclusive cigarette smokers or non-tobacco users. And relative to non-tobacco users, studies have found higher concentrations, for example, in smokeless users, of plasma lead but not plasma mercury, cadmium, or urinary arsenic.

While we don't have studies on biomarkers of potential harm associated specifically with the candidate product, the Applicant did reference cross-sectional studies analyzing such data compared to cigarette smokers and non-tobacco users. Studies have found that smokers have an elevated inflammation and immune response compared to smokeless tobacco users, generally, and studies have also shown no significant differences in inflammatory response between smokeless tobacco users and nonusers.

So that summarizes the nonclinical, the HPHC nonclinical, and clinical data. Now I'll turn to the epidemiological evidence.

So this was already mentioned by the Applicant. In their application they make a case that the historical

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

epidemiological evidence is relevant in particular to the product under review and this data from the application shows in the -- that the Applicant's moist smokeless tobacco products have held a large market share over time, and that's what the green line shows, so between 68 and 83% of the U.S. Smokeless Tobacco Company's moist smokeless tobacco market share and then Copenhagen Snuff Fine Cut share is also pretty large over time as well.

The Applicant also does note that the production process for U.S. Smokeless Tobacco Company's moist smokeless tobacco products, including the product under review, was essentially unchanged over time, over the time period of these studies, except for refinements such as improved process control and reduced TSNA formation.

In terms of the published literature on smokeless tobacco and lung cancer, we aren't aware, from the published literature, of direct comparisons made between mortality risk for current smokeless tobacco users compared to current smokers. Instead, most estimates compare lung cancer mortality of smokeless tobacco use to never use and cigarette use to never use. Using these comparisons, studies have found higher lung cancer mortality risks for cigarette smokers than for

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokeless tobacco users.

So, for example, data from the Cancer Prevention Study II, which was also mentioned earlier, found lung cancer mortality is approximately 23 times higher for male current smokers and more than 12 times higher for female current smokers than never tobacco users.

This is in contrast to individual studies of smokeless tobacco which, although mixed, have tended to find slightly elevated but non-significant increases in the risk of lung cancer mortality when compared to never use. For example, two meta-analyses found non-statistically significant hazard ratios of 1.8 among U.S. smokeless tobacco users.

To our knowledge, the only published study to examine mortality risk after switching with sequential product use is Henley et al. of 2007, using data from the CPS II study. After 20 years of follow-up, they found men who switched completely from cigarettes to smokeless tobacco experienced a greater risk of dying from lung cancer than those who quit all tobacco. It didn't, however, compare risks among switchers to risks among continuing smokers.

However, if we look at results from other CPS II analyses, they have found that the relative risk for male cigarette

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokers compared to quitters is considerably greater than the relative risk for switching versus quitting in the Henley et al. study.

As was mentioned earlier, the Applicant conducted original analyses of these nationally representative linked mortality data sources, so I won't go over the methods, you have them here, and you've already seen that.

I will just point out one of the analyses conducted by the Applicant, so this looks at lung cancer mortality risk for five different tobacco user groups based on the NLMS analysis. The comparison for each group is never users, so you can see that exclusive cigarettes -- current smoking in blue and current dual use in green are associated with the highest risk of lung cancer mortality. In the NLMS it was 11.5 for both of those estimates. You can see that the dual use estimate is pretty unstable.

And then the lowest risk estimate, which is not statistically significant, was for exclusive smokeless tobacco users, that's in blue, and then those who switch from cigarettes to smokeless tobacco had a risk of lung cancer mortality in between that of exclusive smoking and exclusive smokeless tobacco use, and that was similar to that of former

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokers.

So, in general, these results are in line with the findings from published literature although, as I mentioned, wide confidence intervals reflect the relatively small number of lung cancer deaths observed in some of the tobacco use groups.

Just to round out the discussion about health risks, you know, although the risk of lung cancer associated with smokeless tobacco is lower than that of cigarettes, as was previously mentioned, smokeless tobacco is not without health risks. This slide describes the findings from a 2012 IARC monograph concluding that smokeless tobacco is a carcinogen in humans and that it causes oral cancer, esophageal cancer, and pancreatic cancer.

Epidemiological studies have found relative risks for cancers other than lung cancer are often higher in U.S. studies than Scandinavian studies, which may be due to the differences in HPHCs that are typically found, such as nitrosamines.

In addition to the increased risk of certain cancers, a meta-analysis reported an association between U.S. smokeless tobacco and fatal myocardial infarction and stroke. And while there's relatively little information on smokeless tobacco use

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

among women in the U.S., several studies in Sweden have found associations between smokeless tobacco and adverse pregnancy outcomes.

So moving on to the consumer understanding and perception, as you saw earlier, the Applicant provided sample labels and advertising with the proposed modified risk claim: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces risk of lung cancer." The sample materials provided include a range of print and digital advertisements, as well as a label for the bottom of the can. Although the Applicant stated in its application that its marketing and advertising plans have features that will reduce the risk of youth uptake, FDA does note that the Applicant's plan to display advertisements outside retail outlets and at the checkout counter may expose youth nonusers to advertisements containing modified risk information.

This slide describes the methods of the Applicant's consumer comprehension and intentions study. I won't go through it in detail because you've heard it all, already. I'll just summarize that as we heard from the Applicant, they conducted an online study of approximately 5800 U.S. adult tobacco users and nonusers to examine consumer comprehension of

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the proposed modified risk claim and the effects of the claim on risk perceptions and behavioral intentions.

And as was presented earlier, these are images of the study stimuli. So the study stimuli include an advertisement for the test condition that includes the proposed modified risk claim, while the control condition shows the same advertisement without the modified risk claim. We did want to note that the product shown in these advertisements was named Copenhagen Snuff rather than Copenhagen Snuff Fine Cut, and participants were randomized to view advertisements containing one of the four Surgeon General's warnings for smokeless tobacco.

This slide laid out some of the ways that some of the key outcomes were defined in the CCI study, so it includes claim comprehension and risk perceptions, as was previously mentioned.

So comprehension was assessed, you can see at the top, by asking participants whether, based on the information in the ad, smokers who switch completely from lung -- sorry, completely from cigarettes to Copenhagen Snuff increased, reduced, or eliminated their risk of lung cancer.

There were also risk perception measures that were assessed, basically, in two ways: specific and general. For

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

specific risk perceptions, participants were asked about the likelihood that a person who uses Copenhagen Snuff daily would get six different specific health effects. Participants were asked the same questions for daily cigarette users and they could rate their responses on an 11-point scale from 0 to 100%.

For general risk perceptions, participants were asked to rate the risk level to a person's health of using various tobacco products on a seven-point scale from "not at all risky" to "extremely risky." All risk perceptions asked participants to rate the absolute risk of products. However, relative risk was computed indirectly by comparing the general risk perception ratings of different products.

So this figure, it's very similar to a figure that was presented by the company, just with different colors, but what's shown here is the distribution of responses to the comprehension question across different user groups. And what we see is that the majority of consumers who viewed the proposed modified risk claim were able to correctly answer a multiple-choice question assessing the comprehension of its meaning, and that's what's shown in the yellow portion of the bars.

So based only on the information shown in this ad, smokers
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

who switched completely from cigarettes to Copenhagen Snuff reduce risk of lung cancer, that's what's shown in the yellow.

A relatively small proportion of consumers, approximately 6%, misinterpreted the claim to mean that switching to Copenhagen Snuff would eliminate the risk of lung cancer, that's what's shown in the red bars, the percent, just a small fraction across the groups.

The modified risk claim did not have a significant effect on absolute risk perceptions for specific diseases, including lung cancer, among consumers assigned to the test condition. So the top figure shows how participants in the test condition rated the likelihood that using Copenhagen Snuff daily would negatively impact health. As you can see, there was minimal change from pretest to post-test across all groups. So the six different groups are represented here each with a pre- and post-test percentage.

The bottom figure shows the same participants, how they rated the likelihood that using Copenhagen Snuff daily would cause lung cancer. Again, we see minimal change from pretest to post-test. So, overall, viewing the advertisement with the proposed claim did not substantially reduce risk perceptions from pretest to post-test, including both perceptions of

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

overall health risk or lung cancer risk, in particular.

The Applicant examined consumers' perceptions of risk associated with using half a can of Copenhagen Snuff daily and these perceptions were compared with consumers' perceptions of the risks associated with smoking 15 cigarettes daily, using half a can of other smokeless products daily, using nicotine replacement therapy as directed, quitting all tobacco, and never using tobacco products. For these analyses the Applicant did not provide any tests of statistical significance.

In the figure here, we show mean risk perception scores at post-test for using Copenhagen Snuff, indicated by the grey bars, as compared to smoking cigarettes, indicated by the blue bars. These bars are presented for both the test and control conditions and for all five user groups.

As you can see, consumers rated smoking 15 cigarettes daily as somewhat more risky than using half a can of Copenhagen Snuff daily. However, we don't see substantial differences by study condition, so essentially mean risk perception scores among consumers in the test condition were similar to that in the control condition.

As the Applicant mentioned earlier, the CCI study did include an oversample of young adults, with 944 young adult

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

participants, and these participants were categorized as either tobacco users or nonusers. Similar to the findings among other adult participants, a majority of young adults who viewed the proposed modified risk claim were able to correctly answer a multiple-choice question assessing comprehension of its meaning.

When looking at the effect of the modified risk claim on perceptions of risk among young adults, the modified risk claim had a significant effect on one risk perception item: risk for "negatively impacts health." In the nonuser group, viewing the proposed claim decreased perceptions of overall health risk from using Copenhagen Snuff.

While statistically significant, this finding is difficult to interpret. The decrease in mean risk score was small, 1.1 points on a 100-point scale, and the difference seen at post-test was due to both an increase in risk perceptions in the control group as well as a decrease in risk perceptions in the test group.

There were no significant differences for any of the other five specific risk perception items among young adults, including both users and nonusers.

So now I want to turn to likelihood of use and impacts to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

the population. I'll begin by presenting some findings from observational studies used to assess the characteristics and behaviors of Copenhagen -- users of Copenhagen products in the absence of modified risk claims. I'll then present findings from the Applicant's CCI study designed to assess consumer intentions to try and to use Copenhagen Snuff when presented with the proposed modified risk claim. Finally, I'll discuss briefly the population model that the Applicant presented.

Okay. The Applicant used several different observational studies to assess characteristics and use of Copenhagen products. Both the PATH Study, a large, nationally representative longitudinal study of tobacco use and health among adults and youths in the U.S., and a study called the Altria Client Services LLC Tracking Study, or the ALCS Tracking Study, an ongoing, nationally representative, mixed mode survey used to measure tobacco use prevalence among adult respondents.

In analyses completed by the Applicant, both PATH and the ALCS Tracking Study included information specific to Copenhagen. The PATH Study asked participants to identify the brand, for example, Copenhagen, and sub-brand, for example, Copenhagen Snuff. The ALCS Tracking Study asked about use of Copenhagen Fine Cut. And of course, both of these studies

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

collected information in the absence of a modified risk claim.

In addition to the observational data, the Applicant also submitted two original studies, the Altria Client Services Clinical Study and the CCI study, which we've already heard about. The ACS Clinical Study is a within-subject laboratory study that evaluated the pharmacokinetic and subjective effects of a test moist snuff tobacco product produced to the specifications of Copenhagen Original Fine Cut Snuff.

Effects of the test product were compared with those of participants' usual brand of cigarettes and Nicorette Fresh Mint nicotine gum under conditions of brief exposure. Participants were adult daily smokers who were non-daily users of moist snuff and had no recent history of nicotine gum use. They were not exposed to the modified risk claim.

The methods of the CCI study have already been described, so I won't go into them again.

So in terms of current use of smokeless tobacco and Copenhagen Snuff Fine Cut in particular, published data from Wave 1 of the PATH Study found, in general, smokeless tobacco use, excluding pouched snus, is more common among those who are male, non-Hispanic white, living in nonurban areas and aged 25 to 49. Smokeless tobacco, in this case, includes loose snus,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

moist snuff, dip, spit, and chewing tobacco. In both the ALCS and PATH Study, users who reported Copenhagen Snuff as their last or usual brand reported using moist smokeless tobacco on more days per month than the overall category of moist snuff users.

And as the Applicant mentioned, in the PATH Study, about 1.5% of youth non-light smokeless tobacco users, those are youth who reported using smokeless tobacco more than 10 times in their lifetime and last used smokeless tobacco within the past 30 days, 1.5% of them reported using Copenhagen Snuff as their last or usual brand used compared to 9.4% of adult established smokeless tobacco users age 25 and up.

However, when expanding the analysis of the PATH Study to any Copenhagen product, FDA found that that number jumps to 40.8% of 12- to 17-year-old past 30-day non-light users, so that's reporting any Copenhagen brand, not the specific Copenhagen Snuff brand.

In terms of dual use and switching, published studies have found that switching behavior from exclusive smoking to exclusive smokeless tobacco use is generally low among adults. In a systematic review published by Tam and colleagues, the proportion of users switching from exclusive smoking to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

exclusive smokeless tobacco use was about 0 to 1.4%. Analyses of national surveys have also found switching, those kind of switching behaviors, to be infrequent. When we look at dual use, we see that both the ALCS and the PATH Study found approximately 20% of Copenhagen Snuff users also reported past 30 day use of cigarettes.

Next, I'll just touch briefly on the Applicant's ACS Clinical Study. This study found that nicotine was absorbed more rapidly from usual brand cigarettes than from the test moist snuff product or Nicorette gum.

In addition, the study found differences in subjective effect measures between products. For example, participants rated the test moist snuff product as significantly less pleasant than usual brand cigarettes.

Across all subjective effects measures, ratings were generally higher for cigarettes than the test moist snuff product or Nicorette gum.

Taken together, plasma nicotine and subjective effects data from this study suggest the test moist snuff product has abuse potential that may be lower than usual brand cigarettes and similar to or higher than Nicorette gum.

Some study limitations are worth noting, including the
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

very brief duration of controlled exposure, lack of dependence measure, and the study inclusion was limited to participants who were cigarette smokers with a history of moist snuff use. Nevertheless, data from this study suggests that exclusive smokers may not be very likely to switch to exclusive use of the candidate product.

Turning our attention to measures of likelihood of use from the CCI study, as was presented earlier, the CCI study assessed intentions to try, use, dual use, and switch to Copenhagen Snuff as well as intentions to purchase the product, quit smoking, and quit all tobacco.

Intentions to dual use were assessed via a single measure that asked participants the extent to which they agreed with the statement, "I plan to use Copenhagen Snuff in addition to regular cigarettes." Consumers provided their rating of agreement with each behavioral intentions measure using a six-point scale.

I know this table is busy with a lot of numbers, but this table shows mean pre- and post-test scores for intentions to try, use, switch, and dual use Copenhagen snuff across different adult tobacco user groups in the control and the test conditions. The findings show that the modified risk claim had

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

no significant effects on behavioral intentions. The one exception to this, an increase in intentions to use among adult smokers not planning to quit, is difficult to interpret because intentions to try, dual use, and switch to Copenhagen Snuff did not differ between test and control.

This statistically significant difference seen at post-test was due to a decrease in intentions to use in the control group, as well as an increase in intentions to use in the test group.

When looking at adult nonusers of tobacco, the modified risk claim also had no effects on behavioral intentions in this group, including former users, never users, and young adult nonusers of tobacco products. Among these user groups, the Applicant's research found no statistically significant differences in intentions to try or use Copenhagen Snuff based on whether the advertisement did or did not include the proposed claim.

As mentioned in the earlier presentation, the Applicant used population health modeling to further estimate the population health benefit of the proposed modified risk claim. The model looked at the U.S. male population, given that males represent the overwhelming majority of U.S. smokeless tobacco

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

users.

Inputs for this model included excess relative risk, transition probabilities, and estimates of the effect of the proposed modified risk claim on tobacco use behavior. The estimates for the excess relative risk came from the linked mortality studies conducted by the Applicant, transition probabilities were pulled from the published literature, and the effect of the proposed claim on tobacco use behavior came from the CCI study.

It should be noted, as we noted earlier, that the Applicant used the numerical differences between CCI study conditions even though those differences were not found to be statistically significant.

The Applicant presents results in terms of the comparisons between the Base Case scenario, so existing tobacco product use, and the Master Case, which is product use with the proposed claim, which represents estimates -- what the Applicant described as the most likely estimates for each of the transitional probabilities.

Using the single cohort approach with a cohort of one million males, the Applicant estimates that there would be a difference of 1120 survivors at age 73 between the Master Case

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

scenario and the Base Case scenario.

The Applicant took the cohort results and used a time-staggered, multiple cohort approach to extend the results from the single cohort to the overall U.S. native-born male population over time and overall, it was estimated in the application that authorization of the proposed claim for Copenhagen Snuff Fine Cut would result in 7500 additional survivors in the U.S. native-born male population after a follow-up period of 60 years.

Okay. In summary, we see that despite higher levels of certain HPHCs in the candidate product compared to cigarette smoke, epidemiological evidence demonstrates that risk of lung cancer is lower among cigarette smokers who switch to exclusive use of smokeless tobacco than those who continue smoking.

We do, however, see higher levels of certain HPHCs in Copenhagen Snuff Fine Cut than some other smokeless tobacco products, particularly Swedish snus, and note that epidemiologic studies have linked smokeless tobacco to adverse health outcomes.

Although most consumers responded correctly to the claim comprehension item, there was little evidence that the claim affects perceptions of risk or intentions to use the product

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

among users or nonusers.

Clinical and epidemiological evidence further suggests that few cigarette smokers may be likely to switch completely to exclusive use of smokeless tobacco.

The computational modeling provided by the Applicant, based on their assumptions of product switching, estimated a relatively small net population health benefit over 6 decades from market authorization of the candidate product with the proposed modified risk claim.

With that, I'll end my summary of FDA's assessment, and myself and the team are available for clarifying questions.

DR. MERMELSTEIN: Great. Thank you, Dr. Apelberg.

Questions from the Committee. And we can also pick up questions from the prior session, so it's open for general clarifying questions.

Dr. Ossip.

DR. OSSIP: I'm curious why the Applicant didn't report any biomarkers of exposure or potential harm for your particular product, since it's been around for so long.

MR. MURILLO: I'm going to ask Dr. Sarkar to come up and comment on that. We looked at the literature and we focused, really, on the epidemiology, but I'll ask Mohamadi to answer

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

your question more completely.

DR. OSSIP: And I think the question would probably apply to the epidemiology, as well, specific to your product.

DR. SARKAR: So the biomarkers of exposure and the biomarkers of potential harm, we relied on the published literature which covers the category but includes Copenhagen Snuff within it. When we were looking at the different lines of evidence, we relied on epidemiology as the -- in the hierarchy of evidence, the most weight in assessing the health risk of the candidate product.

DR. MERMELSTEIN: Mr. Zeller.

MR. ZELLER: Question for the Applicant on lung cancer mortality risk among former smokers. Does the reduction that you described hold up regardless of how long somebody had smoked or are there differences in how much the reduction in risk goes down depending upon how long somebody smoked?

MR. MURILLO: Yeah. Gary, can you take that, please?

MR. HARVEY: Can we see Slide Number 2 or Number 1, please? So your question goes to the risk among the former smokers dependent on when somebody quit smoking.

And so in our analysis, we looked at this particular analysis for lung cancer, if you'd like to see it we can show

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

similar ones for all-cancer and all-cause, and what we see is no evidence of any increased risk among the former smokers who are using smokeless tobacco or perhaps a modest increased risk, but depending on the time frame in which somebody quit, there could be a big difference.

And so for the people who quit before the age of 40, there's a dramatic difference, then, and you see that in the far right bar. And so for people who quit, say, before the age of 30, you're looking at perhaps saving 10 years of lost life and so there's a big effect there. We also see a significant difference when we're looking at people who quit between the ages of 49 or 40 to 49, but as we can progress and look at quitters in their 50s or 60s or even after that, then those risks start to converge to that of current smokers. And so say if you're in your 60s and you quit, you might not see any decreased risk immediately or at least measurably with what we have in the epidemiological evidence, but we don't see any risk whatsoever that using smokeless tobacco products among the current smokers in terms of any quit time period would increase their risk over their baseline risk.

(Off microphone discussion.)

MR. HARVEY: I'd like to follow up --

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

(Off microphone comment.)

MR. HARVEY: Now, I think you had two questions, one related to the HPHCs and then the second question was what about Copenhagen Snuff with respect to the epidemiological evidence we showed. And so I'd like to pick up on that second question, if I could. Can we look at Slide Number 2, please?

And so this is the same analysis that I showed you before for all-cancer mortality risks except here we also pull out the risk related specifically to snuff, so instead of all moist smokeless tobacco, which includes chew, now we're limiting it just to snuff. And so we did that in the literature, where possible, and also in our analysis.

Now, Copenhagen makes up, I understand, about 40% of the snuff users and so that's the population. Within these surveys that we have, it doesn't specifically identify Copenhagen Snuff use, but it does identify snuff use and that's also the same that we see within the literature.

And so what we found when we look at not just moist smokeless tobacco over all, but snuff, in three examples in the published literature and in our analysis, we see that it doesn't change the estimates at all. And so we saw no elevated risk for moist smokeless tobacco for all cancer, same thing for

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

snuff, but in all cases the snuff users had a much lower risk for all cancer as compared to the current smokers.

MR. MURILLO: Thank you, Gary.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: The other mortality that we often think about is cardiac mortality related to the product. Do you have data on that?

MR. MURILLO: Yes. Gary, come on back.

MR. HARVEY: Can I see Slide Number 2, please? We did look into this. And so this is the same kind of structured slide that you've seen before with the literature and also with our analysis, and what we see is in the literature we see some elevated risk in terms of heart disease mortality risks, in most of the studies, not in the Accortt, the second one there, Accortt 2002, but for the other ones there is an elevated risk.

We also looked for that in our NHIS and NLMS analyses and you can see the results there. We see no statistically significant elevated risk. We do, in all cases, see that the current smoker risks are significantly larger than the smokeless tobacco user risks.

So it's the same broad point that we had before that if you are a population of smokers, you would benefit not only

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

from quitting, but if you're not going to quit completely, then switching to smokeless tobacco products, at least based on the published epidemiology and our analysis, which suggests a lower risk for all the causes you've seen but also for diseases of the heart.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: So with regard to the messaging and the plans for the marketing using these messages, I mean, I think it's great that the marker that starts the message focuses on smokers, and I guess one of the things that I'm curious about is the extent to which you have plans for marketing that would be more guaranteed to reach smokers than nonsmokers as, for example, Altria is proposing for inserts inside of cigarette products to promote Juul and that can help to allay some concerns about exposure to the messaging that is outside of that smoker target group. I don't see that laid out here in your plans, but could you speak to that?

MR. MURILLO: Yes, we certainly have not ruled that out. We like the idea given the nature of the message, that is -- if you could put up Slide 2, please. Given the nature of the message it's a little copy heavy and we think it's important to follow this layout based on the qualitative -- that

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Dr. Plunkett presented, it's a little much for an insert but we haven't ruled it out.

Now, we do reach smokers very directly, over 10 million of them, in our adult smoker database, so these are people who have signed up over the last decades and have been third-party age verified to verify age and have asked to receive mailings from one of the Philip Morris U.S.A. brands and what we're referring to is the ability to send this sort of communication to those folks directly, be it in snail mail or electronic mail. But we haven't ruled out doing inserts or onserts in cigarette packs for this product, which is why we also think -- I take the point that point of sale can be seen by kids and nonusers. Our point-of-sale material typically is on or at the tobacco category and we think it's important when people are looking at the tobacco category and looking at the cigarette fixtures specifically, that they have the opportunity to see this message as well.

DR. THRASHER: Just a quick follow-up on that. So have you used this consumer database in the past to promote Copenhagen without this modified risk claim?

MR. MURILLO: We have to some extent, as we also have to promote other alternative products such as e-vapor products or

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

oral tobacco derived nicotine products. Of course, the message is important.

DR. MERMELSTEIN: Dr. Ossip, did you have a question?

DR. OSSIP: Actually, I have two questions. One is how has the currently available product differed from the -- whatever formulation of the product was available at the time the epidemiologic studies were conducted that included the Copenhagen products? And then the second question -- actually, maybe I'll hold on that for now, let me just ask that first question.

MR. MURILLO: So the changes have been minimal and really focused on our attempts to lower the ongoing generation of tobacco-specific nitrosamines that we've been talking about, so we've made a number of changes to the product over time to try to lower their nitrosamines. Other than that, the product differs very, very little from the product that we're applying for.

(Crosstalk.)

DR. OSSIP: Second one, okay. If we look at CC-69, you list a comprehension question on what is the effect of switching completely to see if they understand your message and this is a perfectly fine question to do that. Do you have any

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

data on the extent to which users would understand that they have to switch completely versus dual using?

MR. MURILLO: Yeah. Stephanie, would you comment on that, please?

DR. PLUNKETT: The data we have comes for our qualitative study. In our qualitative study in Phase 1 we actually looked at 135 different combinations and part of those combinations reflected the behavior change necessary for the claim to be true and Slide 1 shows you what those different combinations were. One was to say "using this product instead of," and you see that many of the consumers still believe that they could smoke and use this product. We also said "using this product as an alternative to," and that also led to many believing that they could still smoke.

So we decided to use "switching completely" because we wanted the claim to reflect what is accurate to the scientific data and consumers understood that they could no longer smoke cigarettes.

DR. OSSIP: So sorry, what are the numbers? I'm trying to interpret those.

DR. PLUNKETT: Sure. This is the percent of individuals believing that it was -- it required a hundred percent MST

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

usage and zero cigarettes in order to get the benefit of the claim.

DR. OSSIP: So 1D is 15%, they have to have exclusive use of --

DR. PLUNKETT: That's correct. So the last bar -- so the first bar prefix at 1A is this "product instead of," 1B is "using this product as an alternative," 1C is "switching completely," and 1D is "exclusive use."

(Off microphone comment.)

DR. PLUNKETT: So in 1C you see 14 out of 20 respondents and 1D is 15 out of 20.

DR. OSSIP: So sorry, 1D is 15 out of --

DR. PLUNKETT: Twenty respondents.

DR. OSSIP: Out of 20, okay. So that's not percentage, it's absolute numbers, right? Okay.

DR. PLUNKETT: Each column represents a respondent.

DR. OSSIP: Thank you.

MR. MURILLO: Thank you, Stephanie. Don't go far.

DR. MERMELSTEIN: Sally, you had a question first?

MS. HERNDON: I was going to Dr. Thrasher's comment, so if somebody wanted to --

DR. MERMELSTEIN: Well, while we're on this slide is there
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

a specific -- okay then, Sally, go ahead with your other question.

MS. HERNDON: Can you step us through the third-party age verification process kind of step by step and also let us know if it is in place now or it is being proposed based on this application?

MR. MURILLO: It is in place and has been in place for a number of years. Over the years we've been able to improve it. So, for example, back in the early 2000s when we first established it, we literally had to collect copies of government-issued ID or view them and record them at places where we had events.

Now we're able to use systems like LexisNexis that allows us to input in the moment of collection, let's say it's an event, the information, have it third-party verified, meaning the person's identity and age is verified against a series of, in some cases, mortgage or bank or government databases after consent and then we're able to verify it. Similarly, when you first log in to one of our branded websites, you are challenged immediately and you have to go through this process.

So you enter information, you're challenged to enter information, the intent of the challenge is to identify you are

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

you and that you are of age and information is then bounced against a series of third-party databases and then you're either in or you're not in.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: Dr. Wackowski earlier raised a question about the design, the pretest/post-test design, asking changes immediately after being presented information. Is there a reason why or would it be possible to do a longer-term follow-up on those who are already participating to see if those differences held up over time?

MR. MURILLO: Why don't I ask Dr. Plunkett to address that?

DR. PLUNKETT: Let's put up the design slide one more time, Slide 1. So this slide shows that there were pre- and post-measures taken throughout the study. It was not a long-term follow-up, this was a one-time single-point time. That said, the claim was available throughout the duration of the study, so just want to clarify that.

The reason that we did include those pre measures is because we knew, from our qualitative research, that individuals brought in preexisting attitudes and beliefs about the product. We wanted to make sure that that was not

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

confounding the data in any way.

While the study was designed to be randomized, we knew that we were filling to specific quotas, so we weren't sure how many people at the end would not be randomized, therefore we wanted to make sure that we didn't have any potential confounds. So that was the nature of the pre/post design.

DR. WEITZMAN: Thank you.

MR. MURILLO: It's not clear, based on the nature of what we believe the issue is, that there's this tremendous preload, that if leaving them with the claim for 3 days or 7 days or 8 days was really going to make much of a difference. I mean, I think it's going to take a while for that to occur. If you think about Dr. Plunkett's presentation on the theory planned behavior, we're going to have to move that perception of the opposite information for a while before we're able to see, I think, market change.

DR. MERMELSTEIN: Dr. Stepanov. Irina.

DR. STEPANOV: Yeah, I wanted to get back to tobacco-specific nitrosamines. So NNK is a lung-specific carcinogen and we don't see really high levels of lung cancer among exclusive smokeless tobacco users. One of the potential reasons is that smoking also exposes people to high levels of

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

inflammatory agents and there is evidence that inflammation significantly enhances carcinogenicity of NNK.

Also thinking that while average kind of prevalence of smoking is relatively low at this point in history in the U.S. population, there are subpopulations where it can be as high as 40, 50, and 60% and these are people who are at lower income, let's say living in proximity to sources, environmental sources of exposure to inflammatory contaminants. Certain occupations, let's say miners, taconite workers who have really high levels of exposure and inflammation in the lung.

Given all that, is there a way to take a look at epidemiological data, existing data or what would switching to smokeless tobacco in this subpopulation, how that would be different in terms of eventually developing lung cancer, thinking that they continuously are exposed to still meaningful levels of NNK, if you look at biomarkers, and they are also exposed to inflammatory agents that enhance the systemic carcinogenicity of NNK.

MR. MURILLO: Yeah, I understand the question. I'm going to ask Gary to talk about some of the subpopulations that we looked at.

MR. HARVEY: As I mentioned, we did a lot of sensitivity
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

analyses looking in this sort of broad area. The first one I'd like to share with you, let's pull up Slide Number 2. So here's an analysis where we are looking exclusively at current smokers, so going to this issue that perhaps within the current smoking population the role of smokeless tobacco use might have a different role because of the reasons you've mentioned. And so what we have here is on the far left of the chart with the red bar is just the baseline risk of the current smokers and so we're looking at the three different diseases. In the blue box we see the lung cancer risks and then in the orange box we see all cancer risks and then finally, over in the purple box, the all-cause mortality risk, so overall mortality risks.

And so while we don't have the ability to go look, say, to miners or to a variety of different areas, we do look here at the current smokers and essentially trying to see is there any evidence that there's some kind of elevated risk among the smokeless tobacco users as compared to current smokers who don't use smokeless tobacco. And as we studied that, we saw -- essentially, we don't see the evidence of any kind of elevated risk there. Either for men alone or for men and women combined in either the NHIS or the NLMS data.

Just to follow on to this, can we show Slide Number 3,

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

please? Slide Number 3 is the same type of analysis we just saw that was limited to the current smokers except this one is exclusively former smokers, so wondering, again, kind of jumping off from your question, maybe there's something going on with the former smokers putting them at risk for any, in this case, lung cancer, all cancer or all-cause mortality with respect to their use of the smokeless tobacco products. And when we look at these various former smoking groups, we again don't see any elevated risk whatsoever.

And so when we explored this topic and we looked at a variety of sensitivity analyses, we just don't see the evidence that these smokeless tobacco products is elevating those risks.

DR. MURILLO: Thank you, Gary.

DR. MERMELSTEIN: I'm just going to check with Dr. Kozlowski first on the phone. Lynn, did you have any questions?

DR. KOZLOWSKI: No, not at this point.

DR. MERMELSTEIN: Okay. Then Dr. O'Connor, you had a follow-up question, still?

DR. O'CONNOR: So this goes back to the consumer perception studies, because I've seen in your epidemiologic analyses you've been careful to look at men only versus men and

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

women. Did you do that in a consumer perception study? Have you looked at this stratified by sex? Because I would imagine, given males are the predominant users of smokeless, that they may have a different pattern of response than women do and I'm curious as to what that looks like, particularly in this experimental context.

MR. MURILLO: Yeah, the answer is they're the same. I just checked with Stephanie to make sure there wasn't a reason for her to come up here and say anything else about it. We did look at it and it's about the same.

DR. MERMELSTEIN: Dr. Duffy.

DR. DUFFY: So, similarly, I was wondering what the mean age was or the age ranges was, it says you oversampled 24-year-olds in that study.

MR. MURILLO: We oversampled 18 to 24.

DR. DUFFY: Oh, okay. But did you have, like, all age ranges?

MR. MURILLO: Yes.

DR. DUFFY: Okay, because I just wondered if was it skewed to the younger ages at all?

MR. MURILLO: No.

DR. DUFFY: Up to age, like, 70s, 80s,
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

or --

MR. MURILLO: No. No, so we have -- I have a terribly busy slide that would show this, but it essentially was all over the place, including 55-plus. We simply oversampled 18 to 24. Since we don't talk to kids, the suggestion was well, whether they're like kids or not, they are adolescents and maybe we should oversample 18 to 24 and we did.

DR. DUFFY: Oh, okay. I wonder, because I know just from my early work on warning labels.

MR. MURILLO: Yeah. It was a nationally representative sample other than --

DR. DUFFY: Right.

MR. MURILLO: -- oversampling 18 to 24.

DR. DUFFY: Because younger people don't tend to care about things like heart disease and lung cancer. They care more about pregnancy and bad breath and impotence and those types of effects than they do chronic diseases, which come later in life, so I wondered if the sample was skewed towards younger at all, maybe that's why they're not paying a lot of attention to the lung cancer.

MR. MURILLO: Yeah.

DR. DUFFY: Just a thought, anyway.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: In the FDA summary of the evidence raised in the MRTPA, they raised the issue of permeation enhancers, so I wanted to ask about this. They state that potential permeation enhancers and the influence exposure to HPHCs are incorporated into the product and the question is maybe getting back to my question about, you know, no data actually either biomarkers or epidemiologic data on your specific product.

Can you comment on the role of permeation enhancers? Are these uniform across the products that were tested, say, in the epidemiologic or the biomarker studies? Are there unique permeation enhancers in your product? Are there new permeation enhancers that are not in the products that may have been in the pool of smokeless tobacco products previously tested?

MR. MURILLO: So let me break that down and answer one question at a time. So with respect to -- we are aware of the recent, particularly recent literature on permeation enhancement, particularly dermal permeation enhancers.

For Copenhagen Snuff, as we've said, the formula has been essentially unchanged for decades and probably over a hundred years. There are permeation enhancers that we see in the literature that are in other MST products, not in Copenhagen

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Snuff. That said, there are ingredients that may act as permeation enhancers that have been in the product throughout the period and so all of that would be reflected in the epidemiology, both the extent to which that there is permeation enhancement within our product, Copenhagen Snuff, and also to the extent that there is permeation enhancement of other sorts with other ingredients in other products.

DR. MERMELSTEIN: Dr. Wackowski.

DR. WACKOWSKI: Just going back to the perception study again, so I think Dr. Apelberg made a comment that the stimuli used and actually, the image of the product didn't have the descriptor Fine Cut on there, so can you just clarify if the image of the product in the stimuli, is that -- is that for Fine Cut? Does the Fine Cut product have the descriptor Fine Cut and is the image that was tested the actual image of the product that is being proposed?

MR. MURILLO: It is the product that is being proposed.

(Off microphone comment.)

MR. MURILLO: Right. So the actual can, and don't worry, this is empty, the actual can for Copenhagen Snuff Fine Cut is what was shown and was shown in all the stimulus. It generally does not, to my recollection, include the words -- well, it

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

does say original fine cut in the side label, so most people -- Copenhagen Snuff Fine Cut is the complete name of the stock keeping unit. Most people refer it to as Copenhagen Snuff. But in any event, it is on the can. Is that okay?

DR. WACKOWSKI: Yeah, yeah.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: Again, around the consumer perception study, Dr. Apelberg pointed to how, you know, there's really just one result that shows up as being statistically significant, which is amongst the adult smokers who are not planning to quit where you see a potential difference in intentions to use, but then you don't see any differences for any of the other indicators, intention to try, intention to switch, intention to dual use.

What makes you feel confident that this is not just kind of a quirk? Every once in a while you're going to get a statistically significant result after so many different tests and you did a lot of tests. What gives you confidence that this datum is meaningful in the context of all the other null findings?

MR. MURILLO: Yeah, I would say that everything is moving in the right direction with respect to, for example, adult

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

smokers not planning to quit. As we've conceded, yes, it is not significant but everything seems to be moving in a positive direction. And as Stephanie described and again, going back to the theory of planned behavior and other such theories, I don't know that we're going to see these fast lifts given the preloads. What we're trying to do is see if we can take a step in the right direction to at least start educating smokers with the correct information.

DR. THRASHER: Can I just follow up on that? One of my questions earlier was around the quasi-experimental design and if you look at Slide -- well, 44, I guess it is, in Dr. Apelberg's presentation, it does show that the groups were kind of nonequivalent with respect to these different attributes before they were exposed to the advertising.

So, again, is this an example of something that might worry you that the groups that you're comparing are not as similar as you would hope they would be and so your ability to kind of infer from that comparison is compromised?

MR. MURILLO: I'll ask Dr. Plunkett to comment on that.

DR. PLUNKETT: So you're correct, that's what I was referring to previously and one of the reasons why we wanted to make sure to have that pre/post design and we treated pre as a

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

covariate in most of our analyses. I think what we're seeing with the data is looking now at converging lines of evidence, thinking back to the theory of planned behavior, which is what Joe just mentioned. We know that attitudes need to change before intentions and then intentions would likely lead to a change in behavior.

And so it's only with one group that we start to see things moving in the right direction and that's in the adult smokers not planning to quit. And we see a small change in risk perceptions in that we have a four percentage point decrease in the misperception of a higher risk for lung cancer, and that's Slide 2, with that corresponding two percentage point increase in the accurate perception, and then we see a trending in the behavioral intentions for adult smokers not planning to quit.

Slide 3, please. Looking pre to post, a 1.3 percentage point increase in try, 1.8 percentage point increase in use, one for dual use and two for switch. But these are all -- these are just trends, they are not statistically significant, but they're converging lines of evidence for adult smokers not claiming to quit, but things are moving in the right direction.

MR. MURILLO: Thank you, Stephanie.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. MERMELSTEIN: Dr. Bierut, did you have --

DR. BIERUT: So I have a question both to the FDA and with you guys, and it has to do with two different slides that we have. So the FDA Slide Number 26, I believe, the NMLS linked mortality analysis, and then your guys' Slide CC-45 and CC-46. And in part, looking at -- looking at the reference for the never smokers, which is what I believe the FDA -- no, it's not that one. It's on page 14.

MR. MURILLO: I think it might be 26.

DR. BIERUT: Twenty-six?

UNIDENTIFIED SPEAKER: Twenty-six.

DR. BIERUT: Yes, 26. But for you guys, 45 and 46.

MR. MURILLO: Got it.

DR. BIERUT: Okay. So I'm trying to -- the reference group, I think, is never smokers for the FDA. Yeah, this one. So the reference is never smokers for the FDA. And then if I look at the exclusive smokeless tobacco use, you know, we're getting a point estimate of three and the confidence interval is wide, but when we're looking at the data that you were presenting, you know, really the point estimates are all right around one and I'm just trying to kind of wrap my head around what the differences are. And also, I have a question, what

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

about people who are using dual use? I mean, how are they getting coded in this, too?

MR. MURILLO: Okay, you want to start?

MR. HARVEY: Yeah, I understand your question. Let's start with -- start with Slide Number 1 and -- well, actually before we switch, so we're going to jump off from this blue bar that we see on the bottom with the hazard risk of three, so I'll explain the difference.

DR. BIERUT: Right.

MR. HARVEY: Now let's go to Slide Number 1. And so when you look at Slide Number 1, if you look at the hash -- the far right hash bar, it says men and women NLMS and you see a hazard ratio of 2.53, I think you're asking 3, 2.53, what's --

DR. BIERUT: Okay.

MR. HARVEY: What's the difference?

DR. BIERUT: I'm okay with that.

MR. HARVEY: Oh, okay. I can explain if you'd like, but go ahead.

DR. BIERUT: Go, go, go explain.

(Laughter.)

MR. HARVEY: Okay. We've done analyses of various populations and so this is an analysis where we are looking at

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

exclusive never tobacco users and so we're looking at the risks of the smokeless tobacco users who've never smoked compared to never tobacco users and that's where you get the risk of 2.53 or 2.09, so it goes kind of right to the heart of the never tobacco users.

In the other analysis, as I mentioned, various populations, but in that one we have everyone in the analysis in the sense that there's current smokers, former smokers, and every combination, there's all these different groups, so you see the hazard ratios differ a little bit but not statistically different.

DR. BIERUT: So these you were really being very stratified, so in the people here they were not current or former combustible tobacco smokers?

MR. HARVEY: In this particular chart, no, they were not. They were limited to only never smokers, but let's put up the current smokers. We did look at current smokers, so the dual users, if you will, and we also looked at former smokers. And so among the dual users, we're going to pull that chart up, it's the same one we saw before, so this is Slide Number 1. We looked at dual use and current smokers in a couple of different ways and so in these analyses, we are limiting exclusively to

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

current smokers and so we're looking at the risks of the smokeless tobacco users over and above that of the non-smokeless tobacco users but both of which are -- or all of them are current smokers.

We do other analyses which are completely consistent with what we see in the literature where we're pooling together, say, current smokers and never smokers, so sometimes we pool groups, sometimes we disentangle that group, like you see here. In all cases, the results are really quite robust and pretty consistent.

DR. BIERUT: So I'm from the Show Me State --

MR. HARVEY: Sure.

DR. BIERUT: -- and you know, part of it is you're switching around the reference group, which I understand that you do that because you're trying to understand different aspects of it, but it's hard for me to kind of keep on leaping back and forth and change my reference group. So have you done the analyses against never smokers and then kind of lined everyone up against the never smokers?

MR. HARVEY: Yes. Why don't we look at Slide Number 3? And so here's an analysis, and I'll explain the difference. We start on the right. So this is that chart but ours are

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

vertical and the other ones were horizontal, but aside from that -- and I think our order is slightly different, but this is the same data that you see in the prior chart. And that does split everything out.

So each group, each of these bars, to be -- it's a separate main effect where there's no overlapping effects. On the left we see the analysis from the NHIS. Now, the NHIS analysis is more robust, there's a lot more deaths in NHIS overall, lung cancer, but in particular cancer and mortality. When we did the NHIS analysis specifically to lung cancer, looking at the most fine level of analysis we could do, we couldn't take that analysis out of the research data center because it had less than five deaths in a couple of spots.

So what I'm showing you instead, and we can look at it in a variety of different ways, is the analysis for the pooled current smokers and never smokers together, so this is a main effects analysis and we're looking at the risks of currently using ST versus not currently using ST. The one on the right, everybody's split out into separate groups.

And so we do look at it compared to never smokers, sometimes we look at it compared to former smokers and sometimes current smokers -- and you're right, those are

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

different groups -- and the idea was just to kind of search everywhere we can, is like do we see anything, is there any elevated risk? Sometimes we look at different control variables to see what's going on and there is simply no analysis that we could do where the risks of the current smokeless tobacco users approach that of the current smokers.

For lung cancer, all cancer, all-cause, heart disease, anything else, it was just across-the-board lower risks for the smokeless users, even jumping around looking at different baseline populations.

DR. MERMELSTEIN: We also have, from the FDA, just a response to the question.

DR. DAY: Hi, yes. Hello? Hi, Hannah Day, epidemiologist, CTP Office of Science. I just wanted to clarify. Actually, if you could leave their last slide up, it was HR-27. That last slide, HR-27, matches the FDA Slide 26, which I believe was your original question. I'm going to follow up on that a little bit and I'll let the Applicant jump in to correct me.

My understanding is that perhaps one of the original slides you're asking about, which was perhaps CC-46 or 45, I believe that was run on the P0 population, if you're following

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

along the application, whereas this HR-27 was run on the P4 population. So that's, like he was explaining there, the different populations it's run on. I'm not certain if the NHIS on this slide is also run on the P0 population.

So we have on this slide, 27, is the P0 population versus the P4 population. We did know that there were some differences in n 's between the two populations. I believe that may be due to loss of participants due to missing covariates but again, I'll let the Applicant explain if there are further questions.

DR. MERMELSTEIN: Can you just clarify the P0 and the P4 populations?

DR. DAY: Unfortunately, I don't have someone who will pull up a certain slide for that. My understanding is the P0 population is limited, as he mentioned, to just those two groups, the current smokeless tobacco users versus the never smokeless/never smoker users. So it's those two groups in the P0 population, where the P4 population is the entire population.

So if you picture it as a 3x3 table, which is, I believe, how they presented it in the application, in the P4 population you have all nine cells of a 3x3 table populated, where in the

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

P0 population you only have two of those cells. And perhaps that's a little too much detail without a visual, so I will let the Applicant respond if there's a better way to clarify that.

DR. MERMELSTEIN: Yeah, I think we got so restricted and one is complete, I think we've got that. Thank you.

Okay, Dr. O'Connor first.

DR. O'CONNOR: So I've actually forgotten what I was going to ask.

(Laughter.)

DR. MERMELSTEIN: Well, I'll move forward and then get back.

DR. O'CONNOR: Yeah, go ahead.

DR. MERMELSTEIN: Lynn, Dr. Kozlowski, did you have now a question?

DR. KOZLOWSKI: Well, I had a comment and I think, in my experience researching smokeless tobacco, the perception of risk is only one factor that might influence intention to use. It's widely viewed as a disgusting product by nonusers of oral tobacco and I can imagine some spouses would threaten to divorce their husbands if they started using oral tobacco. There are other aspects of use besides the perception of risk that provide an impediment for many people using smokeless

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

tobacco products.

DR. MERMELSTEIN: Good point, thank you.

Okay. All right, Dr. O'Connor and then Dr. Weitzman.

DR. O'CONNOR: So Dr. Kozlowski triggered what I was going to ask, which is you've leaned a bit on the theory of planned behavior and the idea of intention being a key predictor later on of behavior change, but you've only focused on the one path going from attitudinal change to behavioral intention and do you have measures of subjective norm or behavioral control or self-efficacy?

This goes to Dr. Kozlowski's point about the other factors, social, socioeconomic factors or demographic factors that might drive people's baseline interest in using these products in the first place.

MR. MURILLO: Yeah. We do not. You're right, we do not. We focused on this incoming beliefs point. What I will say, as I said in our opening statement, is that we realize that the appeal of Copenhagen Snuff is limited. It is mainly adult male users age 35, if I could get that demographic slide up, 35 and over.

However, we do see, within PATH, for example, that people do go, as a matter of fact, from smoking to using Copenhagen

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Snuff, in fact -- Slide 2 up, please. And we see this happening. So there is something there that can happen and has been shown to happen. We also see that, from PATH, that in general, smokers that have a correct risk perception relative to other products are four times more likely to switch to that product than not.

So if we can begin to at least move the needle, take one step with respect to information that is currently not available to smokers and knowing that (1) 23 out of the 40-odd-million smokers have already said, in PATH, that they would be interested in a product if it had a reduced risk communication with it; (2) in fact, smokers with the correct smokeless tobacco and smoking relative risk perception are four times more likely to switch than those who have not had that correct perception; and (3) as a matter of product choice, we know that Copenhagen Snuff is a product that people had used to move from smoking to smokeless tobacco use. That gives us some hope that at least if we can start with this communication we might start moving the needle.

DR. MERMELSTEIN: Thank you.

Dr. Weitzman.

DR. WEITZMAN: I have a question about impact on
Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

population. Can we look at slide CC-110? It's on page 55. What assumption was used to come up with 60 years following claim authorization? How did you come up with that?

MR. MURILLO: Right.

DR. WEITZMAN: Why did you use that?

MR. MURILLO: I'll ask Dr. Black to answer.

DR. BLACK: We selected 60 years to allow for the latency of health effect on transitions over time. And so we -- the simulation actually started about 80, 84, 85 years before it ended. So the claim is authorized 15 years into the simulation such that we would have multiple cohorts in 5-year increments moving forward allowing for a full population to be evaluated by the end of the simulation representative of the U.S. population.

DR. WEITZMAN: Am I the only one who doesn't quite understand that?

DR. BLACK: So let's --

DR. WEITZMAN: I don't --

(Crosstalk.)

DR. BLACK: All right, let me try to help. Which slide were you -- let me put up Slide 3. So here you can see that the concept of a multiple cohort model is that you have

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

staggered cohorts entering the simulation throughout the run, and so the first cohort entered within the first 5 years and we had another cohort within the next 5 years and so forth all the way until we built a full U.S. male population representative -- representative of the U.S. male population by the end of the simulation and that took into account people aging throughout the simulation. Those at the beginning could potentially age all the way through 85 years.

And Slide 2 might help provide some -- thank you. Slide 2 might -- can you pull up Slide 2? Here you see where the benefit is really taking place. The benefit occurs for those who enter the simulation earlier, such that they had more time to benefit from having transitioned.

DR. WEITZMAN: So the column on the far right is not the -- is the age at entry into the cohort? What does the column --

DR. BLACK: You mean the far left?

DR. WEITZMAN: On my far right.

DR. BLACK: Okay.

DR. WEITZMAN: Sorry.

DR. BLACK: Yes, where it says age group.

DR. WEITZMAN: Right. No, I was talking about the far --

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

DR. BLACK: The far right is the difference in premature deaths prevented between the base case and modified case by the end of the simulation.

DR. WEITZMAN: And the age group on the far left, what does that refer to?

DR. BLACK: That is the age distribution representative of the U.S. male population in 2075 which matches, actually, the U.S. census projection within 3%.

DR. WEITZMAN: But 0 to 4-year-olds --

DR. BLACK: Right.

DR. WEITZMAN: -- have nothing to do with using smokeless tobacco products. I'm still confused.

DR. BLACK: That is true, it is highly unlikely. In fact, it's impossible for a 0 to 4-year-old to initiate. That said, we wanted to represent the full U.S. male population and so we entered 0 to 4-year-olds starting from the beginning in five-year increments. So by the end, you are correct, there are some 0 to 4-year-olds because they have -- they were literally born by the end of the simulation. What impact do they have? Absolutely none. You can see there that the impact is zero.

DR. WEITZMAN: So wouldn't the appropriate denominator start at the age at which people are at risk for showing

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

deleterious effects from this product?

DR. BLACK: So the age -- the cohorts are aging in, so --

DR. WEITZMAN: Right, I understand that.

DR. BLACK: And so we allow for 60 years of aging post-authorization of the claim. And by the way, if you -- if we had allowed this to go even further, at some point you wouldn't see a difference between either the base case or modified because all individuals would die at some point.

DR. MERMELSTEIN: Okay, Dr. Apelberg.

DR. APELBERG: Yeah, can I just ask you a clarifying question about this? Because I noticed that the estimates that you have are different than what I had in my slide and I thought that in your -- as you described this in the application, that the 93,000 -- this estimate for 93,000 represented, like, the whole U.S. smokeless market and then there you sort of scaled it to reflect the impact of, you know, an authorization specifically for Copenhagen products, so if you'd just clarify the difference between those estimates.

DR. BLACK: So the transition rates available in the literature, from Dr. Tam, are at the category level and so those were the transition rates we had to use in our population model. That said, in the consumer study carried out by

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

Stephanie and colleagues evaluated the impact of the claim on intention of Copenhagen Snuff, specifically.

And so you're correct, that 93,000 probably is somewhat of an upper limit in terms of the inputs that we generated, but the 7500 also is probably the lower limit, it's probably somewhere in the middle given that the transition rates from the literature at the category level, the impact of the claim was specific to your intentions of using this specific product. Does that help? A little bit.

DR. MURILLO: Thank you, Ryan.

DR. BIERUT: Can I ask it a slightly different way? So we have 93,000, I'm assuming it is lives kind of saved.

DR. BLACK: Yeah, it is.

DR. BIERUT: So it's 93,000 lives saved over 60 years.

DR. BLACK: Yes.

DR. BIERUT: So it's 1500 lives saved --

DR. BLACK: Yes.

DR. BIERUT: -- per year.

DR. BLACK: Correct.

DR. BIERUT: And then putting that in the view of we have over 400,000 lives lost per year from combustible smoking products at this point, it's -- we're really not doing much at

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

this point in part because the market -- we could argue the market share is too small, a variety of things, okay. But another way to do the math, though, is 1500 per year.

DR. MERMELSTEIN: Dr. Warner, a last question?

DR. WARNER: Yeah, I just was curious. Did you do life years, as well?

(Off microphone response.)

DR. WARNER: What did you get?

DR. BLACK: We observed over two million additional years of life. Two million years worth of life prevented.

DR. WARNER: So you're saying better than 20 --

DR. BLACK: Years additional.

DR. WARNER: Per year. Per person? Okay.

DR. BLACK: Yeah.

DR. WARNER: Thank you.

DR. MERMELSTEIN: Okay, thank you. I think we've had a good run of questions for the Applicant and for the FDA. I want to thank you all for providing thoughtful responses and --

MR. MURILLO: Thank you.

DR. MERMELSTEIN: -- clarifying for us. I want to just preview what our task will be tomorrow so that people are refreshed and prepared to directly discuss what our task is.

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

We'll start with some public comments in the morning and then we're going to have a very focused discussion about the specific questions that we are asked to deliberate on, one vote, and then a discussion. So one question has to do with the scientific accuracy of that specific claim and that's the one vote. And so I think we've got a lot of information today and some specific slides that address very directly that claim and that may be something you want to take another look at. And then we're going to discuss questions about did people understand that claim, their perceptions, and what that might have done to changing any potential behavior as well as other vulnerable populations.

So I think we have a lot of information, crystallize your thoughts so that we can discuss it clearly in the morning after public comments, and just as a reminder, think to yourself, not with each other.

(Laughter.)

DR. MERMELSTEIN: So you can go back to your room and talk to yourself, but we cannot be talking and debating this and clarifying among other Committee members this evening, so maybe getting away from it. I know it's very hard to remind ourselves not to continue the discussion, but that's what we

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556

have to do this evening. So thank you all for your very active listening and participation, and come back bright and refreshed in the morning. Thank you.

(Whereupon, at 4:43 p.m. the meeting was continued, to resume the next day, Thursday, February 7, 2019, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the
matter of:

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

February 6, 2019

Silver Spring, Maryland

were held as herein appears, and that this is the original
transcription thereof for the files of the Food and Drug
Administration, Center for Tobacco Products.

TIMOTHY ATKINSON,
Official Reporter

Professional Video Associates, Inc.
2515 Saint George Way
Brookeville, MD 20833
301-924-1556