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FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

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M E E T I N G

(8:10 a.m.)

DR. MERMELSTEIN: Good morning, thank you all for coming this morning. I'm Robin Mermelstein, Chair of the Tobacco Products Scientific Advisory Committee. I'm going to make a few statements, and then we will go around and introduce the Committee and individuals sitting around the table.

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 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 government 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.

The purpose of this session of the meeting is to discuss the modified risk tobacco product application submitted by Altria Client Services LLC on behalf of U.S. Smokeless Tobacco

Company LLC, for the smokeless tobacco 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 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 as nonvoting representatives. Dr. Bailey is representing tobacco growers, Dr. Johnson is representing the small business tobacco manufacturing industry, and Dr. McKinney is representing the tobacco manufacturing industry. Their role at 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 that 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 representative. However, the nonvoting representative, Dr. McKinney, may not discuss the company's position as such, but may discuss any matter in general terms.

DR. MERMELSTEIN: Thank you. We're going to go around the table and introduce the Committee and others. Again, I'm Robin Mermelstein from the University of Illinois at Chicago.

Sally.

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

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, National Tobacco, representing the small tobacco manufacturer.

DR. McKINNEY: Willie McKinney, I'm employed by Altria Client Services, and I represent the tobacco manufacturing industry.

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

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

DR. APELBERG: Ben Apelberg, Director, Division of Population of Health Science, Office of Science, Center for Tobacco Products.

DR. STEPANOV: Irina Stepanov, University of Minnesota.

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

DR. DUFFY: Sonia Duffy, Ohio State University.

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, New York University School of Medicine.

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

DR. MERMELSTEIN: Thank you. We're going to start today with --

DR. KOZLOWSKI: Wait. And Lynn Kozlowski, University of Buffalo, on the phone.

DR. MERMELSTEIN: Sorry, Lynn, I will remember not to forget. Thank you very much.

Okay, we're going to start today with our Open Public Hearing, these are very brief statements by a variety of individuals. Our first individual is Thomas Briant from the National Association of Tobacco Outlets.

MR. BRIANT: My name is Thomas Briant, and I am the executive director of the National Association of Tobacco Outlets. Thank you for the opportunity to speak to you today about the U.S. Smokeless Tobacco Company modified risk tobacco product application for Copenhagen Snuff Fine Cut.

Congress and the federal government have deemed it appropriate to require health warning statements to inform adult consumers of the risks associated with tobacco products.

Similarly, adults should be informed about tobacco products and any reduced level of harm that they may present.

Copenhagen Snuff Fine Cut confirms the FDA's stated goal of protecting the public health because the product falls on the lower end of the continuum of risk, which has been in place by the Agency and used to compare the level of harm among various tobacco products.

In the event the application is approved by the FDA, then retail stores will be an important place for adult consumers to receive information about the product's reduced harm characteristics. Why? Because there are several means in a retail store to provide information about the reduced harm of those products, including point-of-sale displays, labeling on the product itself, and interaction with store employees about the product. This would allow the retail segment of the industry to serve as an important source of information for consumers about the reduced harm properties of the Copenhagen product.

As I stated at the outset, the American public deserves accurate and scientifically valid information about tobacco products so they can make an informed decision about the reduced harm properties of a product. In order to allow that

information to be provided by U.S. Smokeless Tobacco Company, I urge you to act favorably upon the MRTP application.

Thank you for your time.

DR. MERMELSTEIN: Thank you.

Our next speaker is Alex Clark.

MR. CLARK: Good morning, again. My name is Alex Clark, CEO of Consumer Advocates for Smoke-Free Alternatives Association. I will dispense with the longer introduction, you have our disclosure and written comment in front of you.

While I am here on behalf of CASAA to express our support of the MRTP application for Copenhagen Snuff, we're commenting today on the portfolio of MRTP applications currently under consideration by the FDA.

Prevailing misperceptions about the risks of nicotine and smokeless tobacco is a dominant and reoccurring theme across multiple MRTP applications. All applicants note that these misperceptions are a barrier to honest and accurate risk communication. Moreover, government mandated misinformation about the risks of smokeless tobacco presents a substantial obstacle to achieving our common goal of reducing the early death and disease attributed to smoking.

At each public comment opportunity before this Committee,

CASAA recommends that in addition to approving the MRTP application, FDA and CDC take a more active role in promoting the balancing and corrective statements regarding the relative risks of using smokeless tobacco and smoke-free nicotine products. But we are aware that any such action will be done with an abundance of caution and under intense political scrutiny.

It is also clear that due to several factors including widespread mistrust of applicants, a single MRT application will do little to correct the public's misperception of risk.

As a potential remedy to these obstacles, we offer the following recommendation: Rather than consider each MRT application in isolation, we urge the FDA to approve all of these applications quickly and simultaneously, sending a clear message to people who smoke that smoke-free alternatives are available and that switching is an acceptable path away from combustible products. Thank you for considering our comments.

DR. MERMELSTEIN: Thank you very much.

The next speaker is Ronald Conyea. I hope I pronounced your name right. Sorry.

MR. CONYEA: You got it right. Thank you. This morning I'd like to thank the Committee for the opportunity to speak.

I'm a dark-tobacco grower and sell my tobacco to the U.S. Smokeless Tobacco Company, who manufactures Copenhagen and uses 100% grown American tobacco for its products.

For the past 38 years, my wife and I have grown dark tobacco, which is the vast majority of our income. Tobacco farming has allowed us to pay for our two children to attend the University of Kentucky, where our son studied agriculture. Today, he and our son-in-law, who was also an agriculture major at Murray State University, both work part-time on-farm. Farming drives jobs in Kentucky and in Graves County. Dark tobacco is the primary type of tobacco used in the production of moist smokeless tobacco products. There are 1200 dark tobacco farmers in the United States on approximately 24,000 acres, with a cash value of $190 million per year. I support this application because the United States has a significant adult smoking population for decades.

Public health efforts over the past 50 years have reduced smoking rates, but still today there are over 42 million American adult smokers who either cannot or will not quit smoking. I believe that the majority of these smokers are interested in less harmful alternatives to combustible cigarettes. Moist smokeless tobacco products are one of those

alternatives.

In the July 28th, 2017 announcement of your comprehensive regulatory approach to tobacco, you note that "a key piece of FDA's approach is demonstrating a greater awareness of nicotine. While highly addictive, it is delivered through products that represent a continuum of risk and is most harmful when delivered through smoke particles in combustible cigarettes." I agree and believe a key component to your strategy is your modified risk tobacco product process. Cigarette smokers must be able to purchase less harmful products and have access to relevant and accurate information about those products.

The FDA has several modified risk product applications pending before it for review of claims, including Copenhagen Snuff Fine Cut moist smokeless tobacco. Knowing your commitment to harm reduction and the continuum of risk, I encourage the FDA to thoroughly and quickly review the clearance --

DR. MERMELSTEIN: Thank you.

MR. CONYEA: Thank you.

DR. MERMELSTEIN: Thank you.

Our next speaker is Paul Blair, Director of Strategic

Initiatives, Americans for Tax Reform.

MR. BLAIR: Good morning. I had a set of prepared remarks that I significantly revised last night while watching one of my all-time favorite movies, A Few Good Men. The climax of the movie occurs in the courtroom between Tom Cruise and Jack Nicolson, when Cruise attempts to get Nicholson to admit that he ordered a Code Red. The lives of two innocent men are on the line.

In one of the best scenes of the movie of all time, Nicholson asks, "You want answers?" Cruise says, "I think I'm entitled." Nicholson says, "You want answers?" And Cruise says, "I want the truth," and Nicholson begins, "You can't handle the truth. Son, we live in a world that has walls, and those walls have to be guarded by men with guns. Who's gonna do it? You? I have a greater responsibility than you can possibly fathom. You weep and curse the Marines. You have the luxury of not knowing what I know." It goes on. It's fantastic.

I hope you see where I'm going with this. Congress created the MRTP pathway in part because it recognized the lifesaving potential of telling the truth. The MRTP claim being sought for Copenhagen is simple, accurate, and

substantiated by decades of government supported epidemiological evidence.

People who smoke are entitled to know that the risk of lung cancer is reduced when you switch to a smokeless product like this. The deeply rooted misperceptions about the health risks of smokeless tobacco are themselves a threat to public health. By failing to tell the truth to smokers that there are safer alternatives to cigarettes currently on the market, the data suggests that more people may be smoking cigarettes today as a result.

In conclusion, don't be Colonel Nathan Jessup. American consumers can handle the truth; in fact, they deserve it, and the dictate of the FDA requires that with the evidence you have before you, smokers hear it, they see it, and they can read it. The walls you guard have innocent lives just waiting to be saved on the other side. I urge you to favorably recommend the simple and accurate modified risk communication sought for this product.

Thank you.

DR. MERMELSTEIN: Thank you.

Ross Marchand from Taxpayers Protection Alliance.

MR. MARCHAND: Good morning, my name is Ross Marchand with

the Taxpayers Protection Alliance, and unfortunately, I don't have any movie references or dialogue to make today.

The Taxpayers Protection Alliance believes that the FDA has a unique opportunity to help smokers quit smoking and give customers the chance to try innovative harm reduction products. When products have the potential to save millions of lives, it's helpful if people are told about the benefits. The FDA can do just that as it considers allowing smokeless tobacco manufacturers to notify smokers that completely switching from cigarettes to smokeless products can save lives.

Commissioner Gottlieb has emphasized that cigarettes account for an overwhelming percentage of death caused by tobacco. But strangely, the FDA has continued to campaign against lower-risk alternatives to cigarettes. Copenhagen Snuff has been around since the early 19th century and, like other noncombustible products, smokeless tobacco is far less harmful than cigarettes.

According to official government data from the National Health Interview Survey, regular cigarette smokers are three times more likely to die of cancer than smokeless users. Unfortunately, few customers are aware of that lower risk. The FDA's own survey found that more than 60% of adults believe

that smokeless tobacco is just as harmful, if not more harmful than cigarettes. This just underscores the need to allow for more accurate health labeling which would certainly be beneficial to health of the population on the whole.

But approving health labeling for smokeless tobacco is only one part of a necessary strategy to get people to quit smoking. IQOS is a revolutionary heat-not-burn device that is far safer than cigarettes but delivers that same sensation, but the FDA continues to sit on that application. So I urge the FDA to do the right thing and consider giving customers --

DR. MERMELSTEIN: Thank you.

MR. MARCHAND: -- the necessary information to quit cigarettes once and for all. Thank you so much.

DR. MERMELSTEIN: Thank you.

Next up is Scott Ballin.

MR. BALLIN: Good morning, my name is Scott Ballin, and I've spent over 40 years working on tobacco and nicotine issues and particularly focused on the FDA.

In the brief 2 minutes I have, I'm going to make a few points for consideration as we look to the future about how tobacco products, nicotine products, and alternative products should be regulated.

Commissioner Gottlieb and Director Zeller and others, including myself, have said that we are at an important crossroads. And we are. There's a lot going on at the moment that has to be decided, lots of challenges, but more importantly, lots of opportunities. I concur with the visionary statement made by Commissioner Gottlieb and Director Zeller in July of 2017 and I call on the Agency to ensure that it remain focused on those goals and objectives, including keeping tobacco and nicotine products out of the hands of kids, but equally important, and this message seems to be getting lost in the media, equally important, ensuring that the more than 40 million cigarette smokers have access to noncombustible cleaner forms of nicotine products that can be used to replace the deadly cigarette.

As part of this, the time has come to move forward more expeditiously to provide truthful information and accurate information about these low-risk products to the public and consumers. The public and the consumers have waited too long. I commend the members of TPSAC, the CTP staff, and the manufacturers for their civil discussions that I listened to most of yesterday and I hope will continue today.

I call on the FDA and TPSAC and all of the stakeholders in

and outside of this room to support the idea of engaging in more stakeholder dialogues, including a possible national dialogue that could be organized by the FDA so that we can remove the rhetoric and the emotions that are preventing us from finding serious solutions. Thank you.

DR. MERMELSTEIN: Guy Bentley, the Reason Foundation.

MR. BENTLEY: Good morning, everyone. My name is Guy Bentley, and I'm from the Reason Foundation. Thank you for giving me this opportunity to speak to you this morning.

If consumers of tobacco products are to maximize their welfare, we believe that it is critical that they understand the benefits of quitting and/or switching to different tobacco products. Without clear and accurate information, consumers will be make suboptimal decisions which will damage both their health and welfare.

While not risk free, smokeless tobacco products present substantially less harm to their users than combustible cigarettes. Yet most smokers mistakenly believe both products to be equally dangerous.

While switching from combustible cigarettes to a smokeless tobacco product reduces the risk of a whole range of diseases, the application in question is exceptionally narrow and more

just than in scope. The claim is clearly targeted at existing smokers and is scientifically sound to the point of being axiomatic.

Referring to only one disease outcome, which is strongly linked to smoking but far less so to smokeless tobacco use, the claim also relates to reducing rather than eliminating risk and is careful to emphasize that the risk of lung cancer is reduced only when the consumer completely switches to Copenhagen.

There's little room for confusion in what the Applicant is trying to communicate and indeed, it will require substantially more thought and effort to confuse the message than to understand it accurately. From an individual user's perspective, switching from smoking to Copenhagen presents a clear health benefit.

Given the relatively small portion of the tobacco market which consists of smokeless tobacco and the vanishingly small numbers of youth using the product, there is little reason to believe that granting or requesting the granting of the MRTP order would entice nontobacco users, especially youth, to start using the product.

We firmly believe that FDA should work to educate the public both about the risks of tobacco products, but also the

potential benefits of switching to reduced risk products. It is essential to allow truthful claims about products to be marketed, not just to benefit public health, but also to demonstrate the effectiveness and validity of the current regulatory regime.

Thanks very much.

DR. MERMELSTEIN: Thank you.

Michael Ogden from RAI Services.

DR. OGDEN: Good morning, I'm Mike Ogden, Senior Vice President of Scientific and Regulatory Affairs for RAI Services Company.

It's 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, as today marks the fifth meeting of TPSAC to consider an MRTP application, one thing is beginning to clearly

emerge. There is a wide divergence in the various applicants' approaches to establishing sufficient evidence to justify an MRTP order. In the very brief amount of time I have to address the Committee this morning, let me offer just a few examples:

- The amount of science that is product specific, including biomarker data;
- The risk claims themselves, whether they are for a single specific disease endpoint or for broad classes of disease;
- The balancing information or cautionary statements in the advertisements that applicants have included, if any;
- How information is proposed to be presented to consumers;
- How consumers' comprehension and perception are addressed; and
- How the net population effect is modeled, if at all.

At this point in the evolution of the MRTP application process there is enough disparity to call for FDA to issue more definitive guidance to industry in order to both reduce the burden on industry and, more importantly, to more quickly advance FDA's public health goals. But above all, 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.

Carrie Wade.

MS. WADE: Hello again. My name is Carrie Wade and I'm the director of harm reduction policy at the R Street Institute. Once again I'd like to thank the Committee for affording me the opportunity to present oral testimony today and for putting up with me for 2 days in a row.

As you might remember, one of my program areas is tobacco harm reduction, and I believe that tobacco harm reduction with the use of reduced risk products can work in complement and not to the exclusion of prevention and cessation programs for smokers who can't or don't want to quit.

It's impressive that the FDA's Center for Tobacco Products has had four TPSAC hearings on MRTPAs in the last year and it is my hope that all four, including the application being discussed today, are successful for the benefit of current smokers. Again, it is vital to finally demonstrate that the MRTP pathway works and applications that meet the strict

standards set by the FDA should be awarded authorization in a timely manner.

The very narrow focus for Copenhagen Snuff with the claim that switching completely to this product from cigarettes reduces the risk of lung cancer is clear and appropriate for the audience, those who already smoke.

Furthermore, evidence provided by the U.S. Smokeless Tobacco Company and independent researchers demonstrate this to be true, switching from combustible cigarettes results in lower carbon -- lower levels of carbon monoxide, an 86% decrease compared to combustible cigarettes. Smokeless tobacco products have fewer carcinogens compared to combustible cigarettes which are far less likely to impact lung tissue.

Data from the Applicant's materials clearly demonstrate that the proposed marketing claim did not alter the study participants' perceptions of absolute risk of the products, but did positively impact their knowledge of the relative risk of lung cancer in comparison to combustible cigarettes.

It is my hope that the TPSAC recognizes the potential for the MRTP framework to benefit public health and considers this an achievement in partnership between the FDA and the industry it guides. Each applicant has the opportunity to decide which

marketing claim they choose for approval. The claim put forth to the TPSAC today is perfectly in spirit with the FDA's modified risk tobacco product intended --

DR. MERMELSTEIN: Thank you.

MS. WADE: -- to encourage the use of safer products. Thank you.

DR. MERMELSTEIN: Thank you.

Next, we have a representative from the Campaign for Tobacco-Free Kids.

MR. HENIGAN: Thank you. My name is Dennis Henigan. I'm vice president for legal and regulatory affairs at the Campaign for Tobacco-Free Kids. I want to thank TPSAC and FDA for the opportunity to address the Committee.

In my limited time I'd like to return to a key issue that received discussion at several points in yesterday's deliberations and that is the absence of any evidence offered by Altria or Swedish Match of the impact of these proposed modified risk claims on adolescents.

FDA is now considering four modified risk applications and in no case has the applicant offered evidence of the impact of the message on youth perception. This is despite the fact that both FDA's draft guidance for modified risk applications and

the IOM's 2012 report on scientific standards for modified risk studies stressed the importance of inclusion of youth in consumer perception studies.

In fact, FDA's draft guidance offered to work with applicants to determine the best ways to conduct these studies to avoid any adverse unintended consequences. No modified risk product can possibly be found to benefit the population as a whole, as required by the statute, without an assessment of its impact on youth perception. And for FDA to grant an application in the absence of such evidence would, in our judgment, be contrary to the Agency's statutory obligations.

Indeed, at a time when we face an epidemic of teen use of another product, e-cigarettes, promoted as giving smokers a less harmful alternative, it seems inconceivable that FDA could grant modified risk status without reliable data on youth impact. And postmarket surveillance is not a substitute for rigorous premarket review to prevent adverse public health consequences --

DR. MERMELSTEIN: Thank you.

MR. HENIGAN: -- before they occur.

DR. MERMELSTEIN: Thank you.

MR. HENIGAN: FDA must --

DR. MERMELSTEIN: Thank you.

Next is Naomi Lopez-Bauman.

MS. LOPEZ-BAUMAN: Good morning, Madam Chair and members of the Committee. My name is Naomi Lopez-Bauman, and I am director of healthcare policy for the Goldwater Institute. It's for reasons of harm mitigation, protection of taxpayer resources, and the principle of individual autonomy that I am here to support the application before you today.

You've already heard that most smokers in the U.S. have insufficient or incorrect information about the risks of smokeless tobacco options and how these products can reduce their own risk of death and disease. Today, these cigarette smoking related deaths is an increasing concern for the federal/state Medicaid program.

Medicaid now accounts for more than one-quarter of state budgets compared to just 11% in 1988, and the Centers for Disease Control estimates that more than one-quarter of adult Medicaid enrollees are currently smokers. Smoking related deaths among Medicaid enrollees now account for about 15% of total program spending, and taxpayers pay more than 60% of the nation's total healthcare expenditures on smoking-related illness.

While many state programs include smoking cessation and harm mitigation, more truthful and scientific information should be readily and widely available to support these efforts. The federal government should not limit the access to, or sharing of, truthful and scientific information about these products. Not only are these products already widely available to people around the world, but they also offer a lower-risk alternative to traditional cigarettes.

And let's not forget the important principle of individual autonomy, which should always prevail. After all, we agree that people have the right to undertake seemingly dangerous activities for purely recreational purposes. For example, some choose to base jump, free climb and skydive, and these activities become -- these activities do not become less dangerous by depriving people of safety precautions such as helmets or eye protection. Modified risk tobacco products should be no different.

Thank you for your consideration.

DR. MERMELSTEIN: Thank you.

And our last speaker is Lindsay Mark Lewis.

MR. LEWIS: Good morning. And I thank the Committee for having me this morning and I'm on the final days of head cold,

so if my voice cracks, it's not an emotional reaction to this hearing, but we will go forward.

I'm the executive director of the Progressive Policy Institute in Washington. We are an independent think tank heavily focused on innovation and innovation is what I want to address at this hearing today.

Innovation is part of the FDA's DNA, except when it comes to tobacco products. Before the Committee today is the Copenhagen application and its desire to correctly be listed as a modified risk product. This new generation of innovation in tobacco is something that the rest of the world has embraced as a pathway for traditional tobacco users to quit the harmful use of burning tobacco.

This Committee and the FDA have spent years with these proposals now, of these products, where the science is pretty clear. These innovations dramatically reduce harm to current smokers. Our strong history in the U.S. of innovation has been surpassed by our friends in Japan, Germany, the UK, to just name a few places. These nations have embraced these products and champion the positive development these innovations have for former users of tobacco, burning tobacco.

The regulators in these locations have embraced the

science and innovation. It is a proven fact that by approving these new products they have not created a new generation of tobacco users, but they have equated it to a healthier alternative for adult smokers. Meanwhile, the FDA has not approved these products --

DR. MERMELSTEIN: Thank you, Mr. Lewis.

MR. LEWIS: Oh. I have so much more to say, but thank you.

DR. MERMELSTEIN: Thank you.

The Committee thanks everyone for their really succinct and thoughtful and helpful comments and for taking the time to show up and put the care that you did in it. It's helpful to have the range of comments that we heard, so again, we appreciate the time you took to do this. Thank you.

The Committee is now going to move to starting to discuss our questions at hand and I want to try to keep this bounded by one point at a time so that we can stay focused on the task at hand.

So I'm going to start where we have the first question that's posed to us for our task and that question is that the Applicant has proposed the following modified risk claim: IF YOU SMOKE, CONSIDER THIS: Switching completely to this product

from cigarettes reduces risk of lung cancer.

Now our job is to discuss the available scientific evidence and we will vote on the extent to which this specific claim is scientifically accurate. So I want to just start with a discussion about this and remembering that our comments should really reflect our thoughts about the scientific accuracy, so let's try to stay with that and again, what this specific claim is focused on. So the claim addresses smokers and if smokers switch completely, is their risk of lung cancer reduced?

And I think just to start the discussion that we do have some data that's been presented to us that we can look at -- by both from the FDA and from the Applicant, where we can look at the lung cancer mortality hazard ratios. So from the FDA's presentation on page 14, comparison of former smokers and switchers to current, and then we can also look at the Applicant's presentations on their forms on page 33 -- 23, which was CC-45 and 46, where again the question here is addressing what is the risk if smokers switch?

So we want to look at what are the data that we know from former smokers and what are the data that we might know from switchers. So if we can keep the discussion focused on that, I

think that's what this particular claim is asking us. Comments, thoughts, discussion. Dr. Ossip.

DR. OSSIP: I think the overall evidence that was presented is quite strong about the difference in lung cancer rates. I do have a concern that since the statement is for this product, I would have preferred to have seen some data specifically about this product and I was indeed surprised that given the length of this product on the market or even this class of products from this company with similar profiles, that we did not have product-specific data.

DR. MERMELSTEIN: I think that's an excellent point. I think we were asked to make the assumption, reasonable, that this product represents a good portion of the market share and realistically, from the epi data, backtracking and asking people what specific product would have been -- not feasible. So I'm not sure what longitudinal study we'd be able to get just focused on those people, but you're absolutely right that we're asked to make an assumption about are the general data reflective of this specific product.

DR. STEPANOV: Yeah, I just wanted to get back to the comment that I made yesterday, that most of the definitive data or maybe epidemiology deals with smokers, comparing smokers or

dual users or former smokers or users of smokeless tobacco. So that evidence is very clear that there is a difference in risk.

When it comes to evidence for people who switch from smoking to use smokeless tobacco, it's not -- the reduction in risk is not well characterized. The data is very limited, so we can expect that there will be some reduction in risk, but the data is very limited from charts that were shown yesterday, very consistent between what Dr. Apelberg presented on one of the slides, it's on page 14. You know, this is the big key data piece that 95% confidence interval actually overlaps between current smokers and people who switch to smokeless tobacco products and that could be in part due to limited amount of data.

So not only is there a difference in this exposure and effect scenario, so we are looking at people who just use smokeless tobacco versus people who smoked for a while and then switched. So there is a difference in this scenario, but also population. So data for smokeless tobacco is well characterized for different types of populations, risk difference, sociodemographic characteristics.

Smokers who are targeted would be targeted, now have different characteristics that may affect how susceptible they

would be to continue exposure to NNK, which is a potent lung carcinogen. We know there are ethnic differences in how people metabolize carcinogens, we know there are disparities in how people are exposed to other chemicals that may enhance carcinogens, still NNK.

Now, while the Applicant did not present data specifically on exposure to nitrosamines from this specific product, but there is available data showing that exposure is comparable to what we see in smokers based on biomarkers -- biomarkers. So levels are comparable. Of course, there's many other exposures that are not there.

So while I also have data from my lab, I agree that there was a lot of -- a lot of effort done on reducing nitrosamines in smokeless tobacco, including Copenhagen, it's one of the better examples, so really dramatic reduction and consistent reduction in TSNA, but it is not a low nitrosamine product. At this point, it's not. So evidence is we have something for Swedish snus switchers, it's not necessarily directly comparable because Copenhagen is not a low nitrosamine product.

So while I do agree that there is probably a reduction in risk and there is suggested evidence, but it's not the exact -- extent of reduction is not well characterized. So it was a

long way to make a point.

DR. MERMELSTEIN: But that was a helpful summary. I think another way of looking at this is to take it in a couple of parts. I mean, there are different parts, but one is I think we do have data from smokeless compared to former smokers. That's well established in terms of reducing the risk.

And so then the question is if that's the first part, if smokers become a former smoker, and then if they take up smokeless, what is the -- you know, and they take up this product, what might be -- is there additional risk and what's the relative risk from people who are using this product compared to smokers as well? So I think you could sort of combine those two pieces of data and think about it.

Dr. McKinney.

DR. McKINNEY: Yeah, I do recall the Applicant presenting some data that basically talked about the age in which you switch, as well as how long you actually smoked and then switch. And if I recall correctly, there was still significant reductions in relative risk compared to continuing to smoke.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: So looking at the question that we have here, you know, I think of science as kind of this iterative process

where we're trying to get to the truth and I'm very comfortable thinking that -- believing that this product reduces the risk of lung cancer.

Though we could identify numerous different parts where we don't have the data specifically on this product, though this data is not without harm, when we compare it to combustible cigarettes and when we look at just the multitude of data across countries, in the United States, what the FDA presented, I am extremely comfortable thinking that this reduces lung cancer and, as a physician, I would be very comfortable telling that to patients. I think the issue that we're going to get here, in general, with the FDA is how much harm reduction is there and how do we start comparing the different products. And that is going to be a challenge in the future for the FDA because we have this product and then the next product and what is the standard that we're going to use about how much harm reduction? If we reduce harm -- I'm going to make up numbers here.

So if we think of combustibles at a risk of 100 and not smoking at zero risk, if we're at 25, are we comfortable with that? Would we rather have a product that's a risk of 10? What about 30? And we are going to -- I think the next

scientific issue is going to be how do we measure reduced risk?

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: So I, too, am quite convinced that switching completely results in significant decreases in lung cancer. I do have problems, and it's a variation on what Dr. Ossip said, of stating this about this particular product rather than smokeless tobacco in general. I don't know that this statement isn't misleading to the public, but it's this product rather than the class that this product belongs to.

DR. WARNER: Yeah, I think Dr. Weitzman has made a very important point as a general point for FDA to be considering and that's going to apply to all the kinds of MRTPAs that we're going to investigate. I have had a bit of a sense of deja entendu when listening to this conversation and thinking about the fact that for decades a large number of countries would not accept the fact that smoking caused lung cancer unless they studied it in their own populations and we note that there are some differences. Lung cancer rates among the French are somewhat different than they are among Americans, having to do with tobacco type and so on.

To me, what I understand to be our question right now that we're voting on, this is unequivocally clear that this is

accurate. I understand the concerns about it not being related to this specific product, but I've just never seen any evidence that the kinds of smokeless tobacco we're talking about even begin to approach the risk of smoking with regard to lung cancer.

So I think, to me, this is an easy one. What you make of the MRTPA relating to population effects or individual interpretation, that's another issue, that's a more complicated one.

MS. HERNDON: Therein lies one question I have about process. Is this question proposed to us specifically about individual risk or should we consider population data as well? I'm not sure. That's one of the things I've been talking to myself about when I think about this question and I'm not sure what the charge is.

DR. APELBERG: Yeah, this goes back to, you know, when I sort of laid out the key questions that we have to address. I mean, one of the first ones, and a question that obviously is necessary but not sufficient, is whether what a company is proposing to communicate is accurate, right?

So we want to be able to know that's the case, but that's not the whole story, right, because we have this population

health standard that we have to assess in terms of what the impacts of communicating that information might be, whether consumers will understand it and so forth. So we really have tried to sort of piece -- you know, separate those out.

So this is really about the accuracy of this statement and then the subsequent discussion questions are about consumer comprehension and perception of this information and then the likely impacts of communicating this on different groups and what that might mean for population health.

DR. MERMELSTEIN: Other points about this particular question before we vote?

(No response.)

DR. MERMELSTEIN: Okay, thank you.

So we're going to be using -- oh, Lynn, before I forget, I will remember to ask, did you have any comments you wanted to make?

DR. KOZLOWSKI: I'd say I think I've rarely seen epidemiological data more persuasive with respect to this basic point. That's it.

DR. MERMELSTEIN: Thank you.

Okay, we will be using an electronic voting system and if you look at your microphones, you have three voting buttons,

yes, no, and abstain. So once we begin the vote, you have to press the button that corresponds to your vote and then after the eight voting members have voted, the votes get locked in, results get displayed on the screen, I'll read the vote from the screen into the record and then we will go around the table and each voting member will state his or her name and vote into the record and the reason that you voted.

(Off microphone comment.)

DR. MERMELSTEIN: Nine? Okay. Okay, we're going to begin the voting process for this first question. So again, this is we're asked to vote about the scientific accuracy of this: "IF YOU SMOKE, CONSIDER THIS: Switching completely to this product from cigarettes reduces the risk of lung cancer," and you're voting to the extent that this is scientifically accurate. So for the voting, press on your microphone, please.

(Committee vote.)

DR. MERMELSTEIN: We have a total of nine votes, eight yes, one abstention, zero noes. Okay, we're going to go around the table and asking all voting members just to explain and state your name and what your vote was and a quick reason why. I'll start with Dr. O'Connor.

DR. O'CONNOR: Yeah, I voted yes because I thought the

epidemiological evidence is very convincing.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: I voted yes because I do believe that the data is convincing with the caveat that the data that were presented were not exclusively representative of this product and it's quite possible that the other products accounted for a significant portion of the difference between smoking and smokeless tobacco, but I voted yes.

DR. MERMELSTEIN: Thank you.

Dr. Ossip.

DR. OSSIP: I voted yes because of the strength of the epidemiologic evidence, also with the caveat or the concern that we are making a statement about something that says "this product" and the evidence presented were not for this product.

DR. MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: Yeah, I voted yes because I, too, believe the epi evidence is pretty strong and consistent and even where there were some concerns about switching versus being an exclusive smokeless tobacco user, I think the other evidence was compelling enough to reduce those concerns.

DR. DUFFY: I'm Sonia Duffy and I thought the evidence was strong, so I voted yes.

DR. BIERUT: I'm Laura Bierut, and I voted yes, the evidence is very strong.

DR. WARNER: Ken Warner and I voted yes as well. I think the epidemiological evidence is extremely strong.

MS. HERNDON: I'm Sally Herndon and I voted to abstain. My focus in my work over my career has really focused on population health and it's hard for me to sort that out. Even though I see that the evidence is very strong, I'm also concerned about confounding factors such as length of smoking history, genetic risk, other risk factors such as radon, a little bit of the overlapping confidence intervals and so forth. But it's a pretty clear, simple and specific-to-lung-cancer statement and I appreciate those things about the statement.

DR. MERMELSTEIN: And I'm Robin Mermelstein and I voted yes, I found the epi data quite compelling and clear. Thank you.

Okay, great. So that was our first question. We're going to move now to our second question. So in addition to evaluating the proposed modified risk claim for the scientific accuracy, FDA also evaluates consumer understanding and the perception of the modified risk information. So our task now

is to discuss the modified risk information on consumer understanding and perceptions.

So maybe let's try chunking these and first dealing with the question of did the consumers -- do we have data and evidence that they understood what this means, which is different from did they believe it and what their perception is. But is this clearly stated, is it understandable, do we have any data that they understood this, and then we can discuss, as well, their perception of really what that means and the belief -- I think there are two parts.

Dr. Bierut.

DR. BIERUT: So looking at the Applicant's slides on page 36, I think the data have been compelling that the participants that they surveyed believed that the product is not risk free, that it's moderately to very harmful.

When they used the -- when they did the test on page 39, then did the pre- and post-test, actually what I was struck with is how little it moved and if anything, I think that there is a misperception that the product is -- that they didn't move it in the direction that I think it should be moving in, that it is a less harmful product and that it's -- I would've hoped to see it move more in that direction.

DR. MERMELSTEIN: Thank you.

Dr. Ossip.

DR. OSSIP: I agree with the lack of movement. I think it's not too surprising and I think the Applicants have pointed that out and that it was a limited exposure so, you know, I agree, these things probably take time. I think there are two other compelling questions, one is on page 35, CC-69, which is the informational -- based on the information shown in this ad, smokers who switch completely from cigarettes to Copenhagen Snuff increase the risk, reduce the risk, eliminate the risk. And so, you know, this is a question about did they understand switching completely, what it does. And the second is on page -- let's see, page 37.

How likely is it that these things happen, will happen, to a person who only uses Copenhagen Snuff daily, negatively impact health and mouth cancer, heart and that sort of thing and that's -- that produced some of the results that showed little movement. I think, methodologically, that that was a difficult-to-understand question just because of the wording, the second one, about how likely things will happen to a person but I think, also, it may take more to get movement.

I think the first question, what happens if they switch

completely, I think is a good question about what happens if -- you know, did they get that from the message. But I didn't see a question about do they understand the difference between complete switching versus dual use and I do think that that's a gap in our understanding of the extent to which the public will understand that the risk-benefits have been shown for complete switching. You know, and I don't know, from an FDA standpoint, you know, should there be some standard items that would be a part of the MRTPA to clarify, because we're likely to see more cases like this and this is, you know, really the second time that, in this round, we've seen this issue arise.

DR. MERMELSTEIN: Yeah, I think that's an excellent recommendation, that if there can be a set of standardized questions so that people -- applicants don't have to guess our minds all the

time --

DR. OSSIP: Um-hum, um-hum.

DR. MERMELSTEIN: -- that would be -- facilitate the process greatly, I think, in the future.

Dr. Thrasher, did you have --

(Off microphone response.)

DR. MERMELSTEIN: No, okay.

Dr. Warner.

DR. WARNER: Yeah. I mean, I think there's a really interesting question raised for FDA as a general question and the Applicant said that we've got to get started on educating people and that they're entering this with very strong suppositions as to what the risks are associated with smokeless versus smoking and we know they way overestimate the risks of smokeless, there's no question about that, we see that in every survey that we've ever seen and there's a very clear indication that, frankly, the government is culpable in this with the way they have marketed their anti-smokeless campaigns over the years and I'm going back, way back.

But here's the question, what are we looking for here and what are we looking for more generally in these MRTPAs if we don't see evidence that simply presenting the statement once, even though it's accepted as being factually accurate, moves the needle but it doesn't change behavior because if it doesn't change behavior, then we'll have no population health impact. But the Applicant is also correct, if we don't start saying it, we're never going to move the needle.

And frankly, I think that the needle will be moved in a more profound way if government agencies were to use some of

their media campaigns to start correcting the knowledge of what's going on in the different tobacco products. But I'm not asking as a rhetorical question, I'm very serious, how are -- if not we, how is FDA to interpret the population impact issues if you can't show population impact but everybody agrees that's because everybody's kind of stuck on this misperception of relative risk and that we need to change that perception?

DR. APELBERG: I think we would look for some input from you all on that. I mean, I think, obviously, that's a critical question and what we're here to do is to hear these questions raised and discussed. So I mean, if the Committee members do have specific feedback on, you know, how you would interpret it or, you know, sort of how you would weigh this information in making a decision, that would be something we definitely want to hear.

MR. ZELLER: A couple things to add. First, I appreciate Dr. Warner's comment, but the Committee is not here to talk about what the Agency should or should not be doing in the spirit of public education campaigns broadly. We've put a series of specific questions to you about this particular application.

But as regards the population level public health standard

in Section 911, our interpretation of what Congress wrote is if the evidence is there to support marketing authorization for any product-specific MRTPA, and these come on a product-by-product basis, then, as was described yesterday, it's qualified. Were there to be a marketing authorization, it is time-limited, there will be mandatory postmarketing surveillance, and were the Applicant to try to get a renewal after whatever that limited period of time was, they'd have to submit a new application and we'd go through this again. That's the law. That's not FDA policy, that is the law.

So to the degree that there are questions that might be best answered through things like postmarketing surveillance, just factor that into your thinking as a committee and point out to us, were there to be a marketing authorization, what are some of the critical things that would need to be looked at from a postmarketing perspective.

On the other hand, if there are members of the Committee that can't get past the issues that you've been discussing for the last day on a premarket basis, then this is the time for you to put those kinds of concerns on the table, in the context of this specific application, not in a broader setting of what the Agency should be doing from a public education perspective.

DR. MERMELSTEIN: Dr. McKinney, you had a comment before?

DR. McKINNEY: Yeah, I do, but it's a different topic. So if individuals wanted to comment on that, I'll --

DR. WARNER: Yeah, I fully appreciate what Director Zeller is saying about what our role is, but my understanding is that one of the roles of TPSAC is to try to evaluate population health impacts from the evidence that we are granted. In this particular instance, I don't see much, if any, evidence of population health impact and we can discuss that at a later stage.

But I think the Applicant's observation that the public is not taking this information which will be new to much of it and doing anything with it on a short-term basis and therefore they need to hear this more on a longer-term basis, I just don't see how -- I'm glad that we're not asked to vote on the population health impact in this particular meeting because I wouldn't know what to do with that and I would like some guidance.

I mean, I heard Dr. Apelberg say throw it back on us, on the Committee, and maybe others in the Committee have the right answer to this, but I just find this truly perplexing.

DR. OSSIP: Point well taken. I do think that within the confines of what we're able to do, a single statement like this

presented in a single setting to a group of people, you know, education alone does not change behavior, particularly single exposure, generally. So I think in that case sort of looking at trends, are there any trends that are worrisome that emerge from the data, to make sure there's an adequate assessment, to make sure that there's no obvious damage being done by that, that we can assess, but I do think we would expect that the effects at this stage would be modest.

Also, it's not in the context of a full-out marketing campaign that's likely to occur by, you know, the industry if this is approved and then the effects are likely to be perhaps different, maybe larger and maybe in different directions.

But what we have in front of us to evaluate, I think is, is it adequate in terms of demonstrating that, ideally, there are some trends in the direction that would indicate a potential positive outcome and just as important, that there are no things that look concerning to us in the initial response.

DR. DUFFY: I think, in the same way that we looked at the previous question, we have to look at this question and you're asking us did this move the needle, and I think we all looked at the data and we talked about it quite extensively and it

didn't move the needle in all these slides. So I think we just have to vote the question that they're asking us. And I hear everything you're saying, you know, we would expect that it didn't move the needle, but they're asking us did it move the needle and it didn't move the needle. So we vote what they ask us. I don't know what else to say about it.

DR. MERMELSTEIN: Right, just to clarify, we don't actually have a vote on this, we're just discussing this to --

DR. DUFFY: Oh.

DR. MERMELSTEIN: -- provide them with information.

DR. DUFFY: Okay.

DR. MERMELSTEIN: So we're not going to be asked to --

DR. DUFFY: I see.

DR. MERMELSTEIN: I think what FDA wants to hear is a thoughtful discussion about how this, you know, concerns or encouraging and --

DR. DUFFY: Okay. Well, then I would just say that, you know, from what I see here in the data, the pre/post didn't move the needle and maybe we would expect that it didn't move the needle, but if they're asking us to discuss that question, it didn't move the needle.

DR. HOLMAN: So if I could respond to that and kind of

reiterate what Mitch said a moment ago. Anytime you do a controlled clinical study you have to extrapolate from that, right, and you have to decide what's going to happen when that product, whatever type of product, gets out into the broader population.

And so that's what we're asking you to do is look at this data in this controlled clinical study and extrapolate what would we expect to happen in a broader population if we were -- for example, if we allowed the proposed labeling and advertising to go out.

And the other piece to that is, again, you know, and this is what Mitch was getting at, I mean part of that discussion is what do we think, maybe what type of surveillance would be useful to monitor that because that is a powerful tool that we have to be able to closely monitor what does happen if we were to, you know, authorize a modified risk claim.

DR. DUFFY: Right, and I think that's what people were saying, it's going to take a bigger campaign than just sticking a little piece of statement on a package.

DR. McKINNEY: As I think about the question, I think we have to consider the question in the context of the entire application. The industry is using the best available tools to

answer the question about understanding and perception, and we saw that. And then to extrapolate is a challenge that everyone faces.

So we can discuss it, but we don't know, which is why surveillance and considering surveillance is important as we consider this question unless the -- we need to work on the tools and the predictability of the tools and the studies and how we extrapolate these short-term studies to what might happen in the population.

MS. HERNDON: Thank you, Commissioner Zeller, for your clarification on that. One of the things --

MR. ZELLER: I didn't know I had been promoted.

MS. HERNDON: Oh, sorry.

(Laughter.)

MS. HERNDON: One of the things that I would like for us to consider thoughtfully, and I agree with Dr. McKinney's concern about having the industry go and recruit a bunch of youth and engage them in research, is premarket surveillance about the susceptible population at risk for any given tobacco product and we know a little bit about what susceptible population is at risk for smokeless tobacco products. Primarily rural males, definitely, and in some communities,

white, but perhaps African American and others.

And so if we could think about -- as we consider modified risk claims, think about populations at risk, young people particularly, and what they are going to get from a campaign and how that can be generalized, because adolescent brains are still forming even up to 24, where there was an oversampling -- the addictive nature of nicotine is such that it's not a completely reasoned decision that kids at that age are making when they engage in risky behaviors. So that might be one thing, to seek out some TCORs information and then I think we ought to get to the post-application surveillance question as well.

DR. MERMELSTEIN: So when we talk about special populations, I think the youth will certainly come up.

DR. BIERUT: So I want to just comment on Dr. Warner's thing of who should be giving this message out and I think that that responsibility actually falls on us, as people who are involved in this science, to get that message out and I think that that's -- you know, we have to think of that, of what is our responsibility.

But I want to pivot to the whole idea about surveillance. I'm bringing my physician hat here. I love making decisions

about when I'm going to change before -- as I'm initiating a treatment because I don't like having things bad happening and having to make the decision at that time and so I want -- I'm hoping that the FDA will be thinking at what level, like with adolescent use, I think that's the issue that we're all really worried about is the adolescent use is going to increase or -- and do you have some type of threshold that you will have, you know, if it surpasses a certain number, you know, that's when you start acting and, you know, are concerned.

And I don't know what the number is but I do look at the slide that the Applicants gave at, you know, page 49 of, you know, what is -- we know the data really well and are we going to be worrying about it doubling? What if 12-year-olds go to 2% use? You know, what is that number and a very thoughtful kind of threshold put on to that so everyone really knows what that is because that's our major concern.

DR. MERMELSTEIN: Thank you.

Dr. O'Connor, you had a question earlier?

(Off microphone response.)

DR. MERMELSTEIN: No.

Dr. Kozlowski.

DR. KOZLOWSKI: Thank you.

I'd like to make two discussion points on the potential implications of the proposed modified risk information. I view it as, in effect, sending a message that smoking is more dangerous than smokeless tobacco, as well as saying smokeless tobacco is less dangerous than smoking, and I think that message would be very positive to get out there, that smoking is more dangerous.

And I think also, as the message gets deployed in marketing, there's going to be an implication, if it's approved, of this is somehow an FDA sanction message, which I think would add weight to it. So I would expect greater impact on information that I think the public very much deserves to know. And I also think that the postmarketing surveillance issues become very important and in a review period, if we've added marketing, you don't see any movement based on providing this information, that would be most concerning.

DR. MERMELSTEIN: Thank you.

Dr. Thrasher.

DR. THRASHER: Yeah, I just wanted to comment that I do think that the statement has more support for -- more evidence for consumers understanding the message. I want to underscore that I thought that it was clear compared to other claims that

we've seen in the past, in particular. The fact that it focuses on smokers, I think, is very clear, the target for the message is clear. And so, you know, I certainly feel empathetic towards the idea of kind of getting this out and improving consumer understanding and reducing misunderstanding.

And, I mean, I guess the biggest issue is the one that's already been raised around moving the needle and then the issue of what happens with youth. One of the things that we didn't talk about yesterday that I just wanted to kind of bring up because we did talk about statistically significant results, what little there is of moving the needle, one of the questions or one of the places where we see a significant result is in reducing risk perceptions amongst the non-using young adult population.

And you know, to the extent that that's going to be extrapolated out and built into models, what I would suggest is that reduced risk perception in that particular population may result in increased use. I'm not entirely convinced that that difference is that meaningful, but I just did want to put that back on the table as part of the discussion.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: I'd like to go back to slide -- well, page

49 and I just want to talk about magnitude and population health. So there are about 84 million kids in the United States and there are about 40 million adolescents, so when we look at a figure like 1.4 and we talk about moving, to me those are -- that's a very large number of individuals. So I just don't want us to think that because, in terms of smoking rates or e-cigarette rates, that 1.4% of the youth in the United States is meaningless. That's all I have to say about that.

DR. MERMELSTEIN: Okay, thank you.

I think some of our discussion is going to be very relevant to the third question where we start to talk about what are the special populations and who should we -- you know, likelihood of switching and concern. So I want to try to summarize what I've heard so far, which I think we've probably discussed the second point which is really looking at consumer understanding and perception.

The Committee seems to have expressed some opinions that this was a clear statement and focused and that was helpful, and perhaps helping people to understand the meaning and didn't hear too many concerns other than some about what people will think about completely switching, but -- so understanding and the perception was perhaps, I think, the disappointed but not

surprised that the needle didn't get moved more.

On the good side, I think there was consensus among the Committee that there was not evidence that this did harm or that people thought that, you know, this was a risk-free product or had suddenly thought that this was great. So I don't think that there was damage, potentially, of significant note done by this statement. It would have been nice to have seen more encouraging movement but I think, as we've all said, a limited one message by a messenger that may not be the most credible, to say the least, or believable for just that one period and with limited exposure and without reinforcement by other credible sources, perceptions may be -- you know, may not move much.

But I am hearing the consensus that this was an understandable statement and it was clear. There may be things that need to be tweaked that we can certainly tweak, but not a grave concern that this was a harmful message. So I think it is a reasonable place to start in messaging.

Dr. Warner.

DR. WARNER: Yeah, I have a question and I'm sure it's in here somewhere, but I'd like to know exactly where. With regard to participants' comprehension of the claim, what was

the pretest comprehension?

I'm looking at page 35, Slide CC-70, and that is showing post-test and I mean, it was fascinating that there was no change in the likelihood of health risks on page 37, Slide 74, for any group and any disease but I just wondered, first of all, what the change was in the perception of lung cancer after the claim. And just a comment. I find it fascinating that in the last 2 days we've looked at one MRTPA that covers a whole group of different diseases and there was -- it was faulted to some extent because it also changed the bogus case, the one that wasn't covered in the list, and here we're looking at only one disease which also could be misleading to people because they might think it applied to everything but obviously, nothing seemed to change here according to the data we're presented with. What's the answer with regard to the original -- the change in lung cancer comprehension?

MR. MURILLO: Madam Chair, may I answer?

DR. MERMELSTEIN: Yes, thank you. I was just going to ask for which specific slide.

MR. MURILLO: Just give me one second.

(Pause.)

DR. THRASHER: Can I make a comment in the meantime while

we're waiting? I mean, I think one of the -- the way I interpret some of the discrepancy in the results is around the modality of the information as well. We have a 1-minute video ad talking about a new product that recently has come to the U.S. market, so people may see that innovation as also being part of the package of why it would be different compared to a product that's been on the market for 200 years, and a print ad where there's just text.

MR. MURILLO: So let me try to answer the question this way. In terms of comprehension of the claim itself -- Slide 1 up, please -- answers the question that Dr. Ossip pointed out was asked and that's our slide where we show that participants understood the claim based on the answer to the question. With respect to Dr. Warner's question, I was just making sure I understood it. If you're asking did we test pre, in general, what the risks perceptions were?

DR. WARNER: For lung cancer.

MR. MURILLO: For lung cancer, the answer is no. We only did it in the context of the claim. So if you see the risk perceptions, if I can have Slide 3.

DR. WARNER: Oh, okay, I didn't -- I missed that one. Yeah.

MR. MURILLO: I think you see lung cancer there.

DR. WARNER: So there's no change in that or in anything else?

MR. MURILLO: Right.

DR. WARNER: Okay.

DR. OSSIP: Does CC-77 address that issue? It's on page 39 of the presentation. That gives you a pre/post as well. Ken, is that what you're asking?

(Off microphone response.)

MR. MURILLO: So the focus of that is the -- again, in the context of the claim, the comparison between cigarette smoking and use of smokeless tobacco. So it doesn't precisely answer your question, Dr. Warner, but I agree with Dr. Ossip that it goes to the concept.

DR. MERMELSTEIN: Thank you. So we don't -- oh, Dr. Wackowski.

DR. WACKOWSKI: Yeah, I just wanted to echo my comment from yesterday that I still wonder if, because the pre- and post-tests were done so close in time, whether that might have sort of biased respondents to kind of be consistent with their earlier answers and kind of potentially masked the actual effect of the stimuli. And it would've been useful if this was

a more true randomized experiment or if perhaps there was a third control group that didn't see any stimuli and we had just kind of their perceptions and that could kind of serve as a baseline.

DR. MERMELSTEIN: Thank you, that's a helpful comment.

Dr. Weitzman.

DR. WEITZMAN: I'm sure everybody in the room is familiar with the Truth campaign. One particular message given and then measuring a minute later is a miniscule amount of education that the public needs if we really believe that this is going to benefit the health of the population. We need a sustained --

DR. MERMELSTEIN: Right.

DR. WEITZMAN: -- multipronged sort of effort. I'm not sure who's responsible for creating that. We didn't rely on the government for the Truth campaign. We do need scientific input about what does and doesn't work. But I wouldn't expect one message to move the needle, certainly about behavior.

DR. MERMELSTEIN: Mitch.

MR. ZELLER: Well, now I'm going to contradict my last comment that I made in response to Ken's comment, but to follow up on Dr. Weitzman's comment. When we do public education, the

first phase is building awareness and we do longitudinal evaluations, but the first effort is through what's called reach and frequency because a 1-minute exposure one time should not be expected -- I'm not talking about this application. I'm making a more general comment about when we're in the business of trying to change knowledge, attitudes, and beliefs amongst at-risk youth, the first step, once you have your baseline, is building awareness and you build awareness through some combination of reach and frequency.

And there are actually guidelines from CDC about minimum levels to achieve for reach and frequency. Only then, only then do you have the best shot at moving the needles that we're talking about here when it comes to knowledge, attitudes, and beliefs, which hopefully then are markers for behavioral intent down the road. So when we're in the business of public education, that's the frame that we bring to it.

DR. MERMELSTEIN: Thank you.

Okay, so back to this particular question, which is the implications on consumer understanding and perceptions. I think, again, back to where we were is that this was a clear statement, did not seem to have negative effects in terms of changing people thinking that this was a safe product, no

evidence of harm and -- yeah, Sally.

MS. HERNDON: One question that might be considered in light of that for postmarket surveillance, if this were approved, is to track, in an evidence-based way, the smokers who switch rather than using evidence-based tobacco treatment methods, including the combination of nicotine replacement therapy or varenicline in combination with counseling.

DR. MERMELSTEIN: Yes, I think it's always good to see why people are switching and why they might be using a product and what they're doing, it's always a good thing, so that's great.

So I think we've well discussed about understanding and perceptions and a good discussion. I'm going to suggest we take a brief break now because we have one more question to address which has to do with the potential users which I think is what we've been previewing with a lot of our comment and special populations.

So let's take our break a little early and because otherwise we'll get in the midst of a discussion, so let's take a 15-minute break and come back at just before 9:55.

(Off the record at 9:38 a.m.)

(On the record at 9:55 a.m.)

DR. MERMELSTEIN: Okay, thank you all. We're going to

move to our third primary question, which is to discuss the potential users of the proposed MRTP. And two parts to this question. The first is the likelihood that cigarette smokers will switch completely to Copenhagen Snuff Fine Cut. And then the second part is to consider the health risks from the use of it and those who may likely use it, are there groups of potential concern?

Let's just start with the first one so that we can try to have a more focused discussion, which is what's the likelihood that cigarette smokers will switch completely to Copenhagen Snuff Fine Cut. So I think I'll start by acknowledging that behavior change is tough, getting smokers to change the behavior is incredibly challenging, as most of us know.

So this isn't going to be just turning on a message and a switch and it's not going to happen so quickly and we know that for anybody to make a behavioral change, it takes a lot of concerted effort. Mr. Zeller said that it starts with awareness about what your options are and a variety of factors that may motivate people, and those motivation factors we heard yesterday are more than just risk perceptions but have to do with a specific type of product and how it's positioned and influencers and a variety of different things. So behavior

change takes a lot and one message is not going to move everything, so asking about what's the likelihood that cigarette smokers will switch completely, I think we have to make some assumptions.

And some assumptions is that (a) they have some awareness that there may be some advantages to switching and those advantages can be a variety of different motives, not just risk, and they have the opportunity to switch and that perhaps they see that as beneficial. We also know that there's an addictive component and some evidence presented about whether people get a full range of satisfaction from it.

So I'll just start with the fact that behavior change is hard, we all know that. So other thoughts that people have? It doesn't mean -- we also know that quitting smoking is hard. It doesn't mean that just because it's hard we don't encourage people to do that. So just think about that.

Dr. Warner.

DR. WARNER: Thank you.

So I think that's the principal insight of the 2 days is behavior change is hard. We all appreciate that and I think that's very important. The only place where I think the Applicant has embedded their perspective on behavior change, to

my knowledge, is in the model, the simulation model, is that right? So I do have a question about that. I was thinking about this last night.

You said, when I asked how many life-years were saved, you said it was about two million and that implied roughly 20 years per beneficiary. That would suggest, to me, the risk that there's a problem with your modeling this because that assumes that the people who switch -- and I assume you're assuming no health risk to the person who switches, right, for the base model, basic case?

DR. BLACK: For someone who switches to smokeless?

DR. WARNER: Yeah.

DR. BLACK: There would be 9% risk that of cigarette smoking.

DR. WARNER: Okay.

DR. BLACK: Yeah.

DR. WARNER: So here's the question. I know this from our own modeling work when we've looked -- we published a paper recently on the e-cigarettes and their impact and one of the things that surprised me, but not so much my co-author, was the very small percentage impact in terms of the overall burden of smoking. And we realized one of the reasons for it is that

people in the model, the way the model was built, some of them who switched to e-cigarettes and hence, quit smoking would have quit smoking anyway 2 months, 2 years, 5 years later and that cuts off much of the benefit. If you're seeing 20 years you're not accounting for the fact that some of these people who would've switched are, in fact, people who would've quit anyway, right?

DR. BLACK: So we actually took into account two hypothetical transitions, one of which was would-be quitters being intercepted by the claim, and we assumed that 5% of the would-be quitters would be intercepted. It had a small impact, but we did take that into account.

DR. WARNER: But do you see what I'm saying? If we look over time, a large percentage of the people who switch, that a lot of people who switch may quit smokeless, too, but a large proportion of the people who switched to smokeless would have been quitters without anything over a relatively short period of time and that necessarily cuts into your 20-year figure by a lot, as it turns out, unless you're saying that the only people who are switching are people who would not quit otherwise, at any point. So I'm concerned about the model because that's an impossible outcome if you are allowing for people to have quit

at a later stage without the smokeless. And obviously, one of the concerns here has to be is this an alternative to quitting, so why is that not in the model or what's missing? Pardon?

(Off microphone response.)

DR. WARNER: Well, the reason I'm asking that is they're predicating their notion of population benefit on this model and it seems to me -- I don't know the model, I'm handicapped in that sense, but it seems to me that there has to be a problem with the model to come to the result that there's a 20-year benefit per person who switches. Twenty life-years.

DR. MERMELSTEIN: I think, though, partly let's first deal with the question then, and I can appreciate that, that in terms of the population benefit of -- is that an overestimate is what you're asking?

(Off microphone response.)

DR. MERMELSTEIN: More than that, yeah, yeah. Is there a very quick succinct answer to Dr. Warner's question?

DR. WARNER: Do you understand my concern?

DR. BLACK: I do understand your concern.

DR. WARNER: Okay.

DR. BLACK: And we took into account the would-be quitters being intercepted. We set that at 5%. I think what I'm

hearing you say is that that could have been even higher and if that were true, then the model prediction would be an overestimate. Absolutely.

That said, we did sensitivity testing on initiation against switching and if you could pull up Slide 2, we see here that with an increase of even 100% in initiation, switching, you'd still have a net benefit. In fact, with respect to initiation, you'd have to see an increase up to 250% to offset that very, very modest impact, modest impact of switching. But specific to your question, can we pull up Slide 1?

DR. WARNER: Yeah, that one did not address my question.

DR. BLACK: Yeah. In Slide 1, this is the would-be quitter and so as you see here in our modified case, we assumed a 5% impact. But if there were 100% impact, that would obviously reduce the number of premature deaths prevented and, of course, translated to the years of life are saved.

DR. WARNER: Okay. Well, I won't pursue this now, but I would like to understand the model better. This doesn't feel right to me.

DR. MERMELSTEIN: Okay, thank you.

Dr. McKinney.

DR. McKINNEY: There it is. As I look at the question

what is the likelihood that cigarette smokers switch completely to Copenhagen Fine Cut, and perhaps because of the length of time the product was on the market, but I thought there was a slide that actually showed that smokers do switch completely, even without understanding the relative risk. So it has happened already. But I guess the question is whether or not the claim would further drive that or influence that.

DR. MERMELSTEIN: Okay, thank you.

Dr. King.

DR. KING: Yeah, so I'll start with a quick anecdote. I was talking to my 5-year-old nephew this weekend and he asked me what I was doing this week and I said I'm going to TPSAC and I spelled out what everything stood for and he stopped on the science and he said, so you advise people on science. The S is critical. We're not TPAC, we're TPSAC. And so I think that when we look at this, we have been directed by Congress to convene and discuss the science and that being said, I think for this particular question I'm not convinced the science is as robust as it could be.

And so if you were to ask me to answer this question, I would say the likelihood is probably low. And sure, you know, I'm not expecting a randomized clinical trial, but there's a

lot of ways that we've evaluated the efficacy of things to help people quit over the past several decades, whether it be NRT or even the growing body of literature on e-cigarettes.

And when you look at the literature on the issue of cigarette smokers transitioning to smokeless, it's not that hot and what you see is a lot of dual users and I would argue that it's probably been more robust for e-cigarettes in terms of efficacy than smokeless tobacco. And so I think that that's very important when we have this discussion about what's the likelihood that cigarette smokers will switch completely. There's a lot of theoreticals that are going into the underlying assumptions of the model, which I share the previous concerns around a lot of the parameters in that model. But if you asked me to answer this question based on the existing science, even if you generalize for all smokeless tobacco, I do not think that there is a high likelihood that cigarette smokers at the population level would transfer over. Even if you did educate them based on the current available science, which is what our purview is, it's not there.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: So I look at this question and I have kind of two parts to it, is I how think, that is, you know, who's

really willing to move from cigarette smoking to smokeless tobacco. And cigarettes are really a very nice product in that sense of, you know, quite addictive and, you know, really quite enjoyable.

So one is I don't think a lot of smokers are going to switch just because of, you know, the difference in the product and, in particular, women are really -- I really don't see women using this. And then the second part of the question is if someone is using it, what's the likelihood that they're going to completely use it, and I think that, you know, I would look at the data of what the dual use is that has been presented and, you know, there's a good chunk of dual use but there are people who do transition, you know, completely into this product. So my first part that I looked at is, you know, we're not transitioning all the people into this product but if they do transition, you know, a good chunk remain dual users, but a good chunk do completely quit.

DR. MERMELSTEIN: Right, and I think we're talking about low percentages of complete switch and then on the population level low percentages, too.

DR. WARNER: This is not under the purview of this particular conversation or particular MRTPA, but we do have one

example where there's been a lot of switching to smokeless tobacco and that's Sweden. And I've recently been corresponding with a couple of the experts in Sweden about that and one of the things that they have pointed out is that there was a huge price difference early on, not so much now, but that early on they were taxing cigarettes very heavily, they were not taxing snus much at all and it was -- this was actually relatively shortly after the original Surgeon General's report and the Royal College of Physicians' report. So there was a lot of publicity about the hazards of smoking and then they encouraged the switch by -- it may be unintentionally, by virtue of price policy.

DR. MERMELSTEIN: That's it, there are lots of conditions you can encourage people to change behavior, that's very true.

Dr. Thrasher, then Dr. Ossip.

DR. THRASHER: I guess the data that I see that is most relevant to this question is on CC-86 where the Applicant presents information from their study looking at the change in the likelihood of behavior amongst adult smokers and that's the table that we discussed a while ago, but there's no statistically significant results, but the idea is that, presumably, these are reasonable estimates. They then get

built into the models that Dr. Warner was discussing and a little bit concerned about.

What I find surprising about this table is that dual users switching to Copenhagen is substantially lower, if you trust these point estimates, than cigarette smokers switching to Copenhagen. I would think that if this was to be more compelling, that the people who are already dual-using would be more likely to switch over than the people who are currently cigarette smokers and maybe they've tried smokeless or maybe they haven't, but it just makes me question the use of these data to just kind of drive some of the modeling around this issue.

DR. MERMELSTEIN: Dr. Ossip, did you have --

DR. OSSIP: Yes, thanks. Two other bits of information. One is getting back to a point that I had made earlier, that even from the understanding or knowledge level, we don't really understand the extent to which the consumers would understand that the health benefits come from complete switching versus dual use. So I think that's a gap in the evidence base of what was presented, what was collected and what was presented.

The second is, in the FDA's analysis, they looked at data around abuse liability and based on the literature identified

that this product -- the abuse liability of this product is likely somewhere between cigarettes and nicotine replacement products. And so the projected likelihood or expectation would be that it would make it more amenable to dual use rather than complete replacement on the population level.

DR. MERMELSTEIN: Other comments about the likelihood that cigarette smokers will switch completely?

Dr. McKinney.

DR. McKINNEY: If I recall correctly, the PATH data suggests that they're four times more likely if they have accurate information about the product. That's my recollection of the PATH data.

DR. MERMELSTEIN: So it sounds like what we have known is that yes, some people spontaneously, in the current condition, can switch and do it. They're not high percentages, but it's not unheard of that that happens. Some people become dual users and we know that. So the question is, if you change some of the environment in terms of the messaging and other factors, might that increase? You know, that would be one potential thing, but its probabilities are on the lower side, perhaps.

DR. OSSIP: But I do think that issue of dual use is a concern. I don't know what the recommendation is, other than

having a robust discussion of it here for the FDA. It may influence their decision making or even moving forward. But that is an important issue because the health benefits have been demonstrated for complete switching. And so to the extent that any change in product labeling or product marketing or any characteristics of what's being presented to the public that is not accompanied by very robust messaging and marketing and assessment of impact to really move to get that message out and to support users in moving to complete switching versus dual use, I think without that we may have people who are thinking they're doing something to reduce their health risks but, you know, they're sort of confusing action with progress and in a dangerous way.

DR. MERMELSTEIN: Dr. O'Connor.

DR. O'CONNOR: So one thing I've been thinking of is how would you know, in a sense of, you know, assuming a claim like this goes live and you're now tasked with doing postmarket surveillance, how would you tell how many smokers are switching completely without having longitudinal cohorts where you could actually look at people who you knew smoked at baseline and then followed their transitions over time?

You know, you could look at things like Nielsen data and

market share and you would expect to see if the claim is working as it's intended. The market share for Copenhagen should go up and it should be eating into overall cigarette market share. If that doesn't happen, then smokers probably aren't switching completely. And you've got to think about, too, you know, who is doing the buying and who's using these products. So it's hard for me to separate the question of what's the likelihood versus who are those cigarette smokers who are going to do it and then how do you assess that as an outcome is what constitutes switching completely in a postmarket context where you're not following individuals but you're trying to assess population trends.

DR. MERMELSTEIN: So that's a good point because I think that clearly the appeal of the product varies by the population and subpopulations and so I think what you're saying there is we need a little deeper dive and fine-tuning some of post-surveillance with oversampling of populations that you would think would be more likely to show some change or have this product so that we could really see are we impacting the populations that are -- who might benefit or be most vulnerable. So you're, I think, saying that the postmarket surveillance needs to be a little more targeted and in depth of

subpopulations. So I think that brings us to the second part, who are the groups that --

DR. KOZLOWSKI: Excuse me, can I make one comment, Robin?

DR. MERMELSTEIN: So yes. Yeah, go ahead, Lynn.

DR. KOZLOWSKI: As I think about the likelihood of who will switch completely, I am concerned about those dual users right now who might be moving exclusively to cigarettes away from dual use, because in some cases they're concerned that smokeless tobacco is more dangerous than cigarettes. And so I think there's a group there that's not large that this information might help prevent dual users from movement to exclusive smoking, away from dual use.

DR. MERMELSTEIN: So, Lynn, I think you bring up a really good point, which is somewhat echoing your earlier point that we have to remember both sides here of the point and that we don't want people misperceiving the relative risks of smokeless and resorting back to just mostly combustible use. So it's an excellent point.

Dr. Wackowski.

DR. WACKOWSKI: Just another comment I had or thought about the potential for complete switching is about the claim itself. So you know, we've said that it's relatively simple

and it focuses on lung cancer, which helps its accuracy and simplicity. The flipside of that is, I think, that that could also somewhat limit its potential impact on complete switching because we know that even if smokers accept that it has a lower risk of lung cancer, they're worried about oral cancer risk, which they perceive as being higher or more likely. And so it can be this sort of cancelation effect and I think that can potentially hinder the complete switching. So it's really this double-edged sword, I think.

The other potential consideration with respect to complete switching is, you know, I'd say much -- this particular product, the fine cut snuff, we know can be not the most acceptable product for smokers to use even within the moist snuff category, and so that's another potential consideration.

DR. MERMELSTEIN: Thank you.

Dr. Ossip.

DR. OSSIP: I want to pick up on your first point because I think it really raises an interesting issue which is, what information do consumers have a right to have to influence their decision making to the extent the decisions are guided by, you know, some sort of reasoning? Do they have the right to data on what the actual risk is for particular conditions,

for a particular product, whether it was switching with dual use? So they're getting messaging that this is not a safe product, it's not an alternative versus substitute for cigarettes, it reduces the risk of lung cancer, it can cause oral cancer, but how do you -- but how much? You know, what does -- so you know, I'm thinking if I'm a person trying to make that decision and I want to sort of weigh the health risks, the health benefits, I don't have anything on magnitude, I don't -- you know, the question is so which way am I better off.

And, you know, do consumers have a right to have more specific information to help them make that decision about which way am I better off? You know, am I more worried about getting an oral cancer than I am about getting a lung cancer or -- like you're saying, I'm reducing my risk for lung cancer, but the increase in risk of oral cancer is so great that I'm going to be in bad shape either way and often when people are in a lose/lose situation, they just shut down and disengage from the data or the information that's being presented.

DR. MERMELSTEIN: It's always tough to have that balance of giving accurate -- but you can never give personalized, exact guarantees.

Sally.

MS. HERNDON: I have a procedural question about the process and it was spurred by Dr. Warner's comments earlier about price differential in Sweden. I know that from my experience, from a lot of the investments that the tobacco companies make in advertising, they're beyond what I have seen here of these -- you know, these fairly simple advertisements and go primarily to price promotions where there are discounts.

Juul, in my neighborhood has, you know, said turn in your cigarettes and we'll give you coupons off your first Juul, things like that. If this were approved, are there opportunities for price promotions or is it approved by the simple advertising that's been presented here? I didn't see any price promotions in the proposal.

DR. APELBERG: Sorry, we just had to confer. So, yeah, I mean, I guess just at a high level, the pricing, you know, structure and strategy isn't really within the realm of the MRTP review process. However, you know, discussions of marketing strategy, understanding what the marketing strategy is, you know, would influence our, you know, evaluation of what the likelihood of these different impacts might be.

So, you know, it could be something that would come up,

you know, as part of what a company proposes to do to make the argument that they -- you know, they're going to be directly targeting and influencing the smokers. I think Dr. Thrasher had the -- you know, had the comment yesterday to the company about considering, you know, if a product were authorized, like, you know, are there other ways to sort of directly market to current smokers.

So, you know, I think broadly, it's sort of part of, you know, what we would assess, you know, in terms of what kind of impact we think this might have.

DR. MERMELSTEIN: Back to the question at hand. I just want to make sure that we're covering the ground of are there special populations of concern, youth being the obvious one.

I think we've multiply said the need for tracking youth. You know, former smokers, just to ensure that we're not seeing former smokers. I think those are, you know, the critical populations. One of the other options posed to us is what about users of other smokeless tobacco products that may have lower HPHCs, are they a population that we have some concerns about, that if people switch from one brand to another, one product to another, is that something, since that was posed to us, that we would want to track as well?

DR. OSSIP: I was thinking about that, and maybe it's possible that's a timing issue. So if, let's say, this MRTP were to be approved ahead of an MRTP for a lower HPHC product and have a robust marketing campaign around the new labeling, it could shift users within groups who may establish sort of a new brand loyalty.

It's possible when, you know, the alternate product that they had been using -- you know, they get their MRTP approved and they have their market, that they'd switch back. But I think that would be a risk and it would be due to timing.

DR. MERMELSTEIN: Dr. McKinney.

MR. McKINNEY: When we talk about the HPHC levels and I think about risk, which is exposure and hazard, we're talking about exposure and as I recall, looking at the epi data between the two products, it wasn't significantly different in terms of the relative -- the risk of the products and compared to cigarettes. And so we can focus on the absolute risk, but I think the relative risk here is probably more important and if the constituents are within 2% of one another and not having an impact on the epi data, I mean, I'm a little bit confused about the question and the relevance of the question.

DR. APELBERG: Yeah, I guess I just wanted to jump in. I

mean, speaking of the epidemiological literature, I mean, there is some evidence that suggests there may be differences in risks, you know, from the epi literature comparing U.S. -- traditional U.S. smokeless tobacco to Swedish snus or Swedish products, for example.

So it's really just trying to -- you know, if that's the case and the differences that we've observed and pointed out in terms of the HPHC levels are impacting risk, to what extent, you know, do we need to be thinking about that?

How important is that, you know, in the consideration of what impacts, you know, a claim on, you know, a product that isn't necessarily at the lowest end of the smokeless tobacco marketplace, you know, for HPHCs, what impact might that have and how concerning would that be?

DR. McKINNEY: But that's also making an assumption that those particular constituents are the cause of a particular disease, which it's a link that I don't know that's necessarily been established and the use patterns are different, which is so many unknowns. And the epi data is not -- as far as I recall, not significantly different between those two products and I know the Applicant has some slides that can show that, but --

DR. JOHNSON: One of the most important things to keep in mind here is, is that the epidemiological data from Sweden was developed with a product that's very substantially different in terms of HPHCs from the product that they're currently selling today. They've had a concerted effort over a number of years to reduce those levels and it's a laudable goal and we should all do that, okay?

But the epidemiology that says that it's not creating an unreasonable risk to health was a product that was very similar in terms of HPHCs to the current U.S. moist snuff products. And that was a point made by Swedish Match in the presentation that they made yesterday. If you go back and look at the data, you'll see that that was the case.

So it's not a major difference in HPHCs that's going to drive that and I think it's more what is the product, what is it like, how does it fit into their lifestyle, it's going to be a varying process.

DR. MERMELSTEIN: Thank you.

Dr. -- oh.

DR. APELBERG: Can I just speak for one -- one follow-up to that? I mean, for sure, I think that the -- you know, we've had discussions at this meeting and at previous meetings around

the smokeless tobacco literature in terms of how do you -- you know, how did the product today compare to the historical products that were used during the time of those epi studies both in the U.S. and in Sweden and that, of course, is a challenge.

But I think, I mean, the basic premise is, all things equal, you have an oral tobacco product, if it varies in, you know, what we know are harmful or potentially harmful compounds by three, fourfold, you know, the assumption is, is that it's likely to impart some difference in risk whether it's -- you know, the magnitude of that I think we could argue about but, you know, I guess I'm just not sure if you're arguing that the variation in HPHCs don't really -- aren't expected to translate into differences in risk.

DR. JOHNSON: I'm not arguing that. What I'm saying is, is that when you look at the epidemiological data from Sweden you need to put that into context, what was the product that was actually consumed, what was the level of the various HPHCs that were present in those products when that was being done because that's the relevant exposure for the group that was involved in that study.

DR. MERMELSTEIN: Dr. Stepanov.

DR. STEPANOV: Well, I just -- you know, when we talk about HPHCs, we primarily probably think about tobacco specific nitrosamines and I just wanted to point to a specific study that looked at the relationship between what's in the product, the levels of nitrosamines in the product, and biomarker-based assessment of exposures and it is independently associated with level of exposure, so after adjustment for patterns of use and all other factors. So it is a driver.

Levels of these compounds in the product are directly influencing level of exposure and we do have some prospective epi studies showing that the level of exposure does predict risk of developing corresponding cancers in tobacco users. So it would be -- and if you look at the question, it's groups of potential concern. So I think from that point of view, people who are using lower HPHC-level products, who could switch to Copenhagen, would be that population of potential concern.

DR. MERMELSTEIN: So what we heard yesterday was that there may be user characteristic differences in, obviously, people who use the different products and that some of the Swedish products may appeal to, perhaps, people who are a little more educated or, you know, who may have other resources but they may have a variety of different characteristics than

people who -- for whom the Copenhagen product -- so if that concern is there, I think we can certainly look at different, you know, different user characteristics and how they may play into the product choice, but I think there are differences among those.

So I think all that is saying that the postmarket surveillance in this particular -- given that we're talking about relatively small percentages of the population compared to, say, smoking, means a more challenging postmarket surveillance task for you and, you know, drilling down to identifying who are the potential users and who are likely, so that you may need to do more targeted ways and strategies of indentifying those individuals who are potential switchers.

Dr. Thrasher.

DR. THRASHER: Yeah, I mean, just reflecting on the postmarket surveillance issue, and I guess we're brainstorming a little bit about what would be some good indicators, it just makes me think about how the industry often rolls out marketing campaigns and new products in specific markets and does their own kind of quasi-experimental studies to evaluate new products and new campaigns.

And I don't know whether it's in the -- within the purview

of FDA to think about encouraging that kind of a rollout where you could have relatively comparable groups and looking at sales volume in different markets, whether the market is getting the campaign or not, or getting the modified risk claim or not.

And, again, industry is used to doing that kind of a thing and Altria is particularly well situated to look at this issue given that they have data on both cigarette sales and on the proposed product here, and it seems to me like that would be a reasonable request.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Another group that I wonder is a potential group would be -- given that this product involves expectorating or swallowing, are there -- might there be concerns about others who are not users but are, you know, like the secondhand exposure variant, so youth or you know, children or infants. And I don't know the answer to that, but it's a -- given that there's expectorating. I mean, perhaps for people who swallow, might there be some unique risks, as well, of not expectorating?

So I don't know if there are data, you know, we didn't see any, and I just don't know this portion of the literature very

well about are there concerns for, particularly, children and youth who may be exposed to what gets expectorated.

DR. McKINNEY: Is that a question for the Applicant, if they have an answer? I'm asking Dr. Mermelstein. Or is that just an open question?

DR. MERMELSTEIN: I think it was just an open question.

DR. McKINNEY: Okay.

DR. BIERUT: So one of the themes that we've had in these past 2 days is getting data out to people, getting data out about lower-risk products and I think, following on that theme, I think we should be thinking of the HPHCs and the levels of HPHCs in the products, that it's reasonable for the consumer to know what the different products' HPHC levels are if we really want to move towards harm reduction and be as open and transparent as possible.

DR. STEPANOV: I wanted to follow up on the question about secondhand exposures. I know there has been one or two studies looking at levels of nicotine and NNK, I believe, in houses of smokeless tobacco users and it is definitely a source of exposure, but I don't think it's higher than secondhand smoke exposure. So, you know, if you think about people switching from smoking to smokeless tobacco use it would not lead to a

particular concern in elevated -- for elevated exposures in kids living with these individuals.

DR. MERMELSTEIN: Yes, Dr. King.

DR. KING: Yeah, so I just want to revert back to a lot of the discussion that has been had on the postmarket surveillance and I'd just like to comment that I think a lot of things can be handled before we have to clean it up on the back end. And so I think, going back to the model, there's a lot of concerns with that approach and I completely agree with the variety of populations that have been named in terms of, you know, vulnerable populations that we need to consider but why could those not have been accounted for at the onset so that we could see what the differential impact would be on the population?

And I think that it's an incredibly low bar to say that well, something just doesn't have an effect, so that's not a problem, because we don't really know if it doesn't have a negative effect because all we've assessed is a certain population and not accounted for the other vulnerable populations.

And I'll sound like a broken record, but the youth issue continues to concern me. After I was ceremoniously cut off yesterday, I did do my own homework after I didn't get an

answer and the youth data were from the Teenage Attitudes and Practices Survey, which is a phone and mail follow-up to a household-based survey. So there's still potential concerns around the youth data not being representative. And we heard a 1.4 estimate earlier, but it's actually 5.5% of smokeless tobacco users, so it's quite high, 1 in 20 kids.

And so this is just to reinforce that there's a lot of concerns with the model. This has been, you know, a primary crux to justify what the population-level impact is, which is what the congressional purview is, is population-level impact and I am concerned that this is, you know, just scratching the surface and, you know, I feel like we've been invited to the house and based on what we've seen on the front porch, I can't fathom what atrocities exist in the basement. So I'd like a little more detail on the parameters to ensure that what we've inputted is the most scientifically robust to ensure that on the front end we're making a fully scientifically informed choice besides just saying well, we're going to let it go on the market and see what happens and clean it up on the back end.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: First, I agree with that, I think you stated

that beautifully and I agree with that point. Around the issue of modeling, I want to get back to a point that I had made earlier about how do consumers make decisions, how do they weigh the evidence that they're given and what that means for them in terms of a switch, which way they're better off.

And I wonder, couldn't there be some modeling done even if it's by large population groups for women versus men for different age groups, you know, women, young adult women, middle-aged women or males, by whatever -- however you want to cut it, could there be models that might look at the "where do you have a net benefit from which kinds of decisions." So here in the case of Copenhagen Snuff, if you were to switch, if you were to dual use, if you were, you know, in each if they've already divided into various categories if you're a smoker switching, if you're a dual user who's considering switching.

So at least with some large cuts you can't give -- we're not at the stage of being able to give personalized information to each individual, but it seems like we could be able to model some more -- somewhat more fine-grained analyses to assist in decision making, because what I think consumers care about in the end is which way am I better off and it's a little hard to judge, I think, based on the -- the generic knowledge is good

and it should be given out as it is, but it does make it challenging to make informed decisions and there may be additional levels of analyses that could facilitate that.

DR. MERMELSTEIN: Dr. Bailey.

DR. BAILEY: I just want to --

Dr. Stepanov's comment about secondhand exposure with smokeless tobacco product, I'm just trying to say what would be the means of secondhand exposure from smokeless products compared to secondhand exposure to cigarettes. I'm just trying to see how -- you know, what's the secondhand exposure from smokeless products?

DR. STEPANOV: Yeah, the study that I mentioned looked at surface deposition of nicotine and NNK on surfaces in the household dust of smokeless tobacco users and so the source would be just handling the product if it's loose from the pouches, you know, there could be some deposition from handling the product at home.

And as I said, levels of these compounds were probably comparable, maybe a little on the lower side than in houses of smokers. So that's why I said that it would not be a potential elevated concern for secondhand exposures in children living in these houses.

DR. MERMELSTEIN: Dr. Kozlowski on the phone.

DR. KOZLOWSKI: Yeah, I just want to make a comment about women as a special group. I do note that cigarettes have a warning with respect to pregnancy concerns and I don't believe smokeless tobacco products do and something like that should be considered. It's separate from this particular initiative, but it is a lack of a warning that might be constructive on smokeless tobacco.

DR. MERMELSTEIN: Good point. Thank you.

Other thoughts about other populations of concern?

Sally.

MS. HERNDON: Just to reiterate the previous comment. And so I think some populations of concern are those smokers or other tobacco users or at-risk populations who see this as an opportunity to hide their use, whether they're in a situation where there's a smoke-free policy or, you know, in a home environment or a work environment or public policy environment or with populations who may feel vulnerable by showing their smoking in public, such as pregnant women. So I just want to reiterate that comment.

DR. MERMELSTEIN: Okay, thank you.

Dr. Ossip.

DR. OSSIP: And although we haven't talked much about this, perhaps people who would initiate with this form of tobacco, who might interpret the risk messages meaning, you know, this is something relatively safe or safer for initiation. And I think based on the comment we heard before, it would be an issue, then, not only for the initiator but there would be potential secondhand exposure for other people in that person's household.

DR. MERMELSTEIN: I think the secondhand exposure was less of a concern.

DR. OSSIP: Right, but if it's not -- if it's comparable even on the low end to cigarette smoke --

DR. MERMELSTEIN: Um-hum.

DR. OSSIP: -- I mean, if it's in a previously non-tobacco using household and someone were to initiate even with the smokeless tobacco, it would raise concerns not only for the user, but also for others in the household, even if they are initiating --

DR. MERMELSTEIN: Right, right.

DR. OSSIP: -- with what seems to be a reduced risk product.

DR. MERMELSTEIN: So I think we've all acknowledged that

it can be challenging for the cigarette smokers to switch and that this may be a process over time, that we need to monitor and perhaps drill down on some special populations, certainly looking at change in initiation patterns among youth and young adults and different age groups and former smokers and people who may be more prone anyway to be using the smokeless tobaccos and looking at their transitions across products. So although it's good to have premarket to take care of these issues and ensure that we don't have that mess, as Dr. King says, to clean up, I think it's a combo of both. We never can fully anticipate everything, so trying to think through the populations, who we are most likely to see some effect of change, positive and negative, would be good.

But I think the Committee has done a great job at thoroughly discussing the questions. I hope this has been of benefit to the FDA. I don't know if you have any other questions for us or thoughts.

MR. ZELLER: I don't have any questions. I just want to close with some words of thanks to all participants over both days, the two companies that presented, the incredible FDA Office of Science staff that presented both days, and biggest thanks to the members of the Committee for your preparation,

really quality questions and discussion, all the public participants over the course of the 2 days. This was an extremely productive and, under the Chairman's watch, efficient use of the last day and a half. So on behalf of everybody at FDA and CTP, just a big thanks to everyone.

DR. MERMELSTEIN: Thank you. And thank you to all the applicants for your time and thought, thank you.

Okay, I think we're adjourned.

(Whereupon, at 10:43 a.m., the meeting was adjourned.)

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 7, 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.

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TIMOTHY ATKINSON,

Official Reporter

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