

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

April 9, 2015
8:30 a.m.

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Building 31, Room 1503
10903 New Hampshire Avenue
Silver Spring, MD 20993

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M E E T I N G

(8:29 a.m.)

DR. HUANG: Good morning. We'll go ahead and get started.

I'm Phil Huang. I am the Acting Chair of the Tobacco Products Scientific Advisory Committee. And good morning to everyone, and thank you all for joining us. I want to make a few statements, and then we'll introduce the Committee.

First, 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. So our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that 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 the Chair. And we look forward to a productive meeting.

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

We're 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

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media until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topics during breaks. Thank you.

So now I'll turn it over to Caryn Cohen about the conflict of interest.

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 members from other agencies, two industry representatives, and a representative of the interests of tobacco growers.

With the exception of the industry representatives, all Committee members are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with applicable Federal ethics and conflict of interest laws including, but not limited to, those

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found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

Today's agenda involves 10 modified risk tobacco product marketing order applications filed by Swedish Match North America. This is a particular matters meeting during which specific issues related to these applications will be discussed.

All members of this Committee, with the exception of the industry representatives, have been screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Based on the agenda for today's meeting and the interests reported, FDA has determined that the screened participants are in compliance with applicable Federal ethics and conflict of interest laws. As such, no conflict of interest waivers under 18 U.S.C. Section 208 have been issued in connection with this meeting.

With respect to FDA's invited industry representatives, we

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would like to disclose that Drs. James Swauger and Michael Moynihan and Mr. Hampton Henton are participating in this meeting as non-voting industry representatives, acting on behalf of the interest of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively. Their role at this meeting is to represent these industries in general and not any particular company. Dr. Swauger is employed by RAI Services Company, Dr. Moynihan is employed by Goodrich Tobacco Company, and Mr. Henton is owner/operator of Henton Farms, Incorporated.

To ensure transparency, we ask that all Committee members disclose any public statements that they have made concerning the product at issue. We would like to remind all screened Committee members that if the discussions of today's meeting involve any other products or firms not already on the agenda and for which a screened member has a personal or imputed financial or other conflict of interest, they will need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that they may have with the firm at issue.

I would like to remind everyone present to please silence

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your cell phones if you have not already done so. If you are calling in, please keep your phone on mute unless you are speaking.

I would also like to identify the FDA press contacts. They are Jeff Ventura and Tara Goodin. If either of you are here, please stand up.

MR. VENTURA: I'm here.

MS. COHEN: Thank you. Thank you.

DR. HUANG: Great. Thanks, Caryn.

Now we will go to introduction of the Committee members. And, first, I'm again Phil Huang. I'm the Medical Director and Health Authority with Austin/Travis County Health and Human Services Department in Austin, Texas, and for this meeting I'm serving as Acting Chair.

And so we'll start around the table. And I guess, Mitch Zeller.

MR. ZELLER: I'm Mitch Zeller, Director of the Center for Tobacco Products at FDA.

DR. ASHLEY: David Ashley. I'm Director of the Office of Science in the Center for Tobacco Products at FDA.

DR. CHOINIÈRE: Conrad Choiniere. I'm the Director of the Division of Population Health Science within the Office of

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Science at CTP.

DR. TOMAR: Scott Tomar, Professor, University of Florida.

DR. BOFFETTA: Paolo Boffetta. I'm a professor at Icahn School of Medicine in Mount Sinai, New York.

DR. NOVOTNY: Tom Novotny. I am a professor in the Graduate School of Public Health at San Diego State University.

DR. BICKEL: Warren Bickel. I'm Professor of Psychology at Virginia Tech.

DR. O'CONNOR: Richard O'Connor, Associate Professor, Roswell Park Cancer Institute.

DR. FAGAN: Pebbles Fagan, Associate Professor, University of Hawaii Cancer Center.

MS. COHEN: Caryn Cohen, Designated Federal Official for the TPSAC.

DR. GIOVINO: Gary Giovino, Professor and Chair in the Department of Community Health and Health Behavior at the University of Buffalo.

DR. EISSENBERG: Tom Eissenberg. I'm Professor of Psychology at Virginia Commonwealth University.

DR. RIBISL: Kurt Ribisl, Professor at the UNC Gillings School of Global Public Health.

DR. DJORDJEVIC: Mirjana Djordjevic, Program Director at

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NCI and National Institutes of Health.

MR. TIPPERMAN: Doug Tipperman, Public Health Advisor, Substance Abuse and Mental Health Services Administration.

MR. HENTON: Hampton Henton, Versailles, Kentucky, grower of burley tobacco.

DR. MOYNIHAN: Michael Moynihan, Vice President of Research, Goodrich Tobacco.

DR. SWAUGER: I'm Jim Swauger. I'm the Vice President of Regulatory Oversight at the RAI Services Company.

DR. HUANG: Okay. Welcome, everyone.

And I think now we'll move on to opening remarks from Mitch Zeller.

MR. ZELLER: Good morning. On behalf of the Food and Drug Administration and the Center for Tobacco Products, I want to welcome everyone here today and tuning in to the webcast to this important meeting of our Tobacco Products Scientific Advisory Committee.

Today marks a historic moment. The Tobacco Products Scientific Advisory Committee, or TPSAC, will discuss modified risk tobacco product applications submitted by Swedish Match North America for 10 tobacco products. These are the first-ever MRTP applications to be accepted for filing by the FDA and

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referred to TPSAC for recommendations in accordance with Section 911 of the Federal Food, Drug and Cosmetic Act.

Congress gave FDA an important responsibility when it came to review of tobacco products seeking to make health-related claims. Congress granted FDA the authority to review modified risk tobacco product applications to ensure that claims and marketing about the risks of tobacco products are substantiated and supported by the scientific evidence, so that the public are not again misled about the relative risks of tobacco products, as was the case with low-tar and light cigarettes.

Congress specifically found that many smokers mistakenly believed that cigarettes marketed as low-tar or light caused fewer health problems than other cigarettes. However, scientific studies have demonstrated that there was no reduction in health risk from such products and that these products may actually have increased the risks of tobacco use.

Furthermore, the marketing of these products encourage those who may have otherwise quit smoking to switch to light cigarettes, and encouraged greater numbers of non-smokers to experiment with and initiate cigarette smoking.

Congress set high standards for modified risk tobacco products. In the statute, referring to the evaluation of

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potential MRTTP claims, Congress stated that "It is also essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria."

Applicants must not only demonstrate that the products, as actually used by consumers, will significantly reduce risks to individual users of those products, they must also demonstrate that they will benefit the population as a whole, taking into account both users and non-users of tobacco products.

This means that when assessing the impact of modified risk marketing, FDA must consider the potential impacts on the likelihood that users who would have otherwise quit tobacco use will instead switch to the modified risk tobacco products or become dual users, and on the likelihood that non-users of tobacco products will initiate tobacco use with the modified risk tobacco products and that some will move on to use other tobacco products.

Congress further found that "Permitting manufacturers to make unsubstantiated statements concerning modified risk tobacco products, whether express or implied, even if accompanied by disclaimers, would be detrimental to public health."

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But there is an additional important perspective that must be acknowledged. The provisions in Section 911 of the law represent Congress' acknowledgment that there may indeed be tobacco products that, when appropriately marketed, could significantly reduce the burden of death and disease from tobacco use. And so modified risk tobacco products represent an opportunity to reduce the harms to the public from tobacco use.

What's so critical here is the FDA role. Historically, tobacco companies alone decided what health-related claims they wanted to make for their products in the unregulated marketplace. But the Tobacco Control Act and Section 911 have changed that in a profound way. Now it's FDA who serves as the regulatory gatekeeper standing between consumers and the companies seeking to make claims about their products. And it's FDA who Congress empowered to evaluate requests for the authorization to make MRTP claims.

A few words about what MRTP is and what it isn't. MRTP is not about whether the product itself meets the statutory requirements for getting to or staying on the market. That is what we call the premarket authorization process, which is a completely separate process. Instead MRTP is all about the

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product's promotion and presentation to the consumer.

And a few words about the MRTP process itself. Unlike other types of applications submitted to FDA, such as new drug applications and new tobacco product applications, the law mandates that when MRTP applications are accepted by FDA for filing and review, they must be made publicly available. So these 10 MRTP applications were the first to be made available to the public, and the docket was open for public comment.

The law also requires FDA to take an MRTP application and accept it for filing and review to TPSAC, which we are doing with the meeting today and tomorrow.

This all provides an unprecedented level of transparency and public engagement in FDA's review of regulated tobacco products. FDA must allow the public to view modified risk applications, solicit comment on those applications, and consider those comments when making final determinations.

The determination of whether an MRTP order is appropriate under Section 911 of the Food, Drug and Cosmetic Act is based on the scientific evidence submitted by the applicant, as well as scientific evidence and other information that's made available to the Agency, including through public comments and recommendations from TPSAC.

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Members of the Committee, you have an important responsibility to carefully consider the scientific evidence that's been provided to you in the applications, in the briefing material submitted to you by both FDA and Swedish Match North America, and in the presentations that you will see during this 2-day meeting. Your job is to provide FDA with your assessment and recommendations on the matters brought to you for discussion. We thank you in advance for your contributions over the next 2 days.

As I said earlier, this is the first set of MRTTP applications to be reviewed by FDA and sent to TPSAC. You have a very important responsibility, and you will be grappling with some very interesting scientific issues.

So on behalf of everyone at FDA and the Center for Tobacco Products, I wish you a productive meeting. Thank you.

DR. HUANG: Thanks, Mitch.

Actually, before moving on, I want to call on Dr. Tim McAfee, who's on the phone, I believe, and ask him to introduce himself, another member.

Tim, are you on the line?

DR. McAFEE: Yes. Sorry, Phil.

This is Tim McAfee, and I am the senior medical officer

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representing the Centers for Disease Control.

DR. HUANG: Great, welcome.

DR. McAFEE: Thank you.

DR. HUANG: Next, we're going to have the first presentations on modified risk tobacco product applications from Dr. Raquel Peat and Dr. Conrad Choiniere.

DR. PEAT: Thank you, Dr. Huang and Mr. Zeller.

Good morning to members of the Committee and to all attendees. I'm Dr. Raquel Peat, a branch chief in the Division of Regulatory Project Management in the Office of Science. I'm also a commander in the United States Public Health Service Commissioned Corps. In addition to my many hats, I am the regulatory lead for modified risk tobacco products.

This is a dual presentation with Dr. Choiniere, Director, Division of Population Health Science and the scientific lead for modified risk tobacco products. We will be presenting on modified risk tobacco product applications, both from a regulatory and scientific perspective.

There are two disclaimers in each FDA presentation. I'll be the only FDA presenter that will read aloud each disclaimer.

The first such disclaimer is: "The information in these materials is not a formal dissemination of information by FDA

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and does not represent Agency position or policy. The information is being provided to TPSAC to aid the Committee in its evaluation of the issues and questions referred to the Committee."

The second disclaimer: "This presentation contains statements of preliminary findings and interpretation of the data and information reviewed to date. It must be emphasized that this presentation does not represent final findings, recommendations, or conclusions, and that no final regulatory decision on the status of these applications has been made. Due to the large volume of information contained in the applications, it is not feasible to provide a comprehensive review for discussion at this meeting. Although the entire applications are referred to the Committee, this presentation may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Committee."

The objective of the presentation is to provide a brief overview of the statutory framework for modified risk tobacco products by providing information contained in the Family Smoking Prevention and Tobacco Control Act signed into law on June 22nd, 2009.

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And I plan to outline the modified risk tobacco products applications and orders. In addition, I'll provide an overview of the modified risk tobacco product applications review process, for which we will discuss today.

Dr. Choiniere will finish with a discussion on the Swedish Match North America modified risk tobacco product applications under review and for discussion for this 2-day Tobacco Products Scientific Advisory Committee meeting.

Mr. Zeller briefly indicated what is and what is not a modified risk tobacco product. By way of background, the next two slides will provide an overview as to what is considered a modified risk tobacco product.

Modified risk tobacco products are tobacco products sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. This includes products whose label, labeling, or advertising represents that this product is less harmful or presents a lower risk of tobacco-related disease than other commercially marketed tobacco products; the product or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain, and is free of a substance; the word "light," "mild," "low," or similar descriptors are used in its

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label, labeling, or advertising; or its manufacturer has taken any action after June 22nd, 2009, directed to consumers through the media or otherwise, that would be reasonably expected to result in consumers believing that the tobacco product may present a reduced risk of harm, tobacco-related disease, or exposure to a substance than commercially marketed tobacco products.

In order for a modified risk tobacco product to be legally introduced or delivered for introduction into interstate commerce, an application must be filed with FDA by any person, and FDA must issue an order under Section 911(g) with respect to such product, allowing it to be introduced or delivered for introduction into interstate commerce.

There are two types of modified risk orders. The first of such, risk modification orders, are for tobacco products that have been shown to significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, and benefits the health of the population as a whole, taking into account both users and non-users of tobacco products.

The second of such orders, exposure modification orders, are for tobacco products that reduce or eliminate exposure to a harmful substance and for which the available scientific

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evidence is not sufficient to meet the standards for a risk modification order but suggests that a measurable and substantial reduction in morbidity and mortality is reasonably likely in subsequent studies.

In order for a tobacco product to make claims that the product presents a lower risk of disease, such as in a risk modification order, an applicant must make the demonstrations outlined in Section 911(g)(1), that the product, as it's actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, as well as benefit the health of the population as a whole, taking into account both users and non-users.

There are considerations attributed to a modified risk tobacco product. FDA must determine whether a modified risk tobacco product will significantly reduce harm and the risk of tobacco-related disease to individuals and benefits the health of the population as a whole, taking into account:

- the relative health risks to individuals of the modified risk tobacco products;
- the increased or decreased likelihood that existing users of tobacco products, who would otherwise stop using such products, will switch to the modified risk

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tobacco product;

- the increased or decreased likelihood that persons who do not use tobacco products will start using the proposed modified risk tobacco product;
- the risk and benefits to persons from the use of the modified risk tobacco product as compared to the use of smoking cessation drug or device products approved to treat nicotine dependence; and
- comments, data, and information submitted by interested persons.

There are a number of unique features of modified risk tobacco product applications and orders highlighted here.

FDA must make a modified risk tobacco product application, to include label, labeling, and advertising, available for public comment, with the exception of matters which are trade secrets or confidential commercial information.

FDA must refer the modified risk tobacco product applications to the Tobacco Products Scientific Advisory Committee meeting for its recommendations.

FDA intends to make the decision on the applications within 360 days.

Modified risk tobacco product orders are issued only for

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individual products and not for a class of tobacco products.

Modified risk tobacco product orders are valid for a duration specified by FDA, and an applicant may request renewal of such order.

An applicant who receives a modified risk order must conduct postmarket surveillance and studies.

In sum, in order for a modified risk tobacco product to be legally introduced or delivered for introduction into interstate commerce, a modified risk tobacco product application must be filed with the FDA, and FDA must issue an order under Section 911(g).

An applicant must satisfy the requirements under Section 910 of the Federal Food, Drug and Cosmetic Act. If the modified risk tobacco product is a new tobacco product, it may be brought to market through any of the following three pathways:

- Premarket tobacco product application,
- Substantial equivalence, and
- Exemption from SE.

Now I'll discuss the review process. To provide context to the modified risk tobacco product application review process, I would like to briefly discuss the modified risk

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tobacco product applications currently under review, which were submitted by Swedish Match North America on June 10th, 2014, for 10 snus products.

According to the European Smokeless Tobacco Council, Swedish snus is defined as a smokeless tobacco product for oral use, which is traditionally produced and used in Sweden and manufactured using a heat treatment process which satisfies the requirement of the Swedish Food Act. This definition distinguishes Swedish snus from all other types of smokeless tobacco products, including some snus-like products recently introduced in the United States market, which has distinctly different characteristics.

The Applicant has submitted 10 snus tobacco products varying in name, flavor, package quantity, and portion size. Nine of the products are packaged in pouches. Swedish Match North America seeks risk modification orders for their 10 snus products.

The Comprehensive Smokeless Tobacco Health Education Act currently requires that each smokeless tobacco product package and advertisement bear one of the four required warnings. The Applicant is proposing:

- To keep the "WARNING: Smokeless tobacco is addictive."

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- To eliminate the "WARNING: This product can cause mouth cancer."
- To eliminate the "WARNING: This product can cause gum disease and tooth loss."
- To revise the "WARNING: This product is not a safe alternative to cigarettes."

If granted, the proposed modified risk tobacco products would be required to bear on their packaging and advertising one of the two warnings:

- "WARNING: Smokeless tobacco is addictive."
- "WARNING: No tobacco product is safe, but this product presents substantial lower risk to health than cigarettes."

The modified risk tobacco product applications under review are undergoing the review process, which was divided into four phases. From left to right, the modified risk tobacco product review process starts at Phase 0, noted in pale pink. Applicants have the option for FDA to review protocols for preliminary assessment as well as seeking advice about the modified risk tobacco product applications that they plan to submit.

Once a modified risk tobacco product application is

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received by the Agency, it starts the 360 days in which FDA intends to act on the application, and the application proceeds through the various phases. If a modified risk order is issued, then Phase 4 begins. I plan to go into more detail in the remaining slides with a discussion on each phase.

Phase 1 is the administrative phase. I apologize, this is the acceptance phase. It is an administrative review of a submission to determine whether it is acceptable for processing and further review. In essence, FDA assesses whether the Center for Tobacco Products has jurisdiction under Chapter 9 of the Federal Food and Drug Act.

For example, does the product meet the statutory definition of tobacco product? Is the tobacco product currently regulated? If the answer is no, a "Refuse to Accept" letter is issued and no further action is required. If the answers are yes, an acknowledgement letter is issued, and we proceed to Phase 2.

Again, any person may file a modified risk tobacco product application, and for filing and in our assessment of completeness, the modified risk tobacco application must include:

1. a description of the proposed product and any

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- proposed advertising and labeling;
2. the conditions for using the product, which includes a full description of the way in which consumers will use the product;
 3. the formulation of the product, such as a complete list of uniquely identified components;
 4. sample product label and labeling;
 5. all documents relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related disease and health-related conditions, including information both favorable and unfavorable. An example of this is relevant documents related to study protocol, raw data, study reports;
 6. data and information on how consumers actually use the tobacco product; and
 7. such other information as the Secretary may require, such as postmarket surveillance and study.

Phase 3. This is where the scientific review starts. An FDA review team comprised of scientists in various disciplines evaluate data and information to inform a regulatory science

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decision on the application. The following actions occur in Phase 3:

- The application is made publicly available soon after the modified risk tobacco product application is filed by the FDA.
- Scientists review the modified risk tobacco product application as well as submitted public comments.
- Inspections are conducted for both the clinical and manufacturing sites to assess data integrity and validation of the manufacturing process for the applications under review.
- The modified risk tobacco products are referred to the Tobacco Products Advisory Committee, who provides recommendations to FDA.

At the end of the completion of scientific review, results are issued in an order by Day 360.

The final decision for the modified risk tobacco product application is either a marketing order issued for a specified time, and thus we begin with Phase 4, or if FDA has made a determination that no marketing order will be issued for the proposed modified risk tobacco products, then no marketing order will be issued and sent to the applicant and no further

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action is required.

If authorized for marketing, Phase 4 activities begin and include the following actions:

- The applicant submits a postmarketing surveillance protocol to FDA;
- FDA reviews the applicant's proposed protocol and determines whether to approve the protocol;
- FDA monitors and reviews data submitted as a part of postmarketing surveillance; and
- At the conclusion of it all, if submitted, FDA would evaluate requests to renew a modified risk tobacco product marketing order.

This concludes my presentation on the regulatory overview. I ask that you hold any clarifying questions until the end of the presentation. And we will now provide -- Dr. Choiniere will now provide the scientific overview of the applications under review.

DR. CHOINIÈRE: Thank you, Dr. Peat.

And good morning. As Dr. Peat indicated, I am Dr. Conrad Choiniere, and I am here today as the scientific lead for FDA's modified risk tobacco products program.

What I plan to discuss today are scientific aspects of the

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applications that have been submitted, and the review process as well as a brief summary of the public comments that were received related to these applications. And I will introduce to the Committee the questions that we would like discussed.

When looking at modified risk tobacco product applications, FDA reviews the applications in five scientific areas, and we have recommended that industry submit information, scientific information on these areas. These areas include:

- The health risks of the tobacco product itself, which could include absolute health risks as well as relative health risks as compared to other tobacco products, or health risks to certain subpopulations;
- The effect the tobacco product and its marketing may have on tobacco use behavior among current tobacco users;
- The effect a tobacco product and its marketing may have on tobacco use initiation among non-users, which could include never users as well as former users of tobacco products;
- The effect of the tobacco product's marketing on consumer understanding and perceptions, as well as the

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effect the tobacco product and its marketing may have on the population as a whole.

The Swedish Match North America modified risk tobacco product applications contained information addressing each of the areas identified by FDA, including evidence from various types of scientific studies. These studies included:

- Product analyses (in the fields of chemistry, engineering, and microbiology)
- Toxicological assessments
- Pharmacokinetic studies
- Clinical trials (for cessation and nicotine uptake)
- Epidemiological studies
- Observational studies on health and behavior
- Consumer perception and comprehension
- Population statistical modeling as well as some plans for postmarket surveillance and studies

Swedish Match currently markets General Snus tobacco products. However, the snus products that are included in these applications are new tobacco products, and they appear to differ from those on the market in some respects, such as certain additives, tobacco blends, and flavors.

If FDA were to issue a modified risk order for any of

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these products, the order would only be applicable to the products for which the order was issued. It would not extend to any other snus products currently in the market, whether it is Swedish Match snus products or other snus products.

As you are aware, the applications covered some tens of thousands of pages of documents. FDA is reviewing and has reviewed the entirety of the materials included in the applications. And although the entirety of the applications are referred to the Committee, this presentation may not include all of the issues relevant to the final regulatory recommendation, and instead I intend to focus on issues identified by the Agency for discussion by the Committee. And these issues FDA has identified as critical scientific issues for discussion, which directly relate to the factors FDA must consider when taking an action.

In general, the questions that we will be introducing -- that I will be introducing later in this presentation cover the following topics:

With respect to the relative health risk to individuals, FDA brings to TPSAC questions related to the strength of the association between snus use and the risk of certain oral diseases such as tooth loss, gum disease, and mouth cancer.

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We also bring questions related to the risks of snus use as compared to cigarettes.

With respect to the impacts on initiation and cessation and other tobacco use behaviors, FDA brings to TPSAC questions related to the applicability of the Swedish experience to infer impacts on the U.S. population.

With respect to the ability of the public to comprehend the modified risk information, FDA brings to TPSAC questions related to the impacts of providing modified risk information in the context of a warning label.

FDA also seeks recommendations from TPSAC on postmarket surveillance and studies, should FDA issue an order permitting the marketing of these products as modified risk.

As Dr. Peat indicated, we had public comments, we had a docket open for public comments to be submitted, related to these applications. We opened the docket on August 27th, 2014. At that time we indicated that any comments received prior to November 25th, 2014, would be more likely to be considered prior to referring the applications to TPSAC. In total, FDA has received 149 comments; 120 of those were received prior to November 25th, 2014.

The comments were submitted by individual citizens as well

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as individuals from the tobacco control research community, public health advocacy organizations, and the tobacco industry itself. Those comments addressed a wide range of issues, including legal, policy, ethical experiences, personal experiences with the products, as well as scientific issues.

Given the scope of today's meeting, the comments that I am going to discuss are limited to those that address the scientific issues. Many of these comments raised the same issues that we have identified during our review of the applications.

In particular, there were comments raised about the epidemiological evidence on the health and behavioral impacts of snus use, consumer perceptions of these products, and interpretation of the scientific data.

Some of the comments expressed concerns about the interpretation of epidemiological data and raised concerns for the potential of snus use to increase risk of certain health outcomes, as compared to non-users, such as fatal myocardial infarction and stroke, fatal heart disease, and esophageal and pancreatic cancers.

Other commenters discussed the applicability of the Swedish experience, highlighting features in the environment in

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Sweden that do not currently exist in the U.S., such as restrictions on the advertising for tobacco products or cultural differences or patterns of use of smokeless tobacco products, which could lead to differences in outcomes.

I apologize, the slide advancer is not working.

(Pause.)

DR. CHOINIERE: There we go. I believe this went ahead too far. All right, now it seems to be working.

Other commenters discussed potential impacts on consumer perceptions and that the messaging that is proposed may, for those that were supportive of the applications, correct perceptions about relative risks of snus use; and from those that were not supportive, exacerbate perceptions about relative risks of snus use, perhaps conveying that snus use is safe. And others are concerned that these messages may mislead consumers into believing all smokeless tobacco products carry the same risks as snus.

Other issues cover the range of issues -- other comments cover the range of issues, including uncertainty about the similarities between the Swedish Match products that are in these applications and those traditionally marketed in Sweden, the proper handling and storage of snus products by U.S.

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consumers, and certain methodological issues such as those in the consumer perception study included in the applications.

And now I will introduce to the Committee the questions for your consideration.

With respect to the relative health risks to individual users of these snus products, i.e., the Swedish Match North America snus tobacco products that are the subject of these applications -- and I will say, at this point, that throughout the day we will be discussing these snus products. And so when we use the term "these snus products" or "these products," we are referring specifically to the 10 products that are included in these applications.

So today we ask the Committee to discuss the evidence regarding the association between the 10 snus products and gum disease or tooth loss. And while you discuss this, please address the following issues:

- The biological plausibility that gum disease or tooth loss in snus users would differ from those in users of other smokeless tobacco products;
- Confidence in the information from studies that only include young adults under the age of 25, given that the prevalence of periodontal disease increases with

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age;

- Confidence in the information on tooth loss from the use of snus, where the studies presented in the application evaluated the number of teeth between snus users and non-users in cross-sectional studies; and
- Sufficiency of information from studies where there are small numbers of participants.

After that discussion, we'll ask the Committee to vote on two questions:

- a. Does the evidence support that these snus products pose risks of gum disease to individual users of these products?
- b. Does the evidence support that these snus products pose risks of tooth loss to individual users of these products?

We will also ask the Committee to discuss the evidence regarding the association between these 10 snus products and oral cancer.

Does the evidence support that these snus products pose risks of oral cancer to individual users of these products?

We'll also ask the Committee to discuss the evidence regarding the association between the 10 snus products and

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overall risks to health as compared to cigarettes. There are three accompanying voting questions:

- a. Should the comparison focus on major smoking-related diseases according to population burden or assess all relevant health outcomes?
- b. Does the evidence support the statement that health risks to individual users from using these snus products are "substantially lower" than the health risks from smoking cigarettes?
- c. Does the proposed warning statement adequately communicate the potential health risks to individual users of these snus products?

We will also ask the Committee to assume a counterfactual. We'll assume that the behavior of the U.S. population does mimic those in Sweden with respect to the use of snus.

If that were the case, what information would the Committee need to know about the snus products that are used in Sweden and the snus products that are the subject of these applications, in order to have confidence that the health outcomes observed in Sweden would also be observed in the U.S.?

For example, would it be sufficient to know that the exposures to individual users of Swedish products are

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comparable to the exposures to individual users of these snus products, or would you need knowledge about other characteristics of the tobacco products to determine that the health outcomes would likely be comparable?

With respect to the likelihood that existing users of tobacco products who would otherwise stop using those products will instead switch to these snus tobacco products, and the likelihood that persons who do not use tobacco products will start using these snus products, we ask the Committee to discuss the evidence regarding the likely impact of these 10 snus products on tobacco use behaviors among tobacco users and non-users. The application includes considerable data on the behavioral aspects of snus use in Sweden.

Does the Committee believe that the epidemiological data from Sweden concerning tobacco use behavior provide relevant information on the likelihood that current tobacco users in the U.S. will switch to the use of these snus products, and the likelihood that non-users of tobacco products will initiate the use of these products?

FDA has noted that the applications did not include several types of studies that could be useful in order to assess impacts on behavior, such as actual use studies, some

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selection studies, and other behavioral studies.

Does the Committee believe that the applications include sufficient information on the behavioral aspects of the use of these snus products among the U.S. population?

Time permitting, we will also address questions related to consumer perception and postmarket activities.

With respect to enabling consumers to comprehend the modified risk information and understand its relative significance in the context of total health, the Applicant proposes to include modified risk information within a warning label. FDA has potential concerns that inclusion of information about relative benefits of product use within a warning label may raise additional questions regarding consumer comprehension of the modified risk information and perceptions of the product.

From the perspective of enabling consumers to understand the modified risk information in the context of total health, does the Committee believe it is appropriate, from a scientific standpoint, to include modified risk information within the context of the required warning label as opposed to in a statement separate from, and in addition to, the warning label?

And with respect to postmarket surveillance and studies to

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be conducted by Swedish Match North America, as indicated earlier, should FDA issue an order for any of these products, Swedish Match North America would be required to conduct postmarket studies and surveillance.

So what recommendation does the Committee have for postmarket surveillance and studies?

What elements should Swedish Match North America include in a postmarket surveillance and studies program in order to monitor product use transitions for these snus products, products which traditionally had a low prevalence of use?

What methods does the Committee recommend that Swedish Match North America employ for assessing the impact of a specific modified risk tobacco product marketing on perceptions of behavior in a postmarket setting, particularly among youth?

What sources of data does the Committee recommend for providing information on impacts resulting from the marketing of the products as modified risk tobacco products?

And what additional information does the Committee recommend that FDA request from the Applicant regarding plans to conduct postmarket surveillance and studies?

As you can see, we have a number of issues to address over the next 2 days, a number of potentially complicated scientific

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issues to grapple with. We ask that you keep these questions in mind or before you as you listen to the remainder of the presentations today, so that we can begin our discussion after you hear the presentations, which you'll hear from Swedish Match North America as well as from FDA scientists.

At this point I will ask Dr. Peat to join me at the podium, and we can address any clarifying questions that the Committee may have.

DR. HUANG: All right. And as a reminder, please wait for me to recognize you before speaking into the record. So clarifying questions?

Yes, Dr. Bickel.

DR. BICKEL: So I just want to clarify. To address Question 5 and to look at part (b) of that, where you say -- so I just want to clarify. There is no abuse liability studies of this product, the type of experimental studies that are used at other parts of FDA to determine the extent to which a particular substance may be abused by the relevant population. None of that data is included?

DR. CHOINIERE: There are some clinical studies on nicotine uptake, which I believe would be considered abuse liability studies. Swedish Match, I assume, will be discussing

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those studies as well.

DR. HUANG: Yes, Dr. Novotny.

DR. NOVOTNY: In the guidance for applications for MRTPs, there is a requirement for a NEPA consideration for an environmental impact statement, and I didn't see that mentioned anywhere. I just wonder if that was included in this process as well.

DR. CHOINIÈRE: So I wanted to clarify two things. It is a draft guidance, so these are not requirements on industry. They're available for the public to comment on. But I was going to ask Dr. Benson to address your question related to NEPA.

DR. BENSON: So the NEPA requirement is an environmental assessment, not an environmental impact statement.

MR. COHEN: Please state your name and introduce yourself.

DR. BENSON: Kimberly Benson, Director of Nonclinical Science, Office of Science, CTP. And the Environmental Science Branch resides in my division.

So the requirement through NEPA is an environmental assessment to determine whether an environmental impact statement is needed. And as Dr. Choiniere said, the guidance says that we would like that in the application. But at

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present, that's not a requirement, though Swedish Match did include an environmental assessment.

But what we are doing is taking their information and writing our own environmental assessment for the applications. So that's an ongoing process. It wasn't included in the backgrounder, but it is ongoing right now.

DR. HUANG: I have -- oh, Mr. Henton.

MR. HENTON: For Dr. Peat. The 360-day, I'm confused on the 360-day. What happens on June 5th or so of 2015? What has to happen? I'm confused on that.

DR. PEAT: Yes, the 360 days is in a draft guidance that gives a timetable for that review period. It is our intent to act on the application based on the 360 days in the draft guidance on June 5th, 2015.

But, again, the draft guidance does go into a little bit more information indicating that the date that was given as the preliminary timetable to act on an application, an MRTP application, it's preliminary in the sense that we've never had an experience before of modified risk tobacco products and all of the different parameters that are incorporated in the review process for a modified risk tobacco product.

MR. HENTON: But on that date --

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DR. PEAT: But on that date we plan to issue a decision. We intend to.

DR. HUANG: I have a question for Dr. Choiniere, briefly, regarding the first few questions. Does the evidence support that these snus products pose risks of gum disease to individual users of these products? Does the evidence support that these snus products pose a risk of tooth loss to individual users of the products? And does the evidence support that these snus products pose risks of oral cancer to individual users of these products?

So that's in the context of what's known about smokeless tobacco on these health situations. We don't, for the specific products, have evidence that they have these health risks, right? Because really the question that we're trying to answer is, is there evidence to support, sort of, removal of these warning labels for these particular adverse effects, correct?

DR. CHOINIERE: Correct. Swedish Match provided evidence on their products. Much of it was based on much more broad observational epidemiological studies that may have included other types of products, other types of snus products. And you're correct. In framing the question, we need the answer to this question in order to make a determination about whether

the request is -- I think Dr. Ashley has something he would like to add.

DR. ASHLEY: I'm assuming I can talk. I just do want to make it clear that the questions are related to these 10 products in relation to this application. So what we're asking the Committee to do is look at these 10 products. We're not asking the Committee about all snus products and/or all smokeless tobacco products. The meeting today is about these specific 10 products and the evidence provided by Swedish Match.

DR. HUANG: And I guess my question, just to clarify that, is that we don't have to have the evidence showing these particular 10 products having those adverse effects, but it's in the context of what's also known about smokeless tobacco products and adverse health effects, that we have enough evidence that they would be excluded from having those health effects for those particular 10 products.

DR. ASHLEY: Again, there is evidence, there is broad scientific evidence, but the question is about these 10 specific products.

DR. HUANG: I think we're saying the same thing.

DR. ASHLEY: We probably are.

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(Laughter.)

DR. HUANG: Yes.

DR. DJORDJEVIC: I have a question. Reynolds' health endpoint is reproductive health and the fetal and the mental effect. So are these included also in consideration for the evaluation of these products?

DR. CHOINIERE: The answer is yes.

DR. HUANG: Okay, Dr. Giovino.

DR. GIOVINO: On Question 4 it talks about the product and it doesn't mention marketing, which is quite different. But for this scenario, are we just to not think about marketing, or are we to put that in our thinking?

DR. CHOINIERE: We have compartmentalized these questions to make these issues a little bit easier for you to focus on certain aspects. So for Question 4 we are, yes. And let's assume that the marketing of this product leads to behaviors that are identical to those that occurred in Sweden. Would we be expected to see the same observed health outcomes here in the U.S.?

DR. GIOVINO: Okay, that assumption may be -- I'm concerned about the validity of the assumption, I guess.

DR. CHOINIERE: And we certainly would expect that there

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will be some sort of a discussion about that. And the validity of that assumption is covered in Question 5. So first we ask you, all right, let's assume the behavior is the same. Do you anticipate we would observe the same health outcomes? Then we ask you, well, is it valid to assume that the behaviors will be the same?

DR. HUANG: Other clarifying questions?

(No response.)

DR. HUANG: Okay. Hearing none, I guess, thank you, Dr. Peat and Dr. Choiniere.

And now we -- let's see, we're about right on time, so we're going to take a 15-minute break. And again a reminder. Committee members, please remember that there must be no discussion of the meeting topic either amongst yourselves, with the press, or with any member of the audience. Thank you. And we will reconvene again in this room in 15 minutes. Thanks.

(Off the record at 9:28 a.m.)

(On the record at 9:46 a.m.)

DR. HUANG: All right. So now -- okay. We'll now reconvene.

And for the next section, we're going to hear the presentations from Swedish Match North America. And the first

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presenter, giving an introduction and overview, is Jim Solyst with Swedish Match North America.

MR. SOLYST: Thank you. My name is Jim Solyst. I am the Vice President for Federal Regulatory Affairs with Swedish Match North America. And on behalf of my colleagues here today, we appreciate the opportunity to be here and speak to the Committee and to present the application or applications, because, of course, it pertained to 10 different products.

The way we'll go forward is I will provide a brief overview, sort of an introduction, and then I'll serve as moderator. I'll introduce, first, Dr. Joe Rodricks from ENVIRON, and then I'll come back and briefly talk about the Norwegian experience. And then I'll introduce Dr. Lars-Erik Rutqvist, the Senior Vice President for Scientific Affairs at Swedish Match.

But my job initially here is to give you a sense as to who we are as a company, what we believe in, what we are proposing, which I think you already know by now, and provide a brief overview of the areas of evidence that we will be describing this morning.

We understand that our application represents a significant step in the two-decade-long discussion on tobacco

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harm reduction. We are seeking to contribute and share in the mission of reducing the harm caused by cigarettes.

We believe we share in this mission with others; certainly starting with the U.S. Congress that decided to include provisions for modified risk in the Tobacco Control Act; certainly with the FDA Center for Tobacco Products, which we have been meeting with over the past 2 years, and also so effectively communicated the concept of continuum of risk and addressed the need for a policy on nicotine delivery products in general.

We also believe we share in this mission with the public health and tobacco control communities, who have their dialogue going on, a dialogue that we have benefited from. We have reached out to this community and they have -- the dialogue has been very, very rewarding, I would say.

But there are essential components of tobacco harm reduction in the modified risk process, starting with that the scientific evidence should be the basis of regulatory decision making. This is certainly in the Tobacco Control Act. It's in the DNA of FDA, particularly with the emphasis on regulatory science. And we believe we share that.

We also believe that the public, smokers in particular,

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should be provided with accurate and appropriate information about the risks of nicotine delivery products. That is at the heart of our decision to request the label changes.

We believe that transparency is always essential in the regulatory process, but particularly for tobacco, particularly for modified risk. We believe that we have been aggressively transparent. I mean, certainly, the process is transparent, and it has been stated that the mass of applications is on the website, and there are briefing documents that are now available to the public. But we thought that we were obligated to reach out to various communities and ensure they knew what we were doing well before we even submitted the application.

We believe in governance. We believe in the elements of governance that were addressed in the Institute of Medicine MRTP committee report that was issued in early 2012. Chapter 2 of that report addressed governance. There's more of a long-term need for research governance. But we feel, as a company, we have an obligation to demonstrate governance as well, whether it's an IRB for our premarket consumer perception study or an advisory panel, which I'll describe in a few minutes.

We believe in the benefit of independent outside advice, whether it's coming from the tobacco control and public health

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communities, our competitors or, particularly in our case, our MRTTP advisory panel.

We believe in manufacturing and product standards, whether they're developed by CTP according to the Act, or whether a company undertakes it themselves. We certainly have. We call our manufacturing and product standard GOTHIA TEK.

Now, GOTHIA is derived from the city of Gothenburg, which is the second-largest city in Sweden. It's the home of our snus manufacturing facility. It's also the home of Volvo. Volvo used to own Swedish Match at one point, and we hope that we share with Volvo the commitment to product stewardship. But we get to use the term Gothenburg -- derived from Gothenburg, GOTHIA TEK.

We understand the importance of being the first. There has been a lot of attention. There's been media attention lately. And so it's fair to ask, is this the right product? Is this a product that should be considered by this Committee for the first time? Is this a product with the best evidence, particularly the product-specific evidence? And is this the right company?

We believe, of course, that our snus products, the 10 products that we're addressing today under the General line of

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products in the United States, are the right products. And it is supported by strong evidence. It's a combination of extensive observational evidence from Sweden and Norway, along with clinical trials, our premarket consumer perception study, and a supplementary dynamic population application.

We think it is highly significant that the majority of the evidence we're presenting today is product specific. It's specific to our Swedish Match products. Dr. Rodricks and others will address how the Swedish evidence is Swedish Match snus evidence.

We also believe that it's highly significant that the product-specific observational evidence from Sweden and Norway was collected through studies conducted by government and academia, not by industry.

We believe Swedish Match is the right company. We're not a big tobacco company. We don't manufacture cigarettes. We really don't have a large staff. Our corporate headquarters are in Stockholm, North American headquarters in Richmond. Snus is our signature product. The company and its predecessors have been manufacturing snus since the early 20th century. There was virtually no competition for our products in Sweden until about the 2000s.

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So up until that point we dominated the market; 95-plus percent of the market was Swedish Match snus. Since then, we've maintained a market share close to 90%. So that's what I mean by the evidence in Sweden is specific to Swedish Match snus.

In Norway, which is another heavy snus-using country, we have maintained a market share of about 90% up until 2005. Since then, it's ranged between 90% and 70%. So much of the Norwegian evidence, which I'll present briefly, is also specific to our products.

Here are our presenters. I'll be first introducing Joe Rodricks, who is a founding principal of the consulting firm ENVIRON International, and then I'll come back. And then I'll introduce Lars-Erik Rutqvist from Swedish Match.

But just a few comments about myself. I am fairly new to tobacco and to Swedish Match. I was Swedish Match's consultant. I worked with Joe Rodricks at ENVIRON, and in 2009 I started consulting to the company about responding to the Tobacco Control Act and particularly the modified risk provisions. And then as they increasingly took over my practice, I gave in and joined the company. I was gratified to join the company in 2012.

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But most of my career has been in Washington, working on regulatory science and science policy issues, first with the National Governors Association for 12 years and then I worked for the American Chemistry Council for 12 years, the industry organization, before joining ENVIRON.

So I know how companies work in the regulatory arena, and I believe this company has been doing the right thing. But let's look at their track record.

Certainly, the company has worked well with government authorities in Sweden, where snus is regulated as a food product. And I think a good example -- I mentioned GOTHIA TEK, the manufacturing and product standard. It was developed in coordination with the Swedish food agency.

We have also been very active participants in the FDA or the CTP regulatory science process. I don't think we've missed an opportunity to provide public comments to the record. We view that as an opportunity to get our position out there. We're quite proud of our positions, and so we've taken full advantage of that. I think we've attended every single CTP-sponsored event and have spoken at many of them. We always attend the TPSAC meetings. And Dr. Rutqvist, in January 2012, spoke to the TPSAC when he described the Swedish experience.

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But there are three milestones in the company history that I believe are demonstrative of the company. In 1999, just when the new company, the current company, was formed, they made the decision to stop manufacturing cigarettes. And then 2000 was the formal announcement of the product and manufacturing standard GOTHIA TEK. And then most recently, 2014, the company unveiled its vision statement: A world without cigarettes.

So this history, this track record, we believe, has allowed us to be a leader in this field, particularly the post-2009 Tobacco Control Act environment, and to serve as trailblazers in some ways, to go places where other companies have not gone. And perhaps the best example of that trailblazing role is the MRTP advisory panel.

We first started talking about the advisory panel in late 2012 and we reached out to people in the public health and tobacco control community and asked what they thought of this idea. Could that work? Could there be an independent body advising us as we prepare this application?

And then late that year we reached out to Karl Fagerstrom, a noted nicotine researcher, and of course Swedish, who was familiar with Swedish Match and knew Lars-Erik Rutqvist. And Karl was supportive, but he wanted to reach out to his long-

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time colleague John Hughes from the University of Vermont. And once Dr. Hughes and Dr. Karl Fagerstrom understood how this would operate, that they would be independent, that they would have their own mission statement, their own set of principles, would set their own agenda, they agreed to be the founding members.

And then we added three other members with expertise in risk communication, toxicology, and research ethics and policy. And two of the members are here today in the audience.

Now, for the most part, the advisory panel was a sounding board. We did not ask them to approve the application. We did not ask them to conduct a comprehensive review of the application, but they always had access to it. As we were developing it, we would be meeting and filling them in.

But there was one great opportunity in which they really did impact the application, and that was with the premarket consumer perception study. We had developed a protocol, submitted it to CTP, and CTP basically said, you know, go back and improve it. So we did. And we went back and did a second protocol and submitted that to CTP. And that was the spring of -- winter of 2013.

So the first advisory panel meeting was March 2013 at the

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SRNT meeting in Boston, and the panel spent the day going over that second protocol, making suggestions and improvements. And then after the meeting, additional suggestions came in. We incorporated all the suggestions from the advisory panel and then sent that revised protocol to CTP and met again.

So CTP had the second protocol, and then they had the revised protocol based on advisory panel input. And you could tell that it was comforting, I believe, to CTP that we had that outside expertise. And it made, we believe, the tool that much more effective and credible.

Just in case we're not sure what Swedish Match -- Swedish snus is, it is a small, little teabag-like product, a sachet of tobacco. It goes in the upper lip. It's a spitless product. It's considered to be moist or semi-moist. It's traditionally produced in Sweden. It's manufactured through a heat treatment process. So it does make it different from other smokeless products, certainly, and even other snus-like products. It contains only fine-ground tobacco mixed with water, additives, and flavors.

In Sweden, as I indicated, it's classified as a food product. So that means it contains only food-approved ingredients. It's manufactured in premises that are

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hygienically suitable for food production. And all 10 products, of course, are of the same nature.

The company has done a lot. We've taken on clinical trials, which Lars-Erik will describe. We did the premarket consumer perception study, which Lars-Erik will also describe. We have GOTHIA TEK, the product and manufacturing standard. But what separates our product from everything else is the Swedish experience. And, of course, what happened in Sweden was about the late 1960s.

Men, in particular, started shifting away from smoking towards snus, probably in reaction to the understanding of the health impacts of smoking cigarettes, and there was a gradual change among men towards snus. And by 1990, snus and cigarettes were at equal level with men. And since then, snus has increased and smoking has decreased. And all of this occurred while the overall tobacco rate in Sweden decreased like in other countries.

So the difference between Sweden, and now Norway and other western countries, is that men use tobacco but they don't smoke, they use snus primarily, and they don't suffer from the smoking health effects. And Dr. Rodricks will get into that.

Now, in Sweden, as has been indicated, there was no

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advertising. There is no government statement: Try snus, smokers. But there was sort of a grassroots phenomenon, that as more people kept using snus, their friends and their neighbors would say to smokers, why are you smoking? Try this product. It's a traditional Scandinavian product. It's got to be less dangerous than smoking.

And so there was sort of a grassroots phenomenon that led to that change in Sweden and in Norway.

Now, in the United States there is a history of smokeless tobacco use, but not snus. They use spit-tobacco. And the messages about the possibility of snus being a harm reduction product has not been made clear in the U.S. It could be, in part, from the label. We think that's a starting place, that at least we make the label correct and maybe citizens of the U.S., particularly smokers, will be aware that there are alternatives to smoking. And that's really the motivation behind our application.

You know, I mentioned earlier that we were a trailblazer, and an example of that trailblazing role was the advisory panel. But also we believe we are a trailblazer for the industry. We think we are setting a standard. Not only a standard of being the first application to be complete and

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being publicly available -- and everybody in the industry can read our application, and hopefully they have -- but also the fact that we've been aggressively transparent, the fact that we have an advisory panel, the fact that we believe in governance concepts. We believe we are setting a standard, and that's part of the trailblazing role.

Now, I think you don't really need this next point. It's been stated by Dr. Peat that what we're looking at, the two standards in the law, the reduced individual risk -- in our case we're saying, if you change from smoking to Swedish Match snus, you're reducing your individual risk -- and that by receiving an MRTP order, it benefits the health of the overall population. Or, shorthand, it would be the public health standard.

So we're proposing that we meet the individual risk standard. It would be a public health benefit for us to receive an MRTP. But then we are of course going further. We're stating that we believe there should be warning label changes. The oral cancer, gum disease, and tooth loss labels, we believe, is part of the individual risk standard, that if you're reducing your individual risk, you're also not suffering from these diseases. And, of course, that will be the heart of

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your discussion today.

We also believe if there's reduced individual risk, that means there's substantially less risk to those who are switching to snus. And so we believe that we need to change that label from "not a safe alternative to cigarettes" to "no tobacco product is safe, but this product presents a substantially lower risk to health than cigarettes." And that's all we're requesting, just that label change, in addition to meeting the individual risk in public health standards. And we believe that that request of the label change is consistent with our mission, our shared mission, to reduce the health impacts of smoking cigarettes.

Let me just do a brief overview of the evidence that's in the application and that will be addressed this morning, starting with the human health -- Swedish human health evidence, what we refer to as the Swedish experience. Dr. Rodricks will get into that. And as the chart below in this slide indicates, the Swedish human health evidence pertains to, certainly, individual risk reduction as well as the public health benefit and particularly to the warning label changes.

We have the Norwegian behavioral evidence, which I'll

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return and briefly talk about, which really pertains to the public health standard. We have the clinical trials that Swedish Match sponsored, that Dr. Rutqvist will describe. Dr. Rutqvist will also describe the premarket consumer perception study, which again relates to the substantially less risky warning label. And he will also describe complementary evidence based on the dynamic population model or modeler.

I mentioned GOTHIA TEK several times. Several of my colleagues from Sweden are here today who are experts on GOTHIA TEK, and if you have any questions, they can answer it. You could seek them out during the breaks.

But we believe that this product standard is representative of the company's commitment to product stewardship, and it's indicative of how Swedish Match snus is low in nitrosamines and other harmful and potentially harmful constituents. HPHC is the term of art from the acting guidance.

GOTHIA TEK combines analytical methods, chemical quality control programs, brand-testing programs, chemical management. And there are essentially three parts to the standard: constituent standards, which relates to the HPHCs, manufacturing standards, and consumer information.

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But for the purposes of today's discussion, we believe that having GOTHIA TEK in place, having those low HPHCs, does relate to the individual risk standard. And having a published, well-known product standard benefits the overall public health.

So unless there's clarifying questions for me, what I'd like to do is introduce Dr. Joe Rodricks. Any clarifying questions?

(No response.)

MR. SOLYST: Good. So I used to work for Joe. I've known Joe for many years, since 1983, when we were both much younger. Joe used to be at FDA for 15 years. In his last 4 years he was associate commissioner for health affairs. He left about 1980, I believe, and a few years later he was a founder and now a principal of ENVIRON International.

His expertise is varied, and I could go on for several minutes, but I think he's probably best recognized -- certainly, I always think of Joe as the expert in toxicology and risk analysis, but he has experience in pharmaceuticals, medical devices, consumers products. He has served on, I said, scores -- I think last night he said 34 different National Academy of Sciences committees, which is probably unheard of;

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also Institute of Medicine committees. And he has spoken to FDA Advisory Committees before, as well. And, of course, he's written scientific publications and the rest.

But with that, let me turn it over to Dr. Joe Rodricks.

DR. RODRICKS: Thank you, Jim. And good morning, all.

I'm here to give you a rather high-level view of the work that we have done for Swedish Match over the last 7 or 8 years, and particularly that which informs the MRTP submission on health issues.

I'm not an epidemiologist. I think Jim just mentioned that. But I've been assisted -- I have the names on the slide -- by Carol Ward and Greg Mariano, who are two highly qualified epidemiologists. If we need to go into some details later, if you have questions, we're prepared to do that for you.

Let me give a little bit of background history here. Our company name suggests we're an environmental consulting firm. And indeed we do a great deal of environmental work, but we also work heavily in occupational health and in product safety. I spend most of my time on product safety related issues of all kinds. We are a worldwide consultancy, now with about 1200 scientists and engineers, and we are strictly technical consultants.

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We were approached by Swedish Match for the first time in 2007. They were looking, at that time, for help on sort of a continuing review of the scientific literature as it evolved on their product. And we considered this. I must say, we had not done work for the tobacco industry before this time, so it was a big step for us. We had not wanted to do that. We had done some various minor insignificant things, but generally we avoided that industry. Swedish Match convinced us otherwise, and we began to work with them in 2007.

And then, following the Tobacco Control Act's appearance, they asked us to begin looking into the issue of reduced risk products and the analysis needed to support that.

And so we've submitted a great number of reports. The appendices to the MRTPA contain huge numbers of analyses that we have performed. And I'm going to, as I said, give you -- I'm not going to go into detail on those, but kind of a high-level view of those findings.

This I present as what Jim described as the Swedish experience, which seems to show snus displacing cigarette smoking. I don't present this as evidence for that, but there's a lot of evidence for that. I only present this because this was one of the things that convinced us to go to

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work and help Swedish Match in this project, because it seemed like there was a public health benefit potential in the product. And I became more and more convinced of that as we looked at the data.

The same kind of thing here. This is a cohort in Sweden of about 100,000 and followed very closely, for this graphic, over about 17 years with very careful collection of information on tobacco use habit, and you see snus increasing and smoking decreasing over this period of time. This is one subset of the population. So that was the kind of thing that again convinced us this was a product worth working on.

Let me also mention here that if you are going to create any evidence or deal with evidence having to do with reduced harm products, for products that are on the market, you're going to have to rely very, very heavily, as you all know, on observational epidemiology studies. You don't have much choice in that matter. Other ancillary evidence might help, but the core has to come from observation.

And so there are always problems with that. But I must say, Sweden is an ideal -- almost an ideal setting for those kinds of studies because of national databases that they have there. And then in this particular case we have widespread use

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of the single manufacturer's product, Swedish Match's snus. So the studies that I will sort of summarize or give in summary form are all about the very products that you are asked to make a decision on, not compounded by other -- confounded by other kinds of products.

The other point, the fourth bullet on this slide, is that the studies have been conducted, not by the industry itself, but by academics, by the Karolinska Institutet, who has been involved, for example, in a lot of those studies, a lot of other independent research. So that's a fairly favorable scenario for the data you are asked to look at.

The reports submitted covered many areas, and I'm not going to cover all of these. I'm just going to talk about what we call the snus monograph on health effects, again at a high level. We also have a lot of work on harmful -- the potentially harmful constituents of the product. I must say, it's pretty much like food. It has the same kinds and levels of constituents that you would find in food products. They're all naturally occurring materials like heavy metals and other constituents.

The nitrosamines you find in food -- you certainly do find nitrosamines in food -- are not the same nitrosamines you find

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in snus. They're tobacco-specific nitrosamines. So there we looked at their exposure relative to smoking, and they're really no different. I don't have anything more to say on that, but I thought I'd give you that very brief summary.

These other areas, the three bullets at the bottom, Dr. Rutqvist will be talking about a little bit later today. We'll give you some summary there. But let me go to the literature, what we call the scientific literature on health effects.

So we reviewed all of these. And let me just tell you a little bit about the database here. In addition to chemistry, biomarker studies and toxicology studies, there is a large literature from observational epidemiology, over 100 primary epidemiology studies on human health effects, cohorts organized from the early 1970s and followed through the 2000s.

Fifty health points. The focus on health points related to smoking is because the idea was that we were looking to see whether this product has any of the same effects you find from smoking. And I've already mentioned the last point here. So it's a substantial database that forms the basis for the conclusions we reached.

We went through -- and you may find it a little bit

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tedious to get through, if you really want to go into the details of what we have done. But in our appendices, we have presented tabular summaries of every study and detailed tables of evidence, evidence tables for endpoints with outcome and exposure measurements, confounders, results. All of that is in there. Then narrative summaries as well. And in everything, we've tried -- everything we've done here, we have tried very hard to be completely clear. We use the fashionable word "transparent," but how we get from the data to our conclusions.

So we hope that's all in there. And we can go into any of these in some detail, if you'd like, later, but I'm not going to do that now. I'll just give you, as I said, the high-level view.

We used standard, pretty much, Bradford Hill criteria, criteria that IOM and other institutions commonly use to judge the evidence to establish the strength of the evidence, the weight of the evidence, if you like, for all of these various effects.

And then we came up with what we call conclusion categories, our own categories based on the evidence specific to Swedish snus, into different categories, what we call clear evidence of no association where you have very high-quality

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studies and quite a number of them showing no association at all; clear evidence of an association, again high-quality studies showing associations.

We have, then, more categories that are a little less definitive. Maybe you could find better words for these categories, but these are the ones we chose. No associations but limitations; that is, we've got studies that do not show associations at all, but we know there are limitations in the studies. There are small sizes, small numbers of studies, lack of a control for confounders, those kinds of limitations that are common.

We have a second category. We thought we'd separate out those studies which are pretty consistent in not showing an association. But within the dataset, within the group of studies there, you do see one or two studies with associations, whereas the overall dataset seems to be without one; we thought that deserved its own category. So we call this evidence, overall evidence. The overall weight of the evidence suggests no association, but again limitations in that category.

Then a third category where there's a lot of uncertainty because we could not untangle, for example, confounding in many studies. So we just call those possible associations, a lot of

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uncertainty.

We have another category which you may not accept, although it did seem a little compelling to us. But there are a number of diseases related to smoking which seem to be clearly related to smoke. Respiratory conditions, for example, one would not expect those with snus. You may not accept that idea, but at least we established this category for some of the major smoking-related respiratory conditions but where there's no actual epidemiologic evidence on them.

So here are some of the findings. We have great detail on all of these, clear evidence of an association. There are pretty consistent findings of a small increase in blood pressure and heart rate increases with the use of snus. They seem to be reversible, and they don't get worse over time.

There are lesions in the oral cavity next to where the little -- I think Jim described it as a little teabag that's placed. Again, these lesions do not seem to get worse over time. There's a color that develops there related to snus.

But there are some adverse pregnancy outcomes. A lot of pregnancy outcomes have been used. I don't have the details here, but there are adverse pregnancy outcomes that seem fairly certain.

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On the other side, clear evidence of no association, we think, points very strongly to oral cancer, lung cancer, cardiovascular disease, MI, and stroke. There's a strong database here on all of these, and we think there is no evidence of an association.

These, by the way, if you take these together collectively, may account for close to 80% of smoking-related diseases. So the absence of any snus effect here is, by itself, fairly convincing evidence that you just don't have these diseases related to this product. And they are major, major diseases, of course, for smoking.

Other categories. We have long lists, and I don't have them all here. No associations, but limitations. So the ones on the left you find no association in any study. But the studies have limitations, so you can't get a strong conclusion of no association.

I look at periodontal disease in there. Dental plaque. I know those are issues for your consideration. The evidence on those is no association. There are for periodontal disease and dental plaque about 11 studies that are cross-sectional in nature, so that's an inherent limitation. There's one case-control study. But none of those does show an association.

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In the center category -- we call that evidence overall. It seems to say no association, but you do find individual studies showing association, for example, with dental caries and some forms of gingivitis. The recession is shown in one study. There's a later study, which we think is a better study, which does not show that. So that's kind of how we looked at putting this in the overall evidence category of no association.

And then on the right, possible association but a lot of uncertainty and very hard to untangle these effects here.

I think there was an earlier slide about fatality related cardiovascular disease, MI, with snus. I might point out that there are studies -- the studies on snus causing cardiovascular-related disease are pretty clearly without association. But there are studies, some at least suggesting an association, that once you've had a cardiovascular event in your life and then begin using snus, there may be an effect on mortality in that population, but it's a very hard study to untangle.

These are the kinds of outcomes I thought might warrant its own category. Again, whether this is -- these would be -- the absence of these diseases with snus would be a pretty

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significant contributor to reduced harm, but there's a question of do you actually need evidence on this, or is it just biologically plausible -- implausible that snus would cause these? But, anyway, those are the outcomes there for concern.

We looked at a number -- not all studies made direct comparisons of snus with smoking. Most of the studies are about snus use itself and health outcomes. There are some comparative studies. If you look at the comparative studies, you see the same pattern, you see typically elevated risks of significant diseases with smoking and no elevation with snus in relation to those.

And again, particularly, you are informed about the major smoking-related deaths, lung cancer, COPD, other respiratory causes, cardiovascular disease. So there is an analysis of all of that in our paper as well.

So I guess our overall conclusion is that although we did not do a highly quantitative risk comparison, it seemed apparent to us that for major diseases related to smoking -- I'm repeating myself here a bit -- snus doesn't cause them. As far as we can tell, there's no evidence that they cause them, although studies of course have limits of detection, but the risks are all not detectable in those studies.

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And then if you take the rest of the endpoints related to smoking, there is less convincing evidence about the lack of association, we agree, but that might be considered as well.

So it seemed to me that that analysis itself says that this is a product that presents risks not even remotely close to those of smoking.

And we were not the first to see this. I think we've probably gone through the data in excruciating detail. And I don't know whether all of these bodies did the same thing, but we are not the first to assert that snus is a reduced risk product. No one says it's harmless. The harms are pretty small, it seems to us, and it does -- these are the quotes from some authoritative bodies.

Here, the Swedish National Board of Health and Welfare recently -- they say it's not harmless but poses considerably less risk -- they don't quantify it -- than smoking.

You have SCENIHR, this group which is -- I guess it's equivalent to a European version of our National Academy -- making the comment about the less degree of hazard associated with snus. The Royal College of Physicians has made a similar statement.

So there's a lot of support for this idea. I think you'd

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find that we have a product which has significant harm reduction associated with it, if it's used in the right way. Its use can be managed in the right way. I know those are other issues to come.

So it seemed to us clear evidence of significantly reduced risk for major smoking-related diseases and maybe for other diseases where the evidence is less clear but at least suggestive. And there seemed to be quite a strong science base, to me anyway. You may disagree, but this seems like a very strong science base.

I'll stop there. That's a high-level view of the whole situation. If you have questions about specific findings and have time, we will be glad to do that for you.

DR. HUANG: Okay, I guess we do have some time for some clarifying questions at this point. Any clarifying questions?

Dr. Giovino.

DR. GIOVINO: Thank you, Dr. Rodricks. In your slide on tobacco sales in Sweden --

DR. RODRICKS: Yes.

DR. GIOVINO: -- there is a quite remarkable drop in snus use. It looks around 2006 or 2007. I'd love to know why.

DR. RODRICKS: I would too.

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DR. GIOVINO: As well as why are the data only presented to 2008? I can't imagine more recent data are not available.

DR. RODRICKS: Yeah. This was a graphic that we had available from -- actually, I forget who created this. Dr. Rutqvist could answer this better than I can, because he's followed these trends. I wasn't presenting this, by the way, as evidence that it reduces cigarette use.

DR. GIOVINO: I understand.

DR. RODRICKS: But it was what we saw very early in our look at this. This wasn't a prime project for us, but maybe Lars-Erik could comment on that. I don't have an answer.

DR. RUTQVIST: Of course, there are more recent data, and I think we just took this from a publication. So that's why it's only up to this year.

In recent years, there's been quite high increases in excise taxes on snus, and so we see a lot of hoarding effects between years. And that explains the rather abrupt variations, which you also can see here. If you smooth it out over a 2-, 3-year period, the trends stay up. With a decrease in cigarette sales and the increase of snus sales, it would seem to smooth it out, and you would get rid of the hoarding effects.

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DR. GIOVINO: Can I ask one more?

DR. HUANG: Yes.

DR. GIOVINO: Dr. Rodricks, you made a statement and either I misunderstood it or -- but you said TSNAs in snus are the same as in cigarettes, and I find that difficult to believe.

DR. RODRICKS: Yeah, the exposure we did in our --

UNIDENTIFIED SPEAKER: Could you speak into the microphone, please.

DR. RODRICKS: I'm sorry. Hold on, Carol.

Yes, they are the same chemicals, but yes, different exposures. Now, what we did, we looked at all of the HPHCs that had been measured in snus and found them generally to be similar to, not greater than, exposure through food. There are no tobacco-specific nitrosamines in food. There are other nitrosamines.

DR. GIOVINO: Correct.

DR. RODRICKS: We did a comparison with the intake exposure from smoking, relative to snus, and did not find that snus contributed more than what you'd find from smoke, if you could imagine that. It's in our report. Is that confusing?

DR. GIOVINO: Wouldn't it be much less --

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DR. RODRICKS: Okay, I'm sorry.

DR. GIOVINO: I'm sorry, but wouldn't it be much less than from cigarette smoke?

DR. RODRICKS: The best we could say is it's not greater. It's not easy to take smoking-related data and compare it with data from snus itself. We did it in what we thought was a very cautious way. So we could say it's not greater than. How much less it might be, I don't know.

DR. GIOVINO: I'm not sure you're citing all of the available data.

DR. RODRICKS: Well, that's possible. Yeah, I don't have a better answer for you today. We could learn that, yes.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah, I have the same question because, as I understand it, there are levels of the harmful and potentially harmful constituents in the product. Then there's the human exposure, and the bioavailable may vary --

DR. RODRICKS: Yes.

DR. RIBISL: -- depending on the type of product and its formulation and that there are biomarkers for tobacco-specific nitrosamines. And that bioavailability, you're saying, is not necessarily different between cigarettes and snus, in your

product?

DR. RODRICKS: We don't have the same kind of biomarker data for snus, so we did a comparison assuming similar bioavailability from the two products, and that probably overestimates the intake from snus. But it's not greater. I think that was our only conclusion.

DR. RIBISL: Yeah.

DR. RODRICKS: Maybe that's not clear. Maybe we need to clarify that with the -- there's a report in the appendix about that.

DR. RIBISL: Yeah.

DR. RODRICKS: Yes, sir.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Thanks. I had a couple of questions. You actually have two sort of different products that are being considered here. Nine of -- oh, there are 10, but 9 of them are in a little sachet and one of them is loose, and I don't know if there's any difference in the delivery that would make some difference in the exposure.

But I'd also like to know, what is that sachet made out of? Because I don't have any experience with this, and I'd really like to know what it is. I mean, it's not something

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that dissolves, clearly, or else it would be a small one, I guess.

And the second question I have -- and I don't know if you want to answer that one first, then I could call up with my second question.

DR. RODRICKS: Okay. Well, that's a company question, I think. The question was on the composition of the little sachet.

DR. NOVOTNY: Yeah.

DR. RODRICKS: Yeah, it does not dissolve. Do you want to -- the company has to answer that question. And there was also a question about loose snus, right?

DR. NOVOTNY: Yeah. I mean, it may indicate a separate set of exposures.

DR. RODRICKS: Yes.

MR. HASSLER: My name is Thord Hassler. I'm Vice President of Research and Development for Swedish Match.

The sachet is made of a non-woven -- the sachet material is made of non-woven viscose fiber that is bonded together with a polyacrylate binding material.

DR. NOVOTNY: I didn't quite get that.

(Laughter.)

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MR. HASSLER: No, the sachet material that is used to contain the tobacco is made of non-woven viscose material. So it's a cellulose material and that is binded together, you know, to keep it together as a sheet, with a polyacrylate material. It's a food-grade polyacrylate material.

DR. NOVOTNY: Okay, so cellulose is the word that I picked up on, food-grade material that is, you know, non-dissolvable.

MR. HASSLER: It's non-dissolvable.

DR. NOVOTNY: Right.

MR. HASSLER: Completely non-dissolvable.

DR. NOVOTNY: Right, right.

MR. HASSLER: The whole material is completely non-dissolvable.

DR. NOVOTNY: Okay. Could I ask my second question?

DR. HUANG: Yes, go ahead.

DR. NOVOTNY: This is separate, so I think that's great. Thank you. The second question is, the word "product stewardship" emerged both in Mr. Solyst's presentation and in the slides that you used, and I just wonder if the company could provide its definition of what product stewardship is and how it relates to marketing as well as to post-consumption.

DR. RODRICKS: So we used the term. Actually, I don't

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know how Swedish Match might use it, but we use the term because we do a fair amount of consulting in the area. We don't cover all areas of product stewardship, but it's a matter of making sure the company understands its products, its effects on health and the environment and that, as science develops, they are tracking the science well to make sure they have control of that. So it's from birth to death of a product, the full lifecycle of a product, if you're doing it very, very well. So companies are increasingly asking us for advice on what they call stewardship. That's how we define it, looking at health and environmental effects primarily.

There are other issues as well, like resource issues, sustainability, that sort of thing that we don't do, but it's increasingly part of a company's life. That's how we use the term here. So we're not involved in every aspect of product stewardship for this company, but that's how we define it. Maybe you have another definition.

MR. SOLYST: The best example of our commitment to product stewardship is the GOTHIA TEK manufacturing and product standard. I'm sure other companies have product standards, but ours is published. It's got a long history. It was developed with the Swedish food agency. And I think that's, as I said,

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the best representation of it.

DR. HUANG: Dr. Bickel.

DR. BICKEL: I was just wondering if it was possible to get information on the relative price of snus and conventional cigarettes throughout this duration of time, since price is an important determiner. And if those could also include taxes, that would be very interesting. Whether you have any information about the price elasticity, the demand of snus and conventional cigarettes in Sweden in the most recent 10 or 15 years, that would be very important information to share with the Committee.

DR. RODRICKS: That's not for me.

DR. RUTQVIST: I'm Lars-Erik Rutqvist. I'm the Senior Vice President for Scientific Affairs, so I really should be answering this question.

But at least to give you a high-level answer is the fact that historically snus has been cheaper than cigarettes. A can of snus that the typical user would use for about 3 days was about half the price of a pack of cigarettes. In recent years, since the past 4, 5 years, the excise tax has been increased, and this has led to the kind of hoarding effects that I referenced earlier. So now the price of a can of snus is about

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the same as the price of a pack of cigarettes.

DR. HUANG: As a follow-up to that, I just wanted to ask if you might comment on some of the other public health efforts that were going on simultaneously during these times.

DR. RODRICKS: Could you comment, Lars-Erik, on other public health efforts in Sweden to reduce smoking?

That's your question, I guess?

DR. HUANG: Yes.

DR. RODRICKS: Yes.

DR. RUTQVIST: Well, of course, there's been the same kind of public health measures instituted in Sweden as in all other countries. We've had smoking bans. We've had, of course, public education. We've had excise tax increases and so on. So Sweden is no different from really any other European country in this regard. I'm not sure if that fully answers your question.

DR. HUANG: Well, maybe we'll come back. I think --
Dr. Tomar.

DR. TOMAR: Just referring back to the classifications you used to rate the levels of evidence for various endpoints.

DR. RODRICKS: Yes.

DR. TOMAR: I'm a bit confused because although you

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described it as resembling IOM classifications, actually the terminology and the number of categories is quite different from what's used by IOM, IARC, the Surgeon General, and others. And then all of your categories are based on association. It's not levels of evidence supporting a causal conclusion, and as I'm sure you're aware, one of the causal criteria is association. So I'm a little confused by the terminology that you've used and the categorization.

DR. RODRICKS: Yeah.

DR. TOMAR: Clarify that.

DR. RODRICKS: A good question. The basic analysis we went through, I would say, is like the analysis IARC uses, or IOM or others who follow Hill criteria. We didn't get to the issue of causation here. We looked at the associations found or not found, and we used, then, our own words to describe those associations and the evidence supporting them. We didn't think we had to go all the way to the issue of causation, which is always a little bit tricky. The evidence with no association in high-quality studies, you might say, amounts to causation, no association or no causation or causation. You could rephrase them in that way, I would not object to that, but we emphasized associations found or not found.

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DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes. Can you provide just a comment on the relevance of the health effects data on women and also on minority, racial, and ethnic groups?

DR. RODRICKS: I don't think there's information on minority groups of any significance. This was all Swedish experience, all Swedish experience. So that is one of the limitations, perhaps, in the study database as a whole.

On women, do you want to answer that, Lars-Erik?

DR. RUTQVIST: Well, you've pointed out, Joe, that --

DR. RODRICKS: There are pregnancy outcomes.

DR. RUTQVIST: -- there are pregnancy outcomes for each various, as you pointed out, associations, clear associations, and they are all included in the application. The studies are all described in detail in the ENVIRON snus monograph. We have not gone into that, and I think you will understand that later, because we focused on those diseases that make up 80% to 90% of the excess mortality associated with smoking, and pregnancy outcomes are not among those.

DR. RODRICKS: And snus use is not as common among women as among men.

DR. RUTQVIST: No.

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DR. RODRICKS: I added that snus use is clearly not as common -- and I don't have the quantitative difference -- among women in Sweden as it is among men, it's much more common. So the results are strongest for men; we have to say that. But what's been looked at for women does raise the question about certain pregnancy outcomes, not all of them, but no other health effects as well. It's just not as strong a database.

DR. FAGAN: Just a brief follow-up. I'm referring to all health outcomes related to women. So if it's just pregnancy, do you have any data that support these associations with women related to the other health outcomes that are all listed here?

DR. RODRICKS: Yeah, I said the studies include women. I don't have a quantitative figure on the percent of women in these studies. Women use snus in Sweden a lot less than men do. So inherently you have less information on women, but the conclusions I presented on these health outcomes apply to women. They are included in these studies. The adverse findings were related to pregnancy, certain pregnancy outcomes.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: Do any data differentiate on the health effects, differentiate the use of traditional snuff products before GOTHIA TEK and the health effects of most modern products

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using GOTHIA TEK technology?

DR. RODRICKS: GOTHIA TEK does not distinguish the two. GOTHIA TEK came in what year? In 2000. So they're all Swedish snus products that were the subjects of these studies, but the standard was not in place until 2000.

Do you want to add to that?

MR. SOLYST: The standard was announced in 2000. It was evolving throughout the time period in which snus was being manufactured, so it wasn't as if in 2000 things changed dramatically. It was just that GOTHIA TEK was formally announced and published at that time.

DR. HUANG: Dr. Bickel.

DR. BICKEL: I was wondering if you have any -- so I was impressed by the uptake of snus in the population, and I was wondering if you have any data that could suggest whether that was determined by price, perceived health benefits, or greater abuse liability of snus.

DR. RODRICKS: I certainly have not looked at that. I don't know. The question was about what caused the increase in snus use. I think basically that was your question. If you look at the graphic on increased snus use --

DR. BICKEL: Yes. I mean, as you know, price has been

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brought up, health benefit is brought up. And also another potential is that it's more abusable by the tobacco-smoking population, and I was wondering if you had any data that clarified the source of that uptake.

DR. RODRICKS: I certainly don't. I don't know again whether the company has.

DR. RUTQVIST: Well, this was a population trend, and as such, it was obviously multifactorial. The fact that it started some years after the health effects smoking became widely known, I think it indicates that health-related concerns among smokers played a part in it.

But as Jim pointed out, this was a grassroots phenomenon. It was not driven by the marketing. It was not driven by statements from authorities. It was a grassroots phenomenon. It was a return to a traditional product which was the dominating tobacco product about 100 years ago in the country. But I think quantifying the different determinants of a population trend is really very difficult.

DR. HUANG: Yes, Dr. Novotny.

DR. NOVOTNY: Okay, I had a question about GOTHIA TEK. I understand it was a part of a manufacturing standards process, too, but what is the objective of it? Is it to limit the

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constituents? The potential exposures? Can you be specific about what GOTHIA TEK was intended to do as it was put into place?

MR. SOLYST: We can certainly get into that. I don't know about the schedule, though; we're not halfway through our presentation. It may be something we could address tomorrow. We have several people here who can get into great detail on that.

But I'll ask the Chair. Do you want us to proceed with the presentation, or do you want us to spend more time on specific questions?

DR. HUANG: Okay, I think we'll defer that until later and move on.

Dr. Tomar.

DR. TOMAR: Yeah, my question actually somewhat followed on the same line. So if we're going to defer the conversation, we can bring it up later.

DR. HUANG: Yeah, sure.

Dr. Eissenberg.

DR. EISSENBERG: I was just curious when snus started being regulated as a food product in Sweden.

DR. RUTQVIST: 1971.

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DR. HUANG: All right, any other clarifying questions at this point?

(No response.)

DR. HUANG: Okay, we'll proceed with the rest of the presentation then.

MR. SOLYST: Okay, thank you. I am back to talk very briefly about the Norwegian behavioral evidence. The difference between the Norwegian experience and Swedish experience is largely timing, men, similar to Sweden, which is primarily men, switching from cigarettes to snus in Norway. But it occurred in the 20th century, and by 2005 it had become a definite switch among men to snus. At that time the Norwegian Ministry of Health asked their research arm to do some studies to determine why the switch had occurred. What was the impact? Did it lead to cessation?

In the second bullet they list many of the issues. It's almost as if Norway conducted a postmarket surveillance because the product was being used in the country already and they went back and said, all right, what's going on here? And they did look at cessation and they did look at dual use, did look at adolescent initiation, and delayed switching from -- delayed cessation. All of those are part of the public health

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standards that are addressed in the CTP guidance document.

The research was under the direction of Dr. Karl-Erik Lund, and Dr. Lund has published several articles. His most recent article, I believe, is 2013, which summarizes all the previous articles, and it's part of your briefing package from Swedish Match.

The 2013 article contains the line, which I like, particularly as it relates to behavioral evidence, that Norway and Sweden, with its long tradition of snus use, constitutes a natural laboratory in which we can study how snus competes for market share with cigarettes. I think that pertains to some of the questions about the cost of the different products and other impacts on behavioral choice.

I will not get too much into this, but in his 2013 article Dr. Lund presents conclusions. And just some of the statements from the conclusions. In cessation, what basically they found was that snus was a cessation device of choice, that men in particular had tried NRTs. It didn't work for them, and they moved to snus, and that worked better for them as a cessation device. Again, this is addressed in the briefing document that Swedish Match prepared, as well as the Lund article that you have.

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It also addressed dual use, which of course is very important for the public health benefit standard. And essentially what they found was there was not an increase in dual use that paralleled the increase in snus use. And ,again, these other findings are taken directly from the Lund article as well as the Swedish Match briefing document.

You've seen this slide before, and you'll see it again. But if you look to the second level with the Norwegian health behavioral evidence, that relates to the public health benefit standard. It does not relate to the individual risk standard as much, because essentially the Norwegian Ministry of Health accepted the Swedish human health evidence, accepted the fact that there would be individual risk reduction. They were just looking at the behaviors, why this occurred and how it impacted public health in general in Norway.

Let me move on to the rest of our presentation and more formally introduce Dr. Rutqvist. Lars-Erik joined Swedish Match in 2006 after a long career in academic research. He joined as the Senior Vice President for Scientific Affairs. As you can read the slide, previously he was with Karolinska Institutet out of Stockholm, where he was Professor and Head of the Department of Oncology and also Chairman of Research

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Ethics, a broad experience certainly in oncology but also epidemiology and public health.

He will first talk about the clinical trials, so I think it's appropriate that he have experience in designing, conducting, and analyzing randomized clinical trials, and certainly a pharmaceutical and biotechnological company experience. He'll first talk about the clinical trials.

I think it's important to note that that was one of his first initiatives after arriving at the company in 2006, realizing that the company needed to do or should be doing clinical trials. Again, back to the question about product stewardship, this would be an example of it. This was before passage of the Tobacco Control Act. The results were very useful for this application, but the design, of course, occurred before the Act.

But with that, let me introduce Lars-Erik Rutqvist.

DR. RUTQVIST: Thank you, Jim.

In this part of my presentation, I will give a brief overview of two randomized placebo-control trials and a meta-analysis of those trials of snus as an aid in complete smoking cessation.

These trials inform several of the science areas that are

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mentioned in the draft guidance for modified risk applications that was published a few years ago. But perhaps most notably, the trials are relevant to the benefit to the population as a whole, a provision in the statute, and that they provide experimental confirmation of the extensive observational data from Scandinavia on the ability of snus to function as an aid for smokers to quit cigarettes completely through switching to snus.

But the trials are also relevant to the transferability issue, as it were, in showing that complete cigarette cessation with snus can occur also in geographies, settings, without any longstanding history of snus use.

The background to the trials were discussions within the academic and the tobacco control communities in Sweden in the early -- well, about 10, 15 years ago -- about the determinants of the Swedish experience and particularly the role of snus. And there were critics supporting the use of pharmaceutical products like NRTs, who pointed out the fact that there was a lack of experimental data on the efficacy of snus.

And on the European level there were discussions about the transferability of the Swedish experience to other countries. And these discussions prompted academic researchers to reach

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out to the company and initiate discussions about the possibility of the company sponsoring independent randomized clinical trials. We accepted sponsorship for two such trials, one conducted in the United States and the other trial in Eastern Europe, in Serbia.

Jim mentioned that these trials were initiated before the passage of the U.S. Tobacco Control Act. And snus has never been marketed as a smoking cessation aid in Scandinavia, and our applications do not include a smoking cessation claim.

So the sponsorship for these trials was more a reflection again of our stewardship for the snus category, in addition to what Jim mentioned about GOTHIA TEK.

Now, before the trials were initiated, we put in place a quite rigorous governance structure for these studies, and essentially we adopted what I would call the pharma model for governance, because that was something I was used to from my previous work in medical oncology.

But we went beyond that and included elements that you would normally not see in a trial sponsored by a pharma company. For instance, we made a commitment early on to publish the results from the trials, irrespective of the trial outcome. And we also made a commitment to make the data

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available for systematic reviews or meta-analyses.

This slide shows the design of our U.S. trial, and essentially we adopted a design that you see with pharmaceutical smoking cessation aids like NRTs. There was a relatively short period of study product usage, in this case 4 months, and then follow-up continued up until 6 months. And the primary endpoint was continued biologically verified smoking cessation from the target quit data for cessation.

The Serbian trial had a slightly different design. During the first 6 months of this study, the aim was to achieve smoking reduction, and those participants who achieved substantial smoking reduction at 6 months continued in the trial, and during this period the aim was complete smoking cessation. Study product usage continued throughout the period of observation.

When it comes to participants' characteristics, it was interesting to note that our U.S. participants had done, much more frequently, previous quit attempts, 88% versus only 36% in our Serbian trial. And also U.S. participants, 50% of them had previously made failed quit attempts using NRTs, whereas use of NRTs was virtually unheard of in Serbia.

Early on, we decided to perform a meta-analysis of the

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trials because combining the evidence from the trials would allow a more powerful test of whether snus affects the rate of quitting, because it improved statistical precision and thereby allows better insight into the main hypotheses. Also having access to primary subject data allows comparable definitions of outcomes and potential confounding variables, identical statistical analyses, and of course calculation of exact, rather than approximate, probabilities.

This is something just about the design of the meta-analysis. We defined several endpoints, the primary endpoint being continued cessation during 6 months. But we also defined a number of secondary outcomes related to 1-week prevalence rates and continued cessation during the last 3 months or 1 month of the study.

And here are the results from the meta-analysis of the primary outcome. And in terms of the defined primary outcome, the results indicated a two-and-a-half to threefold increase in the success rate among participants who had been allocated to snus versus placebo. And the point estimate of the odds ratio was 2.83, and there was no evidence of significant heterogeneity between the two trials.

I present the results for just one of the secondary

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outcomes. This is the outcome related to continued cessation during the last 3 months of the study, and we saw roughly a two to two-and-a-half-fold increase in the success rate among participants allocated to snus, and no significant heterogeneity between the trials.

It was interesting to note that the efficacy of snus was not affected by any of the baseline characteristics, and this included previous failed quit attempts and previously failed quit attempts using NRTs.

So, in conclusion, these studies show that complete smoking cessation during 6 months was two-and-a-half to three times higher in the group allocated to snus in both Serbia and in the U.S., and for all biologically verified secondary outcomes, the success rate was about twice as high in the group allocated to snus.

So these results are at least equal to those observed with NRTs, and perhaps somewhat better. And this could possibly be related to the difference in nicotine pharmacology and pharmacokinetics of snus versus NRTs. Snus is slightly more cigarette-like, if you will, with a shorter time to C_{\max} than NRTs. And this is illustrated in a set of three separate clinical trials on nicotine pharmacokinetics which are part of

the application, but which I don't have time to go into here.

There was no evidence that the success rate was modified by the baseline characteristics, including the previous quit attempts with NRTs. And in terms of this trial setting, we found that snus was safe and generally well tolerated.

And I think these trial results support and enhance the findings from the observational Scandinavian studies on the role of snus for complete smoking cessation. And obviously complete cessation could be achieved also in geographies without historic use of any form of smokeless tobacco, which is Serbia, or without the history of snus use.

Thank you.

MR. SOLYST: Unless there's clarifying questions for Dr. Rutqvist.

DR. HUANG: Yes, Dr. Bickel.

DR. BICKEL: I have two questions. First, just because you were talking about the use of snus in other European countries, could you tell me what the status of the snus is in the European Union?

And, secondly, with respect to that trial, could you tell me what percent of compliance with the use of snus was during the treatment period?

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DR. RUTQVIST: First of all, use of oral tobacco in the European Union is allowed, with the exception of snus.

As to the question of compliance, I can provide detailed information on that, but perhaps we could go into that during tomorrow's discussion.

DR. HUANG: I have one question. I'm trying to look at the meta-analysis of the study that you did, and I was surprised to see my own community, Austin, included in this. But in terms of the number, *n*, like for snus -- and you had 4% biochemically verified continued smoking cessation. Does that mean that there were five individuals out of the 125 that were successful?

DR. RUTQVIST: I don't have that exact number in my head, but the number seems approximately right.

DR. HUANG: So it is five cases. Okay, thank you.

Dr. Novotny.

DR. NOVOTNY: Yeah, I just want to make sure that this is clear. In the two data reports here, the two bar charts that the U.S. data are reported are not significant in terms of success. Serbia and the U.S. are pretty different places, as I'm sure you're quite aware, and so what we're looking at is the U.S. success here.

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And the other question I had was, has there been any reported studies that you've done, the company, on the comparison of snus to NRTs and other cessation modalities?

DR. RUTQVIST: I'm not aware of any other randomized clinical trials of snus as a smoking cessation agent, and we actually did a literature review before publishing this meta-analysis, and we could not identify any such -- any other studies that could be included in a formal meta-analysis.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: I just wanted to know what was the rationale to choose Serbia as your second venue, given that there is no prior history of smokeless tobacco use, and that prior to giving, you know, smokers opportunity to use nicotine replacement therapy before other tobacco product is introduced.

DR. RUTQVIST: Well, the rationale was precisely what you mentioned. There is no historic use of, I believe, any form of oral tobacco, including snus, in Serbia. So that was an important feature that we took into account when we decided to sponsor this study.

DR. HUANG: Mr. Henton.

MR. HENTON: When you used the word "placebo," was that a packet of non-nicotine containing material?

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DR. RUTQVIST: It was based -- I mean, these products were custom made for this trial, but the active snus products were -- the manufacturing of those was obviously based on our methods for routine production of snus. The placebo products were virtually identical products, and those were based on another commercially marketed product in Sweden, called Onico. That includes no tobacco, no nicotine, and it's frequently used for snus users who want to cut down on their snus use or they use it as a snus cessation aid.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I was actually going to ask the same question. So did your placebo product taste different from your active product?

DR. RUTQVIST: As I said, these products were custom made, and there were different flavors used in these products. But we tried to make them as similar as possible, and I don't think anyone would be able to tell them apart because of the flavor. But obviously if you're a nicotine user, after a few minutes you would probably know whether it's a pouch delivering nicotine or not.

DR. GIOVINO: So they had the same mouth feel and --

DR. RUTQVIST: Yes.

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DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Yeah, just one question. On the Serbian trial, if I understand correctly, people were able to use a product through the entire duration of the trial, if they wanted.

DR. RUTQVIST: Yes.

DR. BOFFETTA: Instead, in the U.S. trial, after Week 16 or whatever, they will not have access to --

DR. RUTQVIST: Right.

DR. BOFFETTA: -- the product. So many of these -- in the Serbian trial, many of the people would have kept using snus after the end of the trial. I mean, do you know how many -- I mean, the two trials seem quite different in the design where you want to assess smoking quitting rate after 24 weeks or whatever, because in one trial there was opportunity to have access to the product and the other was not.

DR. RUTQVIST: I mean, the rationale for that was that individuals who -- in the U.S. trial, I mean in this country, smokeless tobacco is widely available, whereas it is not in Serbia. But it also was a reflection that the trialists in the -- who conducted these trials had different views, so what a proper design in their country would look like. And our U.S.

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trialists preferred a more standard design, similar to what you would see in an NRT trial, whereas our Serbian trialists felt that it would be more appropriate to offer intervention throughout the observation period.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Yeah, I'm sorry. This is actually just a follow-up on my last question. What was the regulatory status of snus prior to 1971?

DR. RUTQVIST: It was considered to be a tobacco product, so it was regulated as other tobacco products.

DR. EISSENBERG: And maybe this is something we can discuss later, but to what extent would the Swedish experience reflect, in part, the change in regulatory status so that snus now appears to be a food rather than a tobacco?

DR. RUTQVIST: Well, Swedish snus has always been manufactured using a heat treatment method. What happened in the early '70s when it came under the jurisdiction of the Swedish Food Act was the toxicologists at the Swedish food authority started to look at this product, and they noted bacterial activity leading to -- possibly leading to formation of nitrosamines, which was a quality problem that was known to the company. These contacts, as Jim pointed out, were the

starting point of the development of GOTHIA TEK as a product standard.

So this was something that started in the early '70s and then gradually evolved, including more and more quality assurance methods, testing of the products and so on, and then finally the introduction of the entire product standard in the year 2000. So this was a gradual process.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, thanks. You say that the success rates with snus did not differ according to a number of factors, including gender. So did you all stratify the analyses by gender to look at the effects?

DR. RUTQVIST: No, we didn't feel that we had to since there was no interaction with gender.

DR. HUANG: Actually, I think, Dr. McAfee, are you on the line? Tim? Are you on the line, Tim? Yes.

DR. McAFEE: I had a quick contextual question about the interesting clinical trial data, which may actually relate to the next slide, which is essentially this is the kind of data that would be presented if Swedish Match -- if you were actually moving forward to try to get authorization from the FDA through CDER rather than the Center for Tobacco Products

for use as a cessation aid. But I'm basically curious of how you see this as impacting or supporting the much more specific and different issue of a modified risk claim that's associated with a change in a warning label. I'm having a hard time seeing how this would either sway positively or negatively that finding.

DR. RUTQVIST: As I mentioned initially, I think these trials are relevant to the provision about benefit to the population as a whole because it demonstrates, as I said earlier, that smoking cessation with snus can happen also in geographies without a long-term history of snus use. And the trials confirm -- provide experimental confirmation to the causal nature of the availability of snus as a determinant of the Swedish experience.

And as I will come back to later in my presentation, having smokers giving up smoking completely is obviously an important aspect on a benefit to the population-as-a-whole issue.

DR. McAFEE: Yes, I see some relationship to that, but I guess the question I would have is if you were thinking of it as being something that would be used as a cessation aid, that would be something that, in order to make that claim or to

market it as such, it would need to go through a different branch of the FDA.

And I'm curious. I assume you're thinking that somehow the changes in the warning label would make it easier for it to be used as a cessation aid or how the cessation, which is a quite different characteristic and requires people to make a conscious effort to quit and use it in a certain manner, how that would necessarily translate to a warning label change.

DR. RUTQVIST: Well, we're not seeking a smoking cessation claim. Snus has never been marketed as a smoking cessation agent. The change of the warning labels, I think, is warranted given the fact that they're fairly incorrect. The label is incorrect at the moment, and I think smokers in general would benefit from having accurate information about the health risks of various products.

And to your question specifically, yes, I do believe that some smokers may be hesitant to switch to this product which, according to the current label, does not provide any benefit to them, compared to continued smoking.

DR. HUANG: I do have a follow-up to that. I mean, isn't it correct that the current Swedish health warning on snus says this tobacco product can damage your health and is addictive?

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DR. RUTQVIST: Yes. As you noted, then, no specific diseases are mentioned, so the warning is more general or generic in nature than is the case for smokeless products here in the United States.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: One more question in follow-up to Dr. Eissenberg's. So if there were bacteria forming, the food scientists noticed that. Can you provide a brief history of like what percent of snus products sold were refrigerated over the decades in Sweden?

DR. RUTQVIST: Well, refrigeration of the products was something -- a feature introduced about the same time as GOTHIA TEK was introduced. I cannot remember the exact year when this happened, and I would need to consult my colleagues who know this better than I, and I can come back to you about the exact year.

DR. GIOVINO: And if I may. You know, in the United States we've had very dramatic shifts of use of various tobacco products because of excise tax increases in the last -- since 2007 or '08. And if it is possible, since tomorrow we're discussing the generalizability of the phenomenon, to get data on per capita consumption that is 2013 or '14, that would be

appreciated.

DR. RUTQVIST: Okay.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah, just two comments. So one has to do with the refrigeration. I notice in the U.S. you often sell General Snus in a refrigerated compartment display, and typically it's outside of where the main back bar is. I think it's because they're looking for a plug. And so they often -- FDA says you can't have self-service, so they often have it locked.

But my question has to do with because nitrosamine formation increases over time if it's not refrigerated, making the product more toxic, do you plan to refrigerate the product in the U.S. typically?

DR. RUTQVIST: To keep the products in a fridge has nothing to do with nitrosamines. Nitrosamines do not form after the product has left the factory, and that is because of the very low micro-bio count in the product. The main reason for cold storage is to preserve product freshness, if you will, the level of the water content and so on, and to prevent snus aging, which consists of a drop in pH and of course oxidation of the nicotine and so on. So this is to preserve a proper

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shelf-life for the product, not to prevent nitrosamine formation.

DR. RIBISL: So you're saying that there are no changes in harmful and potentially harmful constituents if the product is not refrigerated over time?

DR. RUTQVIST: Yes. And I think --

DR. RIBISL: Those constituent levels don't change?

DR. RUTQVIST: Yes, that's true. And I think my colleagues from the lab can show you some slides on that --

DR. RIBISL: Okay.

DR. RUTQVIST: -- tomorrow if you're interested. Perhaps we should continue.

DR. HUANG: Okay, we'll move on with the --

MR. SOLYST: Mr. Chair, we do have the rest of the presentation.

DR. HUANG: Okay. Sure, we'll move on with the presentation now, and then we'll have the final part of the presentation and have another opportunity for clarifying questions.

MR. SOLYST: Okay. Lars-Erik will return and describe the premarket consumer perception study, which is, of course, addressed in your FDA briefing package. It's part of the

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decision making you'll have to make tomorrow.

Just as a timeline for the premarket, this unlike, say, the clinical trials was designed specifically for the applications. As I indicated in my opening remarks, we developed different protocols, always improving the protocol with the input from the advisory panel and in meetings with CTP to ensure that the protocol could go forward. The more serious meetings occurred in early 2013, and then we initiated the study later in 2013 and received the results in February 2014. So they're fairly recent results.

And with that, let me turn it back over to Lars-Erik to describe the premarket consumer perception study.

DR. RUTQVIST: Well, for us, an important background for this study is the statutory language about the labeling of tobacco products. A tobacco product shall be deemed to be misbranded if its labeling is false or misleading in any particular. And if you view that together with the currently four mandated warning statements, it is clear that the scientific evidence that we've submitted as part of our application indicate that the current label for our snus products is misbranded.

And to provide a scientific evidence base for a possible

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change of this situation, we conducted this consumer perception study, which was a quantitative randomized controlled study of more than 13,000 subjects aged 18 to 64 years, half of whom were current users of tobacco products and the other half current non-users of tobacco products. And we had developed a protocol with all of the elements that you would typically see in an academic research setting.

The study was done by an external research contractor that has extensive experience of consumer research and online data acquisition, and the subjects were sourced mainly from consumer panels, but to some extent also via advertising. And we developed this protocol building on the methods that we routinely use for consumer research, but the procedures were enhanced to comply with the FDA guidance. And as Jim mentioned earlier, we received extensive input from our advisory panel. But I would also like to thank the CTP for providing their input at several meetings that we had with them. And all of that input went into the protocol.

So when you look at the final result, I think I can safely say that the protocol conforms with all of the provisions in the draft guidance document specifying how clinical studies should be conducted in support of a modified risk tobacco

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product application.

Study objectives included to assess consumer understanding, tobacco use behavior, or behavioral intent, I should say, and perceptions of health risks among subjects exposed to one out of four existing warning statements and two new test statements. And this was done according to current tobacco use and the demographic subgroups.

Now, before I move into sampling results from the study, I think it's important to consider the linguistic nature of these tested statements. And when you do that, I think it's obvious that the current four warnings represent simple assertions. As such, they should be quite easy to understand, whereas the two new test statements, no tobacco product is safe, which is a simple assertion -- but then these statements go on to try to summarize the whole concept of tobacco harm reduction or continuum of risk in one sentence. And, of course, you would expect such a more complex or nuanced message to be more difficult to understand.

And the rationale that we have for these two statements was that, first of all, we wanted these statements to be consistent with the available literature on health effects of snus. But, of course, we also wanted to make the statements

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consistent with the statutory definition of a modified risk tobacco product, and that language implies a comparison with other products and, in this case, cigarettes.

We felt that the evidence that Joe summarized previously merited an inclusion of the word "substantially" because the health risks of snus are substantially or dramatically less than those associated with smoking. But at the same time we realized that the word "substantially" might be open to interpretation, so we wanted to test also a variant without that particular word. And, of course, we brought up these tested statements with the CTP during our meetings.

I should also point out that these new test statements would be -- if approved, they would be the first time that the American public would be exposed to a comparative risk statement in a warning label.

The study design implied a random allocation to one of the six warning statements. People in the consumer panels were invited to participate in the study until predefined quotas were filled of about 1,100 current tobacco users and 1,100 current non-users for each of the six statements.

This is just an example of the research stimuli used. These were color photographs of the consumer packages bearing

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one of the six statements.

The sample was balanced for a number of baseline characteristics which implied that the study included about 25% to 30% participants aged 18 to 24, and about 30% belonged to minority groups, and about half of the participants had an annual household income of less than 45k.

Now, you can imagine that with a questionnaire which included in excess of 80 questions and a total number of participants in excess of 13,000, this makes this dataset incredibly rich. And you can look at a large number of subsets, and you can focus on, as I said, potentially up to in excess of 80 questions. I cannot go into that much detail here today. I will focus on five of the questions in the questionnaire that had to do with the ease of understanding of the statements, their believability, the relative risk perception of snus versus cigarettes, motivation to buy snus, and unlikely to use snus on the basis of the tested statements.

Now, this is a summary for the total number of participants, how they responded to the "ease of understanding" question, along a seven-point scale anchored at the top with "very easy to understand" and at the bottom with "very difficult." And it was reassuring to find that as many as two-

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thirds of the respondents exposed to the two new test statements rated their understanding in the top two boxes, that is, that the statement was very easy or easy to understand.

And now admittedly, that was somewhat lower than for the existing four current warnings. But I think perhaps the most important observation was that the proportions of respondents who rated the statement to be difficult or very difficult to understand, the bottom two boxes, was quite low. And I think it was ironic really that perhaps the two most misleading statements, that about oral cancer and gum disease, were the ones that were rated as the most believable. Among overall responders, they were significantly less likely to find the two new test claims to be believable compared to all current claims. So here again I find it ironic to see that the two most misleading warning statements were the ones that were deemed to be the most believable.

On the question related to risk perception of snus versus cigarettes based on the warning claim, half of those exposed to either of the two new test statements felt snus would be somewhat less harmful than cigarettes, which was significantly higher than any of the current claims. And I think this result shows that the new statements have the ability to make people's

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risk perceptions of snus more accurate and more consistent with the available literature than the current four warning -- any of the current four warning labels.

On the issue of motivation to buy snus based on the warning claim, both two new test statements would be significantly more likely to motivate overall respondents to buy snus compared to all current warnings, although the proportions were quite small.

On the issue of likelihood to use snus based on the warning claim, again, this is based on the total number of respondents. The test claim of a substantially lower risk than cigarettes was significantly more likely to influence snus usage than most of the other statements. But this increased likelihood to use snus only concerned current tobacco users, because when we looked at current non-users of tobacco, no claim stood out as one that would influence this category to use snus. And this held true also for former users among the current non-user category. They also seemed to be uninfluenced by any of the tested warning statements.

So, in conclusion, the two tested new statements resulted in respondents being better informed about the relative risk of snus versus cigarettes. And the impact on motivation to buy,

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the likelihood to use snus, was restricted to current users of tobacco products. And we could find no adverse impact on current non-users of tobacco product from the tested new statements.

And as to findings among young adults, minorities, and respondents from low-income households, well, the results were similar to those for the total population, taking into account current tobacco use status. So we couldn't find that the study raised unique issues of concern for these demographic subsets.

And, finally, I'd just like to say that the premarket data indicate that the tested two new statements seem to be unlikely to produce unintended consequences.

But in closing -- yeah, I should mention this. The advisory panel was much involved in the development of the protocol for the premarket study. And two of the panel members, together with others, have conducted their own independent analyses, and they looked at slightly different subsets than the analyses that I just presented to you. Thus they classify the responses to the questions a bit differently, they used a different statistical methodology, and publication of these results is under way.

I've seen the manuscript, and obviously I cannot go into

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any details, but let me just say that their findings do not contradict -- well, in fact, they support the analysis that I presented here, including the conclusions included in the modified risk tobacco product applications.

We've been very open with these data. As Jim pointed out, we've perhaps even been aggressively open about it. So the raw data from the study has been made available as part of our application on the FDA website. And I would like to encourage all those who are interested in this study and the findings that I have presented here to conduct their own independent analyses. So thank you.

Oh, yeah, I forget my last slide. I'd just like to point out a circumstance that perhaps is obvious to everybody, but I think it should be pointed out. There will always be an element of uncertainty in premarket studies, irrespective of which methodology you use, irrespective of how you phrase your questions and so on, because in real life, humans don't always act the same way as we say we will in a research setting. We may be influenced by unexpected situational or subconscious stimuli.

So we therefore look forward to do postmarket research and collect data on how these snus products marketed as modified

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risk products actually perform on the market. And there we would see actual behaviors. We have not yet put together a final protocol for that, but we would obviously welcome the input from TPSAC.

Thank you.

DR. HUANG: We'll take a few clarifying questions.

Dr. Choiniere.

DR. CHOINIERE: Actually, I don't have a question. I just wanted to make a point of clarification about CTP's role on the input -- of our input on the design of the study. Swedish Match designed this study. They did request meetings to discuss this study, where they asked us specific questions about what they were doing and we provided responses.

Thank you.

DR. HUANG: Yes, Mitch.

MR. ZELLER: Do you have data on the likelihood to use snus for current tobacco users, that could differentiate current tobacco users based upon quitting intentions?

DR. RUTQVIST: I would have to ask my colleague about that. Was that included in the initial questions characterizing the participants?

MR. RAJAN: Hello, my name is Vijay Rajan. I'm the

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Director of Market Research for Swedish Match.

To answer Dr. Zeller's question, we do have information on quitting behavior or for people who are -- the word escapes me -- the people who are consumers who said that they attempted to quit within the past 12 months. We do have information on that.

MR. ZELLER: Let me follow up. Can you break that out based upon future -- about quitting intentions going forward?

MR. RAJAN: Just give me a second and --

MR. ZELLER: It doesn't have to be now, but I think it would be helpful for the Committee to be provided with that information.

MR. RAJAN: Yes, we do have information on that.

MR. ZELLER: Thank you.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: For the study you have here -- so you've got sort of multiple outcomes that you're looking at in terms of both risk perceptions, likelihood to use, intentions to buy. What we're seeing is basically proportions of agreeing or disagreeing with particular outcomes.

Have you done any sort of mediated process-type models to look at more of the processes of cognition that are going on in

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the consumers, to look at how is the label influencing believability of the message, which in turn may influence likelihood to buy and/or interest in trial? Rather than viewing these all as discrete outcomes, how much of this have you looked at in terms of a process?

DR. RUTQVIST: I think the results I presented is illustrative of the type of analyses that have been included in the modified -- in our applications, and we have not included the type of analyses that you referred to. No.

DR. HUANG: Okay, Dr. Novotny.

DR. NOVOTNY: Yeah, Dr. Rutqvist, this goes back to the clinical trial, but it's germane to what you were trying to do with this larger study, and that is whether or not you had any qualitative data from the clinical trials that could actually inform the acceptability or the intentions of the participants in the clinical trial. Because I noticed that you did the Fagerstrom scale with them, but I wonder if there were -- and also whether or not there were incentives provided to the participants.

DR. RUTQVIST: I believe there was incentive provided to the participants. I cannot say the exact amount.

MR. RAJAN: Almost 13,000 of the participants who --

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(Off microphone comment.)

MR. RAJAN: The clinical trial.

DR. RUTQVIST: Oh, sorry, I thought we talked about the premarket consumer perception study. Again, what was your question?

DR. NOVOTNY: The question was whether you've gotten any qualitative information from the participants in the clinical trial that would have also fed into this concept of the acceptability and intention to quit, et cetera, that they may have had. I noticed that you did the Fagerstrom test on that. And also whether or not the participants in the clinical trial were incentivized.

DR. RUTQVIST: Participants in the Serbian trial were not incentivized. They received no financial compensation to participate. There was financial compensation for the participants in the U.S. trial. I don't know off the top of my head exactly how much that was, but it was considered to be sort of reasonable according to the types of intervention that -- it was considered reasonable by the CRO company that we worked with.

Was there qualitative information collected from the clinical trial? Well, obviously, we collected baseline

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information, standard baseline information on these participants, and that included Fagerstrom score. I'm not really sure which other data you're asking for.

DR. NOVOTNY: Well, the information about how the use of the snus is acceptable or something that, you know, they thought positively about after the end of the trial. You know, it wasn't a crossover, I know, but it seemed like there might have been some good information to gather there.

DR. RUTQVIST: Okay, I understand. No, we did not collect that type of data.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: So in designing a study like this, I would have thought it would be pretty important to present to the participants the actual stimuli the consumers will see in the marketplace. And in that context, I was struck by the missing word in the stimulus that you presented. Can you help me understand why it is you would want to omit one of the most important words, which is W-A-R-N-I-N-G, prior to the stimuli that are being presented?

DR. RUTQVIST: Well, the stimuli presented to the participants of the two test statements was exactly what is shown here and what is included in my presentation.

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DR. EISSENBERG: But none of them are what the consumer is going to see in the marketplace.

DR. RUTQVIST: No, but this was an online questionnaire, so it wasn't possible to show actual consumer packages.

DR. EISSENBERG: You could have put "WARNING:" on the stimuli that were presented to the participants. And it's unclear to me how the results from this study can generalize to the marketplace of the future when the stimuli that you presented are not what people are going to see in the marketplace of the future.

DR. RUTQVIST: Well, these were the statements that were tested.

DR. EISSENBERG: No, I understand that, but why? Why would you not include the word "warning"?

DR. RUTQVIST: Again, this goes back to the rationale that we had for the actual language. We wanted it to be consistent with the science. We wanted it to be consistent with the statutory language. And it is a kind of warning, but I think perhaps adding the word "warning" might be confusing.

DR. EISSENBERG: Well, it may be, but the word "warning" is in the request that you're asking us -- FDA to approve.

DR. RUTQVIST: Again, what is shown here and what I've

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shown you here was the statement that the participants were exposed to.

DR. HUANG: As a follow-up to that, what was the development of those messages that were tested? What did you do to sort of come up with those messages? I mean, I think there was one public comment that actually said this is not even a warning at all, but it's more of a recommendation for use. But how did you develop these, to decide to test these?

DR. RUTQVIST: I think we were partly inspired by the current warning used in Europe or prescribed in Europe for smokeless tobacco products, because that warning does not include any reference to any specific disease. As was mentioned earlier, it only talks about the product being addictive and that it may damage your health, but sort of generic. And it doesn't include the word "warning."

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah, just a comment on the choice of language. And so one of the things you commented, the one that says this product can cause mouth cancer, has about a 4.7 reading grade level. Your one about the product being -- presenting a substantially lower risk to health than cigarettes has about a 10.9 grade level and has about 26 syllables. So I

think that explains some of the ease of understanding was lower, so people had it harder to understand, and they obviously found it a little bit less believable.

But did you think through some of the literacy issues as you were crafting the language for these? And given especially the audience that's going to be buying the products, it's important to be really sensitive to literacy.

DR. RUTQVIST: Yes, of course, we did that. And I think any statement to the general public that tries to summarize the concept of tobacco harm reduction in one sentence is not likely to be perhaps as easy to understand as the current warnings, which are simple assertions basically. So, yes, we did think about that, but again the rationale was consistent with the science, consistent with the statutory definition of a modified risk product. And this was what we ended up with.

DR. RIBISL: But actually to be consistent with the statute, the statute does talk about comprehensive -- that it needs to be understandable to consumers too, though.

DR. RUTQVIST: And I think this study showed that close to two-thirds of the participants rated this as very easy or easy to understand. So I think we achieved our goal in crafting a message that was easily understood. And also, there were very

few participants who scored the bottom two boxes, that is, meaning that it was very difficult or difficult to understand.

So I think we achieved our goal in crafting a message that would be easily understood, even though it tries to summarize, as I said, the whole concept of tobacco harm reduction in one sentence.

DR. HUANG: And I've got questions from Dr. Fagan, Dr. Djordjevic, and Dr. Tomar. So Dr. Fagan first.

DR. FAGAN: This is just a follow-up question because I'm really trying to get clarity on how these messages were developed. With regard to consumer input, did you do any focus groups or did you seek out consumer input into the development of the language for these specific messages?

MR. RAJAN: The whole questionnaire was tested, and we did the cognitive testing with 160 consumers in focus groups before putting it online.

DR. FAGAN: Did they actually help you develop the language for the messages, or did you develop the messages and begin to do some testing with them around it? That's what I'm trying to understand.

DR. RUTQVIST: No. As Vijay pointed out, we did the cognitive testing, and the results indicated that there should

be no problems for participants to understand these messages.

DR. HUANG: But, again, I think the question was that you had developed the messages to be tested first. You did not get the input in development of the messages.

DR. RUTQVIST: No, the input from the cognitive testing was more of a confirmation that we have got it right. We did not use input from those types of activities to craft the message.

DR. HUANG: Okay, Dr. Djordjevic.

DR. DJORDJEVIC: Just clarification between those two messages, and there is no warning. One is about lower risk to health than cigarettes. One is substantially lower risk. How "substantially" is defined, what are the criteria for that?

DR. RUTQVIST: Well, precisely, that was the reason why we included these two different versions, because we realize that the word "substantially" is maybe open to interpretation. But I would say that 80% to 90% risk reduction compared to cigarettes merits the descriptor "substantially."

DR. HUANG: Okay, Dr. Tomar.

DR. TOMAR: I was wondering if you did any age-specific analyses in these, particularly for non-tobacco users. I think your youngest age group was 18 to 24.

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DR. RUTQVIST: Um-hum.

DR. TOMAR: I don't know if you have those data available.

DR. RUTQVIST: Well, obviously, we did analysis according to age, and we couldn't find that age was a predictor as to how understandable or which effect these statements would have. But, yes, our lowest age included in the study was 18 years.

DR. TOMAR: Can I ask a follow-up? So earlier you had presented data from Sweden and from Norway on showing increases in the prevalence of use of snus. I was wondering, in that analysis, if you looked at it by birth cohort.

So two ways that prevalence can increase. One could be smokers switching to snus, and another could be young non-tobacco users adopting snus as their initial form of tobacco. What are the relative proportions that drove that increase in snus? Because I think that relates directly to the age-specific interpretation of these kinds of messages.

DR. RUTQVIST: Now, we should perhaps clarify that this premarket study was used based -- it did not include any Scandinavian participants.

DR. HUANG: All right. And then I do understand, Dr. McAfee on the line has a question. Tim?

DR. McAFEE: Yes, thank you. Yeah, this is in

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appreciation to Swedish Match for doing the study.

I guess I have a couple questions that grow out of one of your last bullet points, which was that you think this helps rule out unintended consequences. And the two concerns I have, I think, which were being alluded to earlier, one is the fact that -- really, what are the unintended consequences we are concerned about? And some would be behaviorally oriented, and some would be related to risk perception.

You didn't actually do any testing of adolescents, which, I'm sure, would have been challenging to get approval for. But, nonetheless, clearly one of our biggest concerns is going to be adolescent uptake in kids who might otherwise not have used a tobacco product. So I'm just curious if you would see that as postmarket surveillance or what your thinking was around that.

And then the second one was that you're reassured by the fact that people state that their perception is that they understood what the meaning of these warning statements were, including your sort of warning statement that tries to summarize harm reduction.

But I'm curious if you actually included any testing of their actual understanding. You said you thought that you

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should use the word "substantially" because the risk reduction is 80% to 90%. But did you ask people whether they thought that what this warning label meant was a 50% reduction or a 99% reduction?

And then I guess I would say one of the things we would be the most worried about, based on current experience in the United States around how smokeless products are actually being used and in fact how e-cigarettes are being used, is that there may be a misunderstanding that people think if they can lower their risk by partial substitution -- and since we know that a lot of smokeless users in the United States, that is their pattern, and it's a majority pattern with e-cigarettes, if you had a warning that said that this product is substantially safer than cigarettes, that some people would interpret that to mean that if I substitute half my cigarettes with snus, I would lower my risk by 50%.

So, again, I assume that you didn't test for any actual understanding of a risk as opposed to just a person's perception if they understood it. But I think it's common in these types of certain things that you actually did try to inventory people's knowledge or understanding as opposed to just a basic they understood it.

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Thank you.

DR. RUTQVIST: I think there were a couple of questions there. Let me try to answer at least a few of them.

You mentioned this issue of dual use. Well, we've included information on that based on studies from Scandinavia, where dual daily usage of smokeless products, snus and smoking, proportions are very low. So it's an unusual phenomenon in Scandinavia, and I'm aware that it's a much more common phenomenon in this country.

And I would put it to you that part of that may have to do with the messaging that the consumers today receive. They receive no information that switching to another product would have any sort of health effect whatsoever. And so I could ask myself, if you're an American smoker, where's the incentive to switch to another product? The message is all products are bad for you, and no product is any safer than another.

You also asked about why did we do a quantitative study as opposed to a qualitative study that perhaps would be more able to fully understand what it meant, that people answered that they felt that the test statements were easy to understand? Well, we went with a qualitative study. We believe that having a large-scale study with this type of design would be the most

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appropriate to address the research issues at hand.

And as always, you can choose different methodologies, different approaches, and at the end of the day you have to make choices. We went with this quantitative large-scale study. And, of course, when you've done the study, when you presented your application, you can always be criticized for why didn't you do it any other way? And I'm sure that a qualitative study would have been -- would have added to this. But I put it to you that it's by no means certain that using an alternative methodology here would increase the predictive ability, as it were, in terms of behaviors.

So I think we have to go to the postmarket situation to be absolutely certain how this influences behavior, which I think, at the end of the day, is perhaps the most important issue.

DR. HUANG: And I do see, looking at my watch -- I do want to reassure you, we do have a little flexibility, so we've got until even 12:30 to make sure that you can finish your presentation and have questions.

There is one more question. Dr. Giovino.

DR. GIOVINO: You mentioned, understandably, that Americans tend to think that smokeless tobacco is as dangerous as cigarettes, and you mentioned messaging. But I think

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Dr. McAfee might have been referring to messaging that Americans are receiving of you use smokeless when you can't smoke. And that's a very relevant issue in this whole -- as we look at the big picture. Have you given any thought to that issue and how you may correct that problem?

DR. RUTQVIST: I've seen the ads used here in the United States for smokeless tobacco; as you point out, use it when you can't smoke. I don't like that kind of advertising. I think it's just smoking -- it helps to prolong smoking. So I don't think that type of advertising should be used.

DR. GIOVINO: I would just follow up, pointing out that certainly, in terms of lung cancer, duration of smoking is a bigger predictor of lung cancer risk than cigarettes per day. So even if people may use smokeless and cut down on cigarettes per day but continue to smoke, thinking they've reduced their risk, they're actually, by continuing to smoke, increasing their duration at a rate that's more harmful than reducing cigarettes per day.

DR. HUANG: Okay, we'll go on with the presentation.

MR. SOLYST: Lars-Erik is clearly the star of the show, and he's going to be brought back for one last presentation on the dynamic population model or modeler.

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Just some background as to how Swedish Match used this application. We stated earlier that we worked closely with the ENVIRON Arlington office, where Joe Rodricks and Carol Ward work. We also worked with the ENVIRON Amherst office, which has epidemiologists. And we expressed interest in the development of a population model because we saw that the guidance seemed to indicate that a model would be useful for an application. So we early on worked with the Amherst office of ENVIRON, as did Reynolds Tobacco.

As the model came to fruition and developed, it was funded largely by Reynolds. But due to our early involvement, we thought it was appropriate to be used in this application. It is supplemental or complementary information to what you've heard today. But we do think it's incumbent upon industry to invest in regulatory science tools such as dynamic population models.

So I'll let Lars-Erik describe, one last time, the application of this model.

DR. RUTQVIST: As you all know, there is a public health standard that defines an MRTP. We felt that the key concept here was the words "benefit to health of the population as a whole."

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And when we thought about how to define benefit to the health of the population as a whole, which is not really well described in the statute and also not elaborated upon much in the draft guidance published by the CTP a couple of years ago -- and we considered the fact that smoking affects several health-related metrics such as the incidence of mortality of a range of diseases. It also affects morbidity in a way that may not be captured by incidence of mortality. And I'm thinking particularly of diseases such as COPD and diabetes. And developing these diseases influences quality of life.

So any of these metrics or a combination of these metrics could possibly be used to define what is meant by benefiting the health of the population as a whole.

But in our applications we have defined benefit as a decrease in population overall mortality, and the rationale for that is that overall mortality is an accepted basic outcome measure in evaluations of public health. Data are readily available. They are unequivocal in most cases. There are no data gaps or conceptual ambiguities of this metric. So we went with total population overall mortality.

And, of course, if you monitor -- if you do population monitoring of effects of the MRTP, this will inevitably

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generate a multitude of early metrics such as prevalence, use in population subsets, et cetera, et cetera. And, of course, it would be only later that it would be possible to collect actual health outcomes.

So, therefore, by a statistical model, it could potentially synthesize relevant metrics to a global measure about likely population effects. It could also be used to model potential population scenarios which included use of an MRTP to model whether certain scenarios would result in a net benefit or an adverse effect.

So to this end, Swedish Match cofounded the early -- together with Reynolds, the early development of ENVIRON's dynamic population modeler in its original version, which focuses on precisely overall mortality. And all the results from modeling presented in the applications are based on this original version of the model. And it was used to compare benefit of switching from cigarettes to snus, to the potential risks of dual use, tobacco initiation via snus, and use of snus instead of complete tobacco cessation.

I will not go into the technical details of this model, but let me just say that it estimates all-cause mortality for a hypothetical population who, at the beginning, have never used

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tobacco and who, as they age, may transition into and out of different tobacco exposure states, including the use of an MRTP. And the output is a comparison of the number of survivors in a base case scenario comprised of current, former, and never smokers followed as they age, with a number of survivors in an alternative exposure scenario that also includes use of an MRTP.

What's particular with DPM and what puts it -- makes it different from many other models that are out there is that it has been validated using observed population data for the U.S. and Sweden. And this is included -- the reference is given in the application. And I think these validation exercises demonstrate that the model can accurately predict life tables in a population with very little or no MRTP use, which would be the U.S., and in a population with quite extensive use of an MRTP, which is Sweden.

This slide summarizes as far as I will go with the details of the model. It was based on a hypothetical cohort of one million never tobacco users followed from age 12 years until age 72, and then age-specific mortality for 5-year age intervals were applied for never, current, and former smokers using the Kaiser Permanente cohort study data and data from the

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year 2000 U.S. census. And the model's transition probabilities, and in the base case, this was derived from U.S. survey data for the years 2005 to 2008.

We assumed an excess relative risk of 0.11 for current users of a low nitrosamine STP product, such as snus versus current smokers, which essentially says that we assumed a 90% risk reduction with snus compared to smoking. And this was based on consensus data published by Levy et al.

We set the excess relative risk for dual users at unity, meaning that we didn't assume any benefit from the decreased number of cigarettes consumed per day by dual users. So, in this sense, the modeling exercises that we present are conservative.

The draft guidance published by FDA a couple years ago suggests a number of scenarios, and it was clear that some of those scenarios would result in a distinctly adverse population outcome. For instance, if you model that some who remain never tobacco users in the base case, instead it initiated MRTP use, essentially an increased use of tobacco in the overall population. And, of course, if you assume some adverse effect from the MRTP, this type of scenario would inevitably result in an adverse population outcome.

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But there are also some scenarios with a distinctly beneficial outcome, like some who initiate smoking in the base case instead initiate the MRTP with a much lower risk.

And there was a mix of adverse scenarios with a mix of adverse and beneficial outcomes. And these can be -- these were quantified using the model. And it also allowed calculation of so-called tipping points, which essentially tells you how much of a beneficial scenario do you need to balance out an adverse scenario, and you can quantify this. And it's all included in the application.

But perhaps to me, the most interesting scenario we modeled was what I call a naturalistic worst-case scenario. The naturalistic part was that we asked the question, what would happen if the Swedish scenario, in terms of transitioning to snus, plays out at least to some extent here in the U.S.? And the worst-case part was that we assumed that returning to smoking as well as a possible gateway effect from MRTP use, that those transitions would double compared to the observed transition rates in Sweden.

And the result -- and I refer you to Table 6-68 in our applications -- showed that there will be a substantial and a statistically significant overall survival benefit even if U.S.

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transition rates to snus were only 50%, 25%, 10% -- and I'm sure we could have gone even lower than those observed in Sweden.

So, in summary, I think the modeling exercises confirm that the introduction of snus would result in a net population benefit even if it's adopted by only a small proportion of smokers.

And what was particularly striking was the profound effect on overall mortality from current smokers quitting, irrespective of whether they quit tobacco completely or they switched to an MRTTP. And this is in line with modeling results that have been published in the literature previously. And perhaps they should come as no surprise, given the vast risk differential between smoking and using snus.

And we would find that there would be a substantial and statistically significant population benefit even if a Swedish scenario, if you will, would only play out to a small extent in a U.S. setting. And, of course, these results relate to the public health benefit part of the definition of the modified risk product.

I should point out, though, that we don't believe that modeling is central to our MRTTP claim. I think modeling can

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provide some interesting perspectives. It could be potentially useful in the postmarket setting, and it is mentioned in the draft guidance. But I don't think that it's a central component of our claim of a population -- a public health benefit with the introduction of snus as a modified risk tobacco product in this country.

Thank you.

MR. SOLYST: Mr. Chair, we'll allow your decision as to how to spend these last 15 minutes. Certainly, we could take clarifying questions on this presentation or any of the presentations that we've made over the last 2 hours.

DR. HUANG: And how about we do that combination? And we'll start out with questions about this particular presentation and also some overall clarifying questions.

Yes, Dr. Giovino.

DR. GIOVINO: So one of your adverse population outcomes is the one -- well, the potentially adverse population outcome I alluded to before is not in your list, which is that some who would otherwise quit tobacco smoking continue to smoke and use snus and therefore prolong their duration of smoking.

DR. RUTQVIST: At the top of my head, I cannot say whether there were any scenarios that we modeled that included that

particular part as the only part of the scenario. It could be done and you could quantify the effect, and you could also mix that with a beneficial scenario, that some smokers would quit smoking by switching to snus. But I would have to check whether there were any scenarios we tested that included that particular component.

DR. GIOVINO: Okay, thank you.

DR. HUANG: Yes, Dr. Tomar.

DR. TOMAR: The assumption of the 90% reduction in risk was based on a paper by Levy et al. from 2004 which really was based on opinion. But, you know, since your application mentioned a number of large long-term cohort studies, I was wondering if you've looked at cohort studies on long-term smokers who then transition completely to snus. What is their observed reduction in mortality and other endpoints?

DR. RUTQVIST: I'm sorry, I don't think that type of study would be able to provide the overall estimate on the risk reduction achieved with a modified risk tobacco product that would be needed to feed into the model.

DR. TOMAR: Well, I would say that's exactly the type of data we would need, rather than basing this model on what was just expert opinion. Again, your application talked about the

large long-term cohort studies. One of the reasons why you felt that Sweden was such a perfect model to look at in making inferences to the U.S. population, the cohort data are there. Have you actually looked at reduction in mortality among smokers who transition completely to your products?

DR. RUTQVIST: In this modeling, we took the data that were available in the literature, and I can tell you that we did modeling that tested the sensitivity of the assumption of the level of risk reduction. And what we found was that yes, the level influenced the results to some extent, yes, but actually much less than I anticipated. And when it comes to the type of studies you refer to, I mean, there are such studies, but I really don't see how we could use the data for those studies to include in this modeling.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Could you go to Slide 8 for me? So could you clarify the second bullet from the bottom, where it says excess relative risk for current users of a low nitrosamine product such as snus? Is that compared to a high nitrosamine current smoking -- what's the implication of saying low nitrosamines there?

DR. RUTQVIST: Now, this is language from the publication

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by the Levy et al. They used the term low nitrosamine STP product, and I think what they thought about was snus. But the language used there was low nitrosamine STP product. So it comes from the publication.

DR. RIBISL: But your product has lower nitrosamines than other smokeless products, the fermented variety that's typically sold in America?

DR. RUTQVIST: Yes, that's correct. But we weren't particularly bothered by that, because even if we assume that snus may be associated with even a lower excess relative risk, using 0.11 would mean that our results would be conservative, and we felt that that was appropriate in this kind of modeling.

DR. HUANG: Dr. Bickel.

DR. BICKEL: So this is a broader question. Given that we're concerned about uptake by people that would not normally use tobacco products, since we're concerned people may be returning if there was a lower -- if they perceived that it was healthier, suggesting the importance of some measure of abuse liability -- and you haven't included it in your presentation. Was that part of the -- somewhere in the overall application that you could bring forward?

DR. RUTQVIST: Yes, I remember your question about abuse

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liability, and I think the clinical trials on nicotine pharmacokinetics addressed this issue about abuse liability. And if time permits, I would love to present them in more detail. I'm not really sure if we have the time today to do it, but I would gladly do it tomorrow.

DR. HUANG: Other clarifying questions?

Dr. Tomar.

DR. TOMAR: Can we go back to the question I asked before that really wasn't answered? So we saw sales data for both Norway and Sweden, showing significant increases over the past couple decades. What proportion of that growth was among never smokers who then initiated tobacco use with your company's products, compared to those who were smokers and switched to snus?

DR. RUTQVIST: This has changed over the years. If you go back to the early '70s, a very large proportion of those who came into the snus category were ex-smokers or they became ex-smokers through a period of dual use. But as smoking has gone down so much, more and more of people who are never smokers come into the category. And then you, of course, question, well, doesn't that represent unnecessary use of this MRTTP product? Well, the Norwegian evidence suggests that these

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people have characteristics that characterizes people who would otherwise initiate smoking.

And I think Sweden, being an average European country -- I mean, the question then of course is, well, if you have a lot of snus users who have never smoked, isn't that unnecessary use? But I think the most reasonable answer to that question is that, had snus not been available, they probably would have been smokers, because that's what they are in all other European countries who don't have access to snus or have not experienced this population trend that we've experienced in Sweden, because the overall proportion of tobacco users in Sweden is by no means greater than in any other European country. The main difference is that the tobacco is consumed in the form of snus rather than smoked in the form cigarettes.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: This is a question for the clinical trial, that it was to a clinical trial. What was the reason not to use -- having one arm testing NRT so that you could compare the efficacy of NRT versus snus?

DR. RUTQVIST: Well, if I take these two European trials, such a study would be of little practical use in that setting because NRTs are prohibitively expensive in that setting. So

it's not available in practice to smokers.

But to answer your question, yes, we could have done a three-arm trial. It would have taken us longer to do the study, and the study aim was, as I mentioned earlier, to provide experimental confirmation of the Scandinavian experience on the ability of snus to help smokers quit completely. And there is extensive information on the efficacy of NRTs. So we really didn't find it of interest to address the research issues at hand to include a third arm.

DR. HUANG: I have a broad question and I just -- you know, because one of the key issues that -- we've been hearing about the Swedish experience and the Norwegian experience, and one of the questions that we have is its applicability and transferability to the U.S. And as we've heard, there are so many different variables that are going on in interpreting this, and that's sort of key to what we have to look at.

So we have one of the public comments that -- you know, we have a letter from the Director-Generals from the National Board of Health and Welfare for Sweden and Norway and Denmark and Iceland that are saying snus does not qualify as a tobacco harm reduction product. You know, there are evidence-based methods for smoking cessation, and the most effective methods

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are combinations of support medication. No scientific evidence for the effect of snus as a smoke cessation aid. And Scandinavian moist snuff has no place in cessation support.

So I want to give you an opportunity just to respond to that, because again we're trying to -- me personally, I'm trying to understand the big picture of how that Swedish experience and the Norwegian experience translate. And so we're hearing this from what should be a big picture interpretation.

DR. RUTQVIST: Yes, I'm happy to comment on that letter. That letter was part of the discussions that I mentioned, which was the rationale for doing the clinical trials, because the paper that is referenced in that letter was a discussion paper that pointed to the lack of experimental confirmation of the extensive observational data from Scandinavia, and it was pointed out that NRTs have this experimental confirmation. So this was part of the rationale for doing the trials in the first place.

And then I should point out that all Swedish health agencies accept the individual risk reduction achieved with snus. This has been the case at least since 10, 15 years. The Swedish government has no position on the population benefit of

snus. That includes also the Swedish public health agency. They acknowledge the individual risk reduction but have not an official position on that issue.

MR. SOLYST: I believe Dr. Rodricks had a slide, a statement from 2012 included. And then in 2011, November 2011, FDA with WHO sponsored a conference outside of Washington that brought together governments to address regulatory issues surrounding tobacco. And there was this presentation from the Swedish government then that emphasized the importance of pregnant women not using snus, but it addressed no other health effects to it. So there are varying messages that you could derive over the years.

DR. HUANG: Thank you. Other clarifying questions?

(No response.)

DR. HUANG: Okay. Then I think we are ready to move on to lunch, everyone. Okay, first -- there was something I was supposed to read. Here we go.

So we will now break for lunch. Committee members, please remember, there will be no discussion of the meeting topic during lunch either amongst yourselves, with the press, or with any members of the audience. Also, Committee members should not seek out the Swedish Match individuals during breaks or

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lunch. All discussion must take place within the context of this public meeting. So we will again reconvene in this room in 1 hour at 1:30. And please take any personal belongings you may want with you at this time. Thank you.

(Whereupon, at 12:27 p.m., a lunch recess was taken.)

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

(1:30 p.m.)

DR. HUANG: All right, it's now 1:30, so we will welcome you back from lunch.

So the next section is presentations from the FDA. And we'll go ahead and start. The first one is Dr. Day presenting on epidemiologic evidence related to SMNA MRTPA snus products and gum disease or tooth loss.

DR. DAY: Hello, my name is Dr. Hannah Day. I am an epidemiologist at the FDA Office of Science in the Center for Tobacco Products. Today I'm going to be presenting the epidemiological evidence related to the Swedish Match North America snus products and gum disease or tooth loss.

I will be just briefly presenting the disclaimers. As Dr. Peat mentioned, we will not be reading these again.

Today I will give a brief introduction, describe study characteristics and results, select methodological issues, and then give a brief summary of my talk.

To begin, I'd like to read the Applicant's conclusions from page 442 of the application.

"No effects of snus use on gingivitis, gingival recessions, and other dental conditions were consistently

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identified among studies that controlled for reporting confounders such as socioeconomic status and oral hygiene habits.

"The use of snus is not associated with periodontal disease or any individual indicators of periodontal disease based on the results of seven studies, five of which accounted for the potential confounding effects of socioeconomic status or oral hygiene habits."

In FDA's assessment, we reviewed the 12 epidemiological studies included in the application. We completed full evidence tables which are available in the FDA briefing document. In these tables in our review, we focused on study design, results, and select methodological issues.

I would like to note that for the purpose of this talk and the backgrounder, we have focused on the results according to study aims. The Applicant did include additional outcomes. In addition, we conducted a systematic review, and no additional studies were identified.

The slides that follow are all based on FDA's independent assessment of the literature.

Regarding the study populations, all 12 studies were conducted in Sweden. There were six cross-sectional studies in

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adults. Two of the studies used the same population, and one adult study included only snus users and no non-users.

In addition, there were five cross-sectional studies and one case-control study that were completed in adolescents and young adults under the age of 25.

For all of the studies, the exposure of interest was snus; however, snus was defined slightly differently across studies. There were four studies that defined snus use as a current yes/no variable, two studies which examined lifetime use of snus (current, former, or never snus users), and the rest of the studies examined snus use related to the frequency of snus use. Three studies looked at daily snus users, one study looked at users who used every day or almost every day, and another study looked at users who took snus regularly.

I have not included Andersson and Axell 1989 in this list, as that was the study that compared loose snus users to portion snus users and did not include any non-snus users.

The outcomes by study aims are listed below. There were three studies that included aims to examine dental outcomes, two studies looking specifically at caries, and one study looking at an individual tooth wear index.

In addition, there were five studies that had specific

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aims to examine gum disease or precursors of gum disease. These included periodontal disease, periodontal bone loss, lesions and gingival recessions, incipient alveolar bone loss, and buccal attachment loss.

There were four other studies that included broad aims, such as to examine oral health status or periodontal conditions.

This table presents FDA's evaluation of the results. As you can see, each row describes a different outcome. The middle column shows studies -- shows which studies found a significant association between snus and the outcomes, and the right-hand column showed studies that found no significant association. The studies in italics presented only unadjusted results.

Once again Andersson and Axell 1989 is not included in this table as there were no non-snus users for comparison.

Now I'd like to describe some select methodological issues.

Regarding study design, 11 of the 12 studies were cross-sectional. This leads to an inability to establish temporality. This is especially of concern if snus users may quit as health problems occur. There were no cohort studies

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included in the application or evidence body. There was heterogeneity in exposure and outcome definitions, and there were no studies that included outcomes of tooth loss. There were several cross-sectional studies that presented descriptive results on the number of teeth.

In addition, there were six studies that were completed in adolescents or adults under the age of 25; however, many oral health outcomes are not seen until later in life.

Regarding precision, only three studies included more than 50 snus users per comparison. Two studies did not mention the number of snus users in their papers. Because of these facts, studies may lack statistical power to detect a significant difference.

I'd like to briefly describe another methodological issue of confounding. Risk factors for gum disease include age, gender, tobacco use, systemic disease, and oral hygiene. None of the studies adjusted for comorbid diseases. The treatment and inclusion of smokers was unclear in many studies and rarely adjusted for.

In addition, adjustment factors were not clearly stated for the relationship between snus and attachment loss in the case-control study.

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The table at left, I will walk you through this briefly, but I would like to note that I have not included the case-control study. As I just mentioned, the confounding factors were not very clear in that study. And I've also not included the Andersson and Axell study as that included no non-snus users.

So the table at the left shows a different row for each of the cross-sectional studies with the lead author's name. Each column represents a different factor that may have been controlled for in each study. Moving from left to right, these columns are gender, age, socioeconomic status, dental health or hygiene, and dual use of cigarettes and snus.

In this table, the text represents studies that were restricted to a certain factor. Checkmarks indicate that the study was adjusted for that factor.

So just to walk you through two examples, the Rolandsson 2005 study restricted the study population to males between the ages of 16 and 25. They matched by age, in addition.

Hugoson and Rolandsson 2011 adjusted for gender, age, socioeconomic status, and restricted their population by excluding dual users.

I won't go through the rest of the table, but I believe

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that illustrates the point that this table is making.

In summary, despite the methodological limitations that I have just outlined, several of the studies in youth populations found an association between snus use and dental caries, gingival recession, or gingival index. One study found an association between snus and tooth wear in adults.

Almost all of the studies presented were cross-sectional, and half included only adolescents and young adults. Many were small in size, most had fewer than 50 snus users, and most did not control for all appropriate potential confounding factors.

In addition, the Applicant does not provide a justification as to why it is biologically plausible that the effects of snus on gum disease and tooth loss would be significantly different from other smokeless tobaccos.

Thank you. I will now take clarifying questions.

DR. HUANG: Okay, any clarifying questions?

Yes, Dr. Swauger.

DR. SWAUGER: Hannah, can you hear me? Sorry.

DR. DAY: Yes.

DR. SWAUGER: I'm just trying to understand your chart. Well, it's on page 9 of this packet. It's the one with your statement, "Despite these methodological limitations, several

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of these studies in youth populations found an association between snus use and" something. And I'm just looking -- I was looking at your bullets, and it's just kind of surprising to me that you use the word several, and it looks like really what you mean is two. Am I missing something? I mean, you talked about 12 studies. You're really only pointing to two. I'm just trying to understand what's your concept.

DR. DAY: Sure. So you're referring to this slide? First, I'd like to clarify.

DR. SWAUGER: Yeah, that one. Thanks.

DR. DAY: Okay. So one thing I would like to point out is that while there were 12 studies for the entire body of evidence between snus and gum disease, various precursors of gum disease, and caries or other factors, each of these studies did not examine each of the outcomes. So you'd have to break it down by study, and I would be happy to discuss that tomorrow, going study by study.

But each outcome did not present 12 studies. It varied by outcome. And there were three associations between snus, one between snus and dental caries, one between snus and gingival recession, one between snus and gingival index, and one between snus and tooth wear. For example, the only study that examined

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snus and tooth wear found an association.

DR. SWAUGER: Can I ask one more question? I guess I'm going to help myself. Out of the 12, is there any one study -- I mean, I don't know this area, so this is a naive question basically. You sort of have gone and checked off the limitations to each of the 12. I'm just wondering, is there any one of them that you pointed out that you actually think is good, strong, sufficient quality? I mean, is there one of them that you could point out that you actually felt was good enough?

DR. DAY: I think that it's hard to discuss that without mentioning a specific study. I think that it's fairly obvious, from my summary, that FDA has some concerns about the strength of this body of evidence, and that is something that we are bringing before the Committee to discuss.

DR. SWAUGER: Dr. Huang, I'm just kind of curious. I mean, we didn't really get a chance -- and I haven't -- we didn't get a chance to hear much about what Swedish Match would have to say about these studies. I'd be kind of interested in just hearing what they think about them in terms of specificity.

DR. HUANG: That can be part of the discussion tomorrow.

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DR. SWAUGER: So if they want to just stand up and offer their own view on these datasets, that would be okay?

DR. HUANG: It will be considered and discussed tomorrow.
Yes, Dr. Novotny.

DR. NOVOTNY: I'm just curious about that loose versus pouched snus study that you excluded from your analyses. Did they find any -- were there any findings there worth mentioning?

DR. DAY: They did find that there was more likely to be gingival recessions in loose snus users compared to portioned snus users. However, we didn't include it for most of this discussion as it really doesn't give us any evidence related to non-use of the product.

DR. HUANG: Yes, Dr. Boffetta.

DR. BOFFETTA: I just wondered whether any of the studies had any type of dose-response analysis based on frequency of duration of use.

DR. DAY: Some of the studies did examine that. If it's something the Committee would like to discuss, I can list the specific studies tomorrow.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: If I understood correctly, in some of the

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other disease categories, the charts that were prepared in the application presented results from the same study that looked at snus users and cigarette smokers. And it was a nice control, because then you could see that the study found, you know, something in cigarette smokers. And then the question was, did it also find that in snus users?

Did any of these studies that you looked at also include cigarette smokers? And if so, in those cigarette smokers, were there -- even though they were young, were there any indicators of these disease conditions?

DR. DAY: So there were a few studies that did include that. Often they found strong associations between cigarette smoking and the outcome studied. However, it should be noted that a lot of the number of snus users was very small. And also cigarette users. So power is an issue in both of those.

DR. EISSENBERG: Can I follow up on that? Yeah, I take that point. I guess I'm particularly addressing the youth issue. And so if it was possible to detect those effects in cigarette smokers, in the young, does that make less of a concern that the snus users were young?

DR. DAY: So I'm just going to try and repeat your question and make sure I understand it. You're saying, if

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there were studies that detected associations between cigarette smoking and the outcomes, would that ameliorate --

(Off microphone comment.)

DR. DAY: In young people -- would that ameliorate the concerns about the outcome and its appropriateness in the comparison between snus and young people? I could have more information on the young study, specifically that included cigarette smokers, tomorrow. But I think your question is a great point and something that we are bringing to the Committee for discussion.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: If I was going to design a study to address this issue, and even the issue of oral cancer, I would ideally design a cohort study, and I would make the referent group never snus users and never cigarette smokers and then include categories of just cigarette smoking and just snus use and both. I mean, obviously, there's no cohort studies. But in my read of what I've read -- but you've read more than I have -- none of the studies actually did that, right? They didn't have a non-snus/non-cigarette referent group.

DR. DAY: I believe there was one study that did look at that. But the body of evidence as a whole, not every study did

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break it down by non-snus/non-cigarette use.

DR. GIOVINO: If you could either remind me of the name of that study now or tomorrow, I'd appreciate it.

DR. DAY: Sure, I would be happy to provide it tomorrow. I don't have the study in front of me.

DR. GIOVINO: Okay.

DR. HUANG: Dr. Tomar.

DR. TOMAR: Yeah, I'm sure she's going to speak to the issue that Dr. Eissenberg raised. There tends to be -- there are primarily different types of periodontal diseases that manifest in smokers compared to the smokeless tobacco users. Again, based primarily on the U.S. data, smoking is probably the major preventable risk factor for periodontitis, where with snuff use it's primarily localized gingival recession that we see.

Periodontitis, while it's strongly and consistently associated with smoking, is an outcome that's rare that you would see in a young smoker. Under 25, you're not going to see a lot of -- I wouldn't say any, but it's going to be a relatively rare outcome. As they age, the differences are pretty profound.

In the U.S., with smokeless tobacco compared to the

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Swedish data, it's actually fairly consistent that the snuff-dippers consistently have much higher prevalence of localized gingival recession, often in the area where they keep their dip.

DR. HUANG: Yeah, Dr. Giovino.

DR. GIOVINO: And how soon does that appear after they start using?

DR. TOMAR: It's a good question because even in the U.S., most of them are cross-sectional studies. But there are studies that were done with adolescents where they found increased prevalence of recession. There are a lot of studies done with relatively young adults. John Green's studies with U.S. ballplayers, you know, many of whom are in their early twenties, had a fair prevalence of localized gingival recession.

DR. HUANG: Any other clarifying questions?

(No response.)

DR. HUANG: Okay, thanks. We will move on to the next presenter, Dr. Chang.

DR. CHANG: Good afternoon. I'm Dr. Cindy Chang. I am an epidemiologist in the Office of Science at the Center for Tobacco Products, and I will be discussing epidemiological

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studies of Swedish snus and oral cancer.

These are the standard disclaimers.

This is a brief outline of what I'll be discussing today. I'll give a quick introduction to the applications as well as FDA's review process. I will be describing the main findings of the epidemiological studies on Swedish snus and oral cancer. I will highlight some select methodological issues and provide a summary for the Committee.

The Applicant requests to remove the warning label that states, "This product can cause mouth cancer."

The Applicant provided six epidemiological studies discussed in the ENVIRON snus monograph, which is Appendix 6A, to support their request.

In their conclusions, the Applicant found no consistent finding of an association between the use of snus and oral cancer.

In FDA's review, we assessed the study results of those same six studies and examined any potential issues with the methods and threats to validity in those studies. We also conducted an independent systemic review; however, no additional studies were identified.

Here I'll give an overview of the six studies. First,

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I'll talk about the cohort studies.

So out of the six, there were three prospective cohort studies. In a cohort study, exposure is assessed at baseline, and people are followed over a period of time so that rates of disease in the exposed can be compared to the rates in the unexposed.

As you can see in this table, all three studies had 26 to 30-plus years of follow-up, as shown in the second column. The third column shows that two of the studies were in Sweden and one was in Norway. The middle column shows how snus exposure was defined. There are differences across studies.

Also worth noting is that in all three studies, only baseline assessment of exposure was used in the main analysis. The second to the last column also shows that the definitions of oral cancer, based on ICD-7 codes, differed across the studies, which I will discuss more later.

Differences in oral cancer definitions, of course, affect the sample size of cases. With oral cancer being so rare, small sample size quickly becomes an issue of precision.

So in this table I highlight some select results from three studies. And as you can see, even though there are three cohort studies, I show about two of the results from each

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study. And so let me just walk you through this table really quickly.

I give the main author and year of the study. I give the snus exposure in the third column, the type, whether it was ever use, current use, or former use. I also give the number of snus users who later developed oral cancer. So you can gauge the type of sample size in that effect estimate.

The middle column is important because it indicates whether the analyses included smokers. The RR is relative risk. And for the non-epidemiologist, a value of less than 1 indicates inverse associations, a value of 1 indicates no association, while a value greater than 1 indicates a positive association or an increased risk.

A 95% confidence interval in the case of whether the RR is statistically significant. If the confidence interval does not contain the value of 1, which is the null value, it is considered statistically significant.

And, finally, in the last column I give the adjustment factors, which are the variables that are included in the model to adjust for confounding.

Now that I've given you an overview of the details I present, I'm going to highlight the positive findings.

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The Roosaar study found that daily snus use was significantly associated with three times the risk of oral cancer as never daily use, based on the relative risk estimates adjusting for smoking, alcohol, and other factors.

In the second row from the same study, we see that the never smoker estimate from Roosaar was elevated but not statistically significant. And I want to point out, if you look at the fourth column, the number of exposed cases, there were only five.

In the other two studies that I've grayed out, neither current nor former snus use was associated with oral cancer.

So now that I've shown the three cohort studies, I'm going to shift gears to the three case-control studies, which were all done in Sweden.

In the study design, in this type of study design, cases or people with disease are compared with controls, who in these studies were drawn from the Swedish population registry. Also in this type of study, disease and exposure are assessed at the same time, so you can't always rule out the possibility that a person's disease status changed their snus use.

In the second column, here we see again the definitions of cases differed across studies. In the middle column it shows

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that controls were either individually matched or frequency matched to cases. In the snus use exposure column, as you can see as well, the definitions differed across studies, and that sample size also differed.

Now, here are just some of the results of the three case-control studies. In this particular slide I'll be focusing on current and ever snus use. This is a fairly dense table, and because for the most part current and ever or ever snus use was not found to be associated with oral cancer, I'm not spending much time describing all of the results.

But I will highlight one finding, one of the results from the Lewin study. Very quickly, this analysis was among males who ever or never regularly used snus. There are nine snus users with head and neck cancer, and the analysis was restricted to never smokers.

So if you look at the effect estimate -- in this case it was the odds ratio, but it's interpreted the same way as the relative risk estimate. So based on the odds ratio, the study found that snus use was associated with almost five times the risk of head and neck cancer as never use.

So, now, these are the same three case-control studies, but I show the results for former snus use rather than ever or

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current use.

Now, unlike the other slide, most of the -- if you take a look at the second to the last column where I give the odds ratio, most of the results show positive associations; however, most did not reach statistical significance.

Now, the studies have a number of really important strengths. In the three cohort studies, all had long-term follow-up, which allows time for cases to develop. Participation rates were high, so selection bias was minimized. All of the data were linked to national cancer registries in Sweden and Norway, and in these registries, loss of follow-up is minimal and cancer diagnoses are accurate, which is a major strength.

The three Swedish case-control studies also had high participation rates, used population registries for controls, and had accurate case diagnoses.

And, finally, for all of the studies, the analyses were adjusted.

Now that I've described the results, I do want to raise some methodological issues of the studies. In particular, there were issues with differences in outcome definitions, confounding, and information bias that raised some

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uncertainties in the studies' findings.

Now, in this table I show all six studies, and the cohort studies are the three rows on top, and the case-control studies are the three rows on the bottom.

Now, oral cancer, as I mentioned, was defined based on ICD-7 codes; however, across the studies, different combinations of ICD-7 codes were used. For example, the cohort study by Roosaar had the broadest definition of oral cancer, as you can see in the third row. In contrast, Luo 2007 had a stricter -- had one of the strictest definitions of oral cancer. Now, this heterogeneity may affect comparability of results across studies.

Another issue I want to raise is the issue of confounding. And as you know, smoking is a strong risk factor for oral cancer. And here I give definitions of smoking in the studies. Now, if not measured correctly, even adjusting for smoking can lead to residual confounding. Two of the authors raise the possibility of residual confounding in smoking-adjusted estimates.

So let's take the four studies where confounding by smoking is removed by restricting to never smokers.

Two studies found positive associations, though only the

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estimate in the Lewin study, the case-control study, was statistically significant. The issue I'm really showing here is that you lose precision when you do this type of analysis, as you can see by the low numbers of exposed cases.

Finally, I want to raise the issue of information bias. It's a concern, especially for exposure assessment.

In cohort studies, one measurement may not accurately represent tobacco use over the whole period, especially the longer the time period is. An example is that if snus users tended to quit over time, the effect of snus may be underestimated.

In case-controls studies, a person feeling symptoms may alter their behavior. For example, they may get an irritation in their mouth and quit using snus.

The last one I want to make is that, as I showed you earlier, in two of the three case-control studies, there were some suggestive associations between ex-snus use and oral cancer.

So now that I've given you the individual study results and methodological issues, I just want to summarize FDA's findings.

Based on the evidence, there doesn't seem to be a strong,

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consistent association. However, we observed positive associations in one cohort study and one case-control study, including estimates restricted to never smokers.

As I mentioned, there are definitely major strengths to these studies, including long-term follow-up, high participation rates, linkages to population and cancer registries, ascertainment and accurate diagnoses of cases, as well as adjustment for confounding.

However, definitions of exposures and outcomes differed, which may affect comparability.

Numbers of cases were low, especially once you start restricting to never smokers, which may affect precision.

Smoking-adjusted estimates may still suffer from residual confounding, and not assessing for changes in behavior may bias the associations.

So, really, the take-home message here is that even though there doesn't appear to be a strong, consistent association with oral cancer and these studies have important strengths, FDA has concerns with the positive findings and potential sources of bias. And because of these concerns, we're unable to completely rule out the possibility of an association between snus and oral cancer.

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Thank you. And I'll take any clarifying questions.

DR. HUANG: Dr. Swauger.

DR. SWAUGER: I'm just curious, just focusing on your last statement, but you've got some concern. And I'm not an epidemiologist.

DR. HUANG: Can you please talk into your microphone?

DR. SWAUGER: Sorry, I was just trying to look at her when I talk.

So I'm not an epidemiologist. So I'm just sort of asking to ask. But when you say you're concerned, I just sort of hear this data differently or see it differently. I look at those data, and your comments about limitations aside, and strengths, I still don't really see much of an association. I'm a pretty simple guy. I look at it, and I'm looking at I've got one study maybe out of six where you saw anything that looked like an association -- and if I remember right, maybe two. But the head and neck cancer basically is the one that you need to be focused on.

When I step back and I think about it more broadly, I was sitting here thinking, while you're talking, about the Lee and Hamling review where they broaden the context and they look at the 15 studies between the U.S. and Europe, and basically, if I

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remember right, they don't see an association. They are statistically significant. I think they had a positive. It looks like a 1.07 or something like that. So in my mind, I don't look at this and see an association at all. So I'm sort of struggling with --

DR. CHANG: Um-hum.

DR. SWAUGER: -- your statements. What drives you to look at that data and say FDA has a concern?

DR. CHANG: So, for me, the way that I assessed the evidence was keeping in mind with what the Applicant was proposing, and what they were proposing was to remove a warning label, that this product can cause mouth cancer.

And so, by assessing the evidence with that in mind, I wanted to be sure that I didn't see any association. And, first of all, I did see some associations. Maybe not in all of the studies, but in some of them. And the other studies that I didn't find associations, I'm concerned with potential sources of bias that may possibly underestimate the association.

So I'm just sort of -- like I said, I didn't see a consistent association. However, I'm not sure that I can completely rule out the possibility of an association, especially given that there is -- I didn't get into it, but

there is biological plausibility. The fact that there is a presence of nitrosamines, it is biologically plausible that this product can cause mouth cancer.

DR. SWAUGER: Well, my guess is we're going to talk about nitrosamines probably half the day tomorrow. But your comments just sort beg the question in my mind, what's the standard? If the standard at the end of the day is any study anywhere happens to show an association, I'm sort of struggling with how anybody ever achieved the standard of saying, you know, snus -- or smokeless more broadly -- ever caused mouth cancer.

DR. CHANG: So that's a critical question, and we would hope that the Committee will discuss that question, because we have that question as well.

DR. HUANG: All right, Dr. Ribisl.

DR. RIBISL: Yeah, I have two questions. So one is how stable is snus use? And this gets at the question of the long-term cohort studies. So we know that cigarette smoking is really stable. Only 3% to 6% of people are quitting each year, so over 94% of people are doing it the next year. Over time it's fairly stable. So is snus use as stable as cigarette smoking? Do we know?

DR. CHANG: I don't know. The one thing I can say is

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that, you know, in a lot of these cohort studies, they were done in adults. And my understanding of smoking is that if they didn't start smoking by then, they're not likely to transition from snus to smoking. So we weren't as concerned about that transition.

DR. RIBISL: How about quitting?

DR. CHANG: The quitting was the greater concern and --

DR. RIBISL: Right.

DR. CHANG: -- I don't have an answer to that. But I think that it's a possibility that we can't rule out, since these are, you know, 26- to 30-plus years of follow-up.

DR. RIBISL: If there's a really high quit rate, you would have even more concern. But if it's pretty stable, you don't have as much of a concern. Okay.

DR. CHANG: That's a good point.

DR. RIBISL: My last question is, did you consider meta-analyzing the results of this or any other of these studies? Because if you were to combine and pool these, especially in the prior presentation where you had a lot of sample sizes under 50 people and so forth, you would really benefit from pooling the data.

DR. CHANG: You know, that's a possibility. I think

pooling the data could get at some of the issues of precision. But as I pointed out, there is heterogeneity in the studies, the way they defined the outcomes and the covariates they adjusted for. So there might be some challenge to pooling the studies if, you know, we feel that there's too much variation. And pooling doesn't necessarily address the issue of behavior change.

DR. RIBISL: Right.

DR. CHANG: The misclassification issue.

DR. HUANG: And Dr. McAfee on the phone has a question.

DR. McAFEE: Yeah, thanks very much. This is clearly a challenge, and I guess I'm trying to see if you have any thoughts about the context. This is an unusual epidemiologic question around do we have enough data to remove a finding, as opposed to do we have enough to say that there's an association?

I would agree with the first commenter, that if we're being asked, should we add this label, it looks shaky. But I think the anxiety about whether there's enough data to remove a finding raises the thought that the issue of power is critical.

And then the other issue is, essentially, because this is a subcategory of all smokeless products for which there was

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larger and stronger evidence for these effects, is it reasonable to sort of go back based on these studies that have a very small number of people and remove a finding?

I don't know the answer to this, but I'm just curious essentially if FDA has thought about how TPSAC should look at evidentiary criteria that are for removal as opposed to creation of a positive finding.

DR. CHANG: Well, that's one of the issues that we'd like TPSAC to discuss tomorrow, is this sort of -- what sort of criteria is necessary for removal of a warning label? That's part of what we're hoping we'll hear from you.

DR. HUANG: And that was part of my question at the beginning of the day, when looking at the actual stated questions that we've been presented with. It's that we don't have to have enough evidence in the positive to show that these products pose risk of gum disease, but that we are making that decision of whether to remove enough evidence to remove it from the warning.

DR. CHOINIERE: Certainly, there would be the potential to have two different standards here. One is a standard for putting a warning on a product, and one is a standard for not putting a warning on a product. And so we've asked you the

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question the way we have because we do think there would be value in hearing your response to that particular question.

But certainly if there are additional thoughts that the Committee can provide in their response to that question regarding whether or not they think the standard should be different for removing a label -- a warning rather than putting a warning on, that would be welcome.

DR. HUANG: Yes, Dr. Swauger.

DR. SWAUGER: It's just Jim. Thanks, though.

Conrad, I got kind of astonished. If I heard you right, you just said that it might be possible that there could be a different standard applied to the notion of whether there's enough data to put a warning on, but you'd apply a different standard for deciding whether to take it off. I find that amazing. I mean, it seems like you'd be more inclined to look at what the data actually say, maybe in the case of specific snus studies and perhaps even more broadly in smokeless and oral cancer in general, and let the data speak for themselves.

I really kind of struggle with the notion that you'd leave warnings on any smokeless product if you didn't think there was enough data to support it being there. I don't want to put words in your mouth, but that's kind of what it sounded like,

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and I couldn't help but, like, sit up and basically go, really? Did he really say that?

DR. CHOINIERE: Yeah, I'm not sure if I'm characterizing it exactly the way you characterized it, but I certainly think that the level of evidence is different in both cases, correct? Not the level of evidence for making a decision here, but the level of evidence as to whether or not smokeless tobacco causes mouth cancer. The amount of evidence we have for that certainly outweighs the amount of evidence that we have related to whether or not snus causes mouth cancer or oral cancer.

And so there's a question on the table for this Committee about their assessment about that evidence that we can then take back and determine whether or not that level of evidence supports the removal of a warning.

DR. HUANG: Okay, other clarifying questions?

Yes, Dr. Boffetta.

DR. BOFFETTA: Well, I have a similar question to the one on the gum disease. Several of the studies that you reviewed also presented some analyses according to amount of snus which was used, and you did not consider this in your review. Is there a reason why? I mean, can you elaborate a bit on this dose-response data?

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DR. CHANG: Yes, thank you for the question, Dr. Boffetta. I did consider dose response. That's an important factor to look at. I had limited time to what I wanted to highlight in my presentation.

If you refer back to the backgrounder, I do point out that at least one of the studies, the Lewin case control study, found a suggestive dose response. It wasn't statistically significant, but it was suggestive. The study by Luo 2007, they also looked at amount of snus used per day, and they did not find a significant trend. Did I answer your question?

DR. HUANG: Okay?

DR. BOFFETTA: Yes, thank you.

DR. HUANG: All right, other clarifying questions? Yeah.

DR. SWAUGER: Just one quick one. I just don't know the data that well. I have specifically been thinking about Lewin, Leween, however you pronounce that last name. I'm wondering -- sorry. I'm under the impression that they didn't control for alcohol use in the Lewin study, and I'm wondering if that actually -- what impact did that have on FDA's interpretation of that study? Because you seem to be fairly focused on that, and I'm just curious.

DR. CHANG: Yeah, it's a good point. And Lewin actually

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did control for alcohol. I don't know how to get back to the slide. So the positive finding that they reported was actually kind of buried in the text, and so I hesitated to state what the adjustments -- which adjustments were made, because it wasn't clear to me. And other estimates in the Lewin study -- alcohol was adjusted for.

The other point I wanted to make about alcohol was that yes, alcohol is actually a very strong risk factor for oral cancer, and two of the cohort studies did not find -- did not control for alcohol, Boffetta and Luo, and it wasn't a huge concern for us because these were the negative studies. So not having adjusted for alcohol did not inflate or overestimate the association. I hope that helped.

DR. HUANG: Mr. Moynihan.

MR. MOYNIHAN: In the Lewin study, it's described as head and neck cancer, but is there information in the report as to the location of these tumors?

DR. CHANG: The Lewin study. So you're asking which cancer sites were included in head and neck cancer? Is that what you're asking?

MR. MOYNIHAN: Well, which sites in which the cancer is reported in the exposed cases actually occurred.

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DR. CHANG: Right. So head and neck cancer in that particular study included oropharyngeal cancer, laryngeal as well as esophageal, and they looked at head and neck cancer all together, as well as each individual site separately.

DR. HUANG: Yes, Dr. Swauger.

DR. SWAUGER: Sorry, I just wanted to have you repeat what you said a minute ago. With regard to going back to Lewin and alcohol, controlling for alcohol, I thought I heard you say that in some of the other numbers that they presented, they did control, but in that one that you're reporting, they didn't. Did I just mishear you?

DR. CHANG: Well, I'm not sure. So they probably did. I don't see why they wouldn't have, since they controlled for alcohol, but I was just trying to be careful and not just assume.

DR. SWAUGER: Fair enough. Can we check? I just don't know.

DR. CHANG: Yeah, there's no way of me knowing, because the point estimate was reported in the text.

DR. SWAUGER: So it wasn't reported in the paper that they --

DR. CHANG: It wasn't reported in the paper.

DR. SWAUGER: Okay, that's the answer I was looking for.

DR. CHANG: Okay.

DR. HUANG: Yes, Dr. Novotny.

DR. NOVOTNY: Yeah, just getting back to the actual specific sites of cancers, I don't know if it's possible to tease out cancers that are proximal, that are contact with the snus rather than the entire, you know, head and neck panoply of cancers. And I don't know if it's possible to do that, but to look at it in a much more specific way.

DR. CHANG: As regards to that specific study or just you're asking --

DR. NOVOTNY: Well, to any of them. You know, try to tease out the actual cancers that are resulting from contact rather than entire sort of exposure to the head and neck, you know?

DR. CHANG: Yeah, I'm not a clinician, so I don't know if I'm --

DR. NOVOTNY: Yeah.

DR. CHANG: -- the best person to address that. But it's --

DR. NOVOTNY: Because the local changes that have been observed, you know, sometimes are an alert -- you know,

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leukoplakia and things like that -- for precursors to cancers.

DR. CHANG: Yeah.

DR. NOVOTNY: And, you know, it just seems like it could stand some specificity.

DR. CHANG: Right, right. I mean, from what I understand about oral cancer is that, you know, it really depends on like how advanced their cancer is. So if it is further advanced, it could very well have spread to other parts that aren't necessarily proximal to where they use the snus.

DR. NOVOTNY: But the diagnosis is actually more anatomically specific rather than spread.

DR. CHANG: Right. Again, I'm not a clinician, but from what I understand, if it's diagnosed at a more advanced stage, it could have started more proximally and spread to a different region.

DR. HUANG: Other clarifying questions?

(No response.)

DR. HUANG: Okay, we'll move on with the next presentation.

Dr. Lacorte.

DR. LACORTE: Good afternoon. I'm Dr. Lester Jao Lacorte, Medical Officer from the Office Science, Center for Tobacco

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Products.

In this presentation I'll discuss the strength of research evidence provided in the MRTP applications on the use of SMNA snus products and the overall risks to health. The discussion will include the risk of snus use and the comparative risk to cigarettes.

The standard disclaimers.

First, in this presentation I'll discuss the content and format of the applications. Then I'll review the Applicant's overall conclusions, followed by FDA review comments. And lastly I'll discuss issues for the Committee to consider related to clinical studies and methodology.

In this section I'll provide an overview of the content and format of the applications.

The applications proposed changes to the packaging labeling for 10 snus products, the proposed labeling changes from "WARNING: This product is not a safe alternative to cigarettes" to "WARNING: No tobacco product is safe, but this product presents substantially lower risk to health than cigarettes."

The Applicant's evidence is based primarily on the Swedish experience summarized in Section 6 of the applications. This

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represents the most extensive and most applicable evidence from research conducted on the use of Swedish Match snus.

The research is derived from several large epidemiological studies supported by the Swedish government and institutions. Disease endpoints selected for comparison were based on endpoints with the highest number of deaths attributable to smoking, according to CDC 2008 estimates.

The literature summary included forest plots for each disease endpoint. The plots depict the visual comparison of the health risks of snus versus cigarettes.

As an example, this is a forest plot the Applicant presented for lung cancer. The summary result for each research study included in the plot is indicated by the solid circle. The horizontal lines extending from the circles represent the confidence interval. The central vertical lines indicate a relative risk estimate of 1, meaning either an increased or a decreased risk.

In this figure, the relative risk estimates for snus use are located on the left-hand side of the figure. All the values are very close to 1, indicating no increased risk. The relative risk estimates for cigarette use are located on the right-hand side of the figure and are consistently much greater

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than 1, indicating in this example outcome a greatly increased risk.

It's important to note that not all studies included in the literature review were included in these forest plots. Only relative risk estimates stratified by, or adjusting for, current tobacco use were included. Common reference exposure groups were used, for example, ever smokers versus ever snus users.

The disease endpoints selected for review were lung cancer, respiratory disease, chronic obstructive pulmonary disease (COPD), cardiovascular disease, stroke, esophageal cancer, pancreatic cancer, stomach cancer, oral cancer, all-cause mortality

Since oral cancer was discussed earlier, this disease outcome will not be discussed as part of this presentation.

In this next section I'll provide an overview of results found in the literature.

For lung cancer, the Applicant concludes that users of Swedish snus are at no greater risk for developing lung cancer than non- or never users of tobacco. The Applicant also concludes that smokers are significantly more likely to develop lung cancer. These conclusions were based on two studies of

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the large Swedish construction worker cohort.

The Applicant concludes that well-controlled epidemiological evidence indicates that Swedish snus is not associated with lung cancer.

FDA notes that the application provides evidence that use of these products would not be expected to be significantly associated with the risk of lung cancer. This is supported in the submitted data.

For nonmalignant respiratory disease, the Applicant concluded that there is no known mechanism for snus causing respiratory disease. Therefore, the Applicant notes, Swedish snus is widely accepted not to be associated with chronic lung disease, even in the absence of epidemiological confirmation.

FDA agrees that the applications provide evidence that chronic respiratory disease would not be expected to be significantly associated with the use of these snus products.

With respect to COPD, the Applicant concluded that COPD was not associated with the use of Swedish snus. Similar to other nonmalignant respiratory diseases, even without supportive epidemiological evidence, it is believed that use of snus is not associated with exposure to the airborne irritants known to cause COPD.

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FDA agrees that the applications provide evidence that these products would not be expected to be significantly associated with an increased risk of COPD. This is supported by the submitted data.

For cardiovascular disease, the Applicant concludes that there is not an increase in the overall cardiovascular disease risk among snus users, while in smokers, the risk is 1.5 to 3 times greater than non-smokers.

The Applicant acknowledges the known acute effects of nicotine, but reports that no increased risk for cardiovascular disease has been detected epidemiologically with respect to snus use, with a possible exception of a moderately increased risk of death due to a cardiovascular event.

FDA notes that the analysis was complicated by the inclusion in some studies of snus users who were also former or current smokers. Additionally, nicotine does affect heart rate and blood pressure, and both parameters were increased in users of these products. There are not adequate data to support a definitive conclusion for the risk of cardiovascular disease in users of these products.

The Applicant also reported literature findings on stroke. The Applicant concludes that the risk of stroke among Swedish

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snus users is no different than that of non-users of tobacco. They report that no studies found an increased risk of all stroke types among current or former snus users. They also report that two recent reviews of stroke reported no increased risk of stroke incidence.

Additionally, the risk of stroke among smokers is at least 40% greater than that of non-tobacco users.

FDA notes, however, that at least one study showed an increased risk of stroke in current heavy snus users. Also, elevations of blood pressure and heart rate were noted in snus users in several studies, which could potentially increase the risk for stroke.

It's also important to note that many studies did not include a complete smoking history for participants. This confounding makes data analysis difficult for drawing definitive conclusions.

The Applicant reports that the summary relative risk estimate among snus users for cancer of the esophagus is 1.6, while the risk for current smokers is several-fold higher.

They also note that epidemiology studies suggest no association between snus use and cancer of the esophagus. However, the Applicant acknowledges limitations in these

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available studies and that inconsistent results from the meta-analysis indicate the need for an additional study on the health impact of snus regarding cancer of the esophagus.

FDA agrees that the risk of cancer of the esophagus associated with snus use is less than the risk in cigarette smokers. However, the risk remains elevated over never users of snus who were never smokers.

The Applicant reports that literature findings on stomach cancer suggest that stomach cancer risk is no different for snus users than for non-tobacco users, while the risk is increased among smokers. They acknowledge that the risk may vary depending on the location of the cancer within the stomach.

No studies found that snus use was associated with an increased risk for overall or cardia type of stomach cancer. However, one study found an elevated risk for the non-cardia type of stomach cancer.

FDA notes that the Applicant acknowledges that these products are a source of carcinogenic nitrosamines. Although we recognize that the pattern of use may be very different in Sweden than in the U.S., the saliva produced during use of snus is often swallowed instead of expectorated. This leads to

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concerns that the nitrosamines present in the saliva could increase the risk of gastrointestinal cancers.

Literature findings were also reported on the relationship between snus use and pancreatic cancer. The Applicant acknowledges inconsistencies and uncertainty around the data for the risk of pancreatic cancer among snus users.

They conclude, however, that despite the inconsistencies, available epidemiological evidence suggests that snus and other smokeless tobacco forms are not associated with pancreatic cancer.

FDA notes that the published literature reports have widely variable relative risk estimates. The studies have inadequacies, particularly in dealing with confounding issues such as concomitant alcohol use, dietary habits, and cigarette smoking. There are not adequate data to support a definitive conclusion for the risk of pancreatic cancer and users of these products.

In reviewing the literature for all-cause mortality submitted in the application, the Applicant notes that two studies observed small increases in all-cause mortality associated with snus use. They believe the studies are inconclusive due to confounding issues and misclassification of

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smoking.

FDA agrees that the issues associated with these studies makes interpretation difficult, and no definitive conclusion can be drawn from the submitted literature.

Based on the literature review, the Applicant makes the following two overall conclusions:

One, use of snus presents a much lower risk of the diseases that results in the highest number of deaths among smokers, namely lung cancer, respiratory disease/COPD, cardiovascular disease, and stroke.

And Point 2, the Applicant overall concludes that there is very little evidence that current use levels of snus in Sweden are associated with any long-term health effects. Firm conclusions cannot yet be drawn regarding the relationship between snus use and possible weight-gain issues, metabolic syndrome and diabetes, hypertension, and fatal MI.

In this last section I'll review some methodology issues and weighing the strength of evidence in the applications. In weighing the evidence reported in the literature, it's necessary to also consider issues related to study methodology and any limitations. These may affect the interpretation of study results, specifically:

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One, the comparison of health risks was based on a visual inspection rather than using specific hypotheses testing for each disease outcome. It's important to note that the apparent differences in the magnitude of the relative risk vary considerably by each disease endpoint.

Point No. 2, the process for selecting studies for inclusion resulted in only a subset of the data. The selection process could lead to very different conclusions. In some cases, when viewed on the forest plot, the relative risk estimates may appear comparable; however, not all studies were included in the forest plots. The Applicant excluded studies when an analysis of smokers adjusted for snus use was not included. Additionally, it's conceivable that many studies on snus use may not be reporting estimates for smoking, since health risks for smoking are well established.

Point 3, some publications also provided analyses conducted on the same study population. I'll explain more on this in the next slide.

Point 4, the full range of health risks due to smoking was not presented, for example, the risk for developing bladder cancer or aortic aneurysm. For many disease endpoints, there are a limited number of studies available, and the health risks

associated with smoking were not addressed with regards to the risk associated with snus use.

And Point 5, no definition is given to specify the meaning of "substantially lower risk to health."

Some additional points to consider.

The first point, conclusions drawn from studies of a largely homogeneous Swedish population may present challenges for generalizability to a more diverse U.S. population.

Point 2, the Applicant provided published literature of clinical studies that used both American snus or snuff and Swedish snus. Specific variations in product formulation were generally not described in the applications. Therefore, the products used in the research could not consistently be confirmed as the same products being evaluated in the current MRTP applications.

And finally Point 3, in many studies, the number of snus-only users was small. This small sample size could affect study results and interpretation.

Additionally, as noted earlier, some studies evaluated the same subjects as other studies, thus producing a smaller pool of subjects tested in the cohort population of interest. The selection bias using the same subjects in several studies may

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produce duplicative results and thus accentuate the reported findings. Selection of a small subset of the population may thus lead to an overestimation of the reported health effect.

Some additional points for consideration.

No. 4, U.S. users may use Swedish products differently, very differently, in terms of product placement in the mouth, exposure time in the oral cavity, and expectoration. Lack of clarity on how the snus products would be used may affect the applicability of Swedish data to the American user.

And the last point, as a whole, the body of evidence around health risks that may or may not be associated with use of these products is considerably smaller than that known for cigarettes.

So, in conclusion, FDA asks the Committee to consider the following three points:

One, the applications provide evidence that use of these products is not likely to be associated with lung cancer, COPD, and chronic respiratory disease. These diseases constitute the highest number of deaths among smokers.

Point 2, in contrast, the applications do not provide adequate data to support a lack of association for use of these products with other disease endpoints that were explored in the

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application, namely esophageal, stomach, and pancreatic cancers, cardiovascular disease, stroke, and all-cause mortality. Cigarette smoking remains associated with an increased risk for all of these diseases.

And the final point, "substantially lower risk to health" does not have a clear definition. There is evidence that use of these products has some negative health effects and that users are still exposed to carcinogens.

Thank you. And I'll take any clarifying questions.

(Off microphone question.)

DR. LACORTE: Within the context of this particular research, I believe it's approximately two tins, but I can double-check for you.

DR. BICKEL: -- people who died from cigarette smoke, so smoke that's associated with the ones -- it was the one versus two. What would be the relative differential that one would expect conventional cigarette smokers -- you know, what proportion is associated with the ones that snus does not seem to share versus the ones that we're unclear whether snus use shares, or you're unclear whether snus shares or doesn't share?

DR. LACORTE: In the application, there was evidence to provide disease outcomes that were associated with smoking

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according to CDC 2008 estimates, and the Applicant attempted to provide some of this information in comparison with their present product, the 10 snus products.

DR. BICKEL: I was just trying to get a sense of whether does lung cancer, COPD, and chronic respiratory disease account for 30%, 40%, 50%, 60% of the mortality that we see with conventional cigarettes.

DR. LACORTE: What was submitted in the application was specific to -- according to the Applicant, 90% -- 80% to 90% of the data that they have on the mortality studies were based on CDC 2008 estimates for smoking and not specific to snus. And it was an attempt at the comparative analysis.

DR. CHOINIERE: I think that we're hearing here about half on the first -- on the health outcomes on the first. We can look into that and confirm that.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: So just to be sure, again, these studies -- none of these studies used never snus users and never smokers as a referent group, did they?

DR. LACORTE: Each study was individual, so some used never snus users and never smokers and others had --

DR. GIOVINO: In the studies of snus, they had snus users

compared to never snus users. In the studies of smokers, they had smokers compared to never smokers or something like that, right?

DR. LACORTE: There was a variation in each study that included those cohort populations of interest. Not all of them were performed and conducted the same, with the same subject population.

DR. GIOVINO: All right, thank you.

DR. HUANG: Okay, it looks like we're ready to move on to the next presentation. Let's see.

Dr. Ambrose.

DR. AMBROSE: Good afternoon. My name is Dr. Bridget Ambrose. I am an epidemiologist at CTP, and today I am going to be speaking on the applicability of the Swedish epidemiological data to the United States.

Today I will start with a high-level overview of the Swedish Match applications, focusing on sections relevant to tobacco use behavior. Then I will present a discussion of considerations for the TPSAC, related to the applicability of Swedish epidemiological data to tobacco use behaviors amongst U.S. consumers. I will then summarize the points for discussion.

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In Section 6.2 and 6.3 of the applications, Swedish Match cites data spanning 30 years across a number of studies and study designs, including repeated cross-sectional and cohort studies, to describe tobacco use behavior patterns among Swedish and other Scandinavian populations. The list of studies presented on this slide is not exhaustive but highlights some of the major studies cited in the application to describe the behavioral impact of snus amongst current, former, and never tobacco users.

In its review of the evidence base regarding the likely impact of the proposed modified risk marketing order on tobacco use among current users and non-users in the United States, FDA is examining the strength of the evidence by reviewing the study design, methodology, potential biases, and the generalizability of the major studies cited in Section 6.2 and 6.3 of the applications, as well as reviewing the ENVIRON report in Appendix 6B.

As previously stated, due to the large volume of information, our goal today is not to provide a comprehensive review of the evidence within these sections, but rather to consider the extent to which the Swedish data might inform inferences made about the U.S. population.

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For the sake of time, I'm going to skip this slide since we had discussion on it earlier.

Among many other conclusions made by the Applicant in Section 6.2 and 6.3, some of which we heard presented earlier, Swedish Match summarizes the evidence regarding the impact of snus on tobacco users as such.

The Swedish data established that, first, there is conclusive evidence of switching from smoking to snus use at both the population and individual levels.

Second, switching from cigarettes to snus is more common than switching from snus to cigarettes.

And, third, snus has been used as a smoking reduction and cessation aid by individuals in Sweden.

In considering how Swedish data might inform the likely impact of the proposed modified risk marketing order on tobacco use in the United States, it is helpful to review some of the factors that influenced the population health impact.

As detailed in the draft guidance, the likely impact of an MRTP will be driven not only by the health risks of the product, but also who uses the product and how; for instance, whether current users switch completely to the MRTP or initiate dual use or, conversely, whether former or never tobacco users

initiate use of the MRTP.

In the applications, Swedish Match describes the likely population health impact of snus in the U.S., stating that the introduction of the Swedish snus, the proposed MRTP, can result in a net population-level benefit, particularly if it is adopted by a sufficient number of smokers. If introduction of an MRTP results in more tobacco users compared to the base case, however, a survival deficit may result. The size of the effect, whether positive or negative, depends on the particular exposure patterns evaluated.

Particular exposure patterns may differ between countries. Utilizing the theoretical framework of the host-agent-vector and environment, or HAVE, model is useful in reviewing factors contributing to tobacco use and how they may differ across populations.

There are biological and psychological factors inherent to the individual, or host, that contribute to the likelihood of tobacco use initiation, and these may or may not be consistent across countries.

In addition, attitudes and perceptions as well as consumer preferences greatly influence the likelihood that an individual might choose one type of product over the other.

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There are attributes of the product itself, the agent, that may differ from one country to another, that may differentially influence appeal, like for instance, packaging, marketing, and labeling of the product.

And, lastly, there is the sociocultural environment in which use of some products may carry a different cultural or traditional context. Differences in tobacco control measures greatly differ across countries, which, for instance, may impact the level of exposure to marketing and marketing messaging.

Lastly, the tobacco market itself may differ, as other alternative products compete for market share.

If we consider the tobacco control environment in Sweden, modified risk messaging is, and has historically been, prohibited on snus packaging. Over time, the health warning labels displayed on snus packaging in Sweden have carried messages similar to those currently appearing on snus packaging in the U.S., warning consumers that the product can damage their health, cause cancer, and is addictive.

Since the Swedish warnings are similar to those in the U.S., the Swedish epidemiological data therefore may be limited in informing the likely impact that the proposed modified risk

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marketing order might have on tobacco use behaviors in the U.S.

As we saw earlier in the Swedish Match presentation, snus is a traditional product that carries great cultural significance in Sweden. Swedish Match itself has identified that the most fundamental difference between the U.S. and Scandinavian experiences stems from snus' status as a traditional Swedish and Norwegian product.

In the applications, Swedish Match further describes the sociocultural phenomenon of the resurgence of snus as a grassroots movement in Sweden. The Applicant states, "The movement began as, and remains to this day, a grassroots phenomenon. In other words, the shift from cigarettes to snus throughout Scandinavia was not the product of a nationally coordinated initiative originating from the centers of political activity, but rather was a trend which started with common citizens at a local level."

Indeed, both the Swedish and Norwegian experiences occurred in the complete absence of a national coordinated advertising campaign and with very little support from the countries' public health and medical communities.

From the Applicant's perspective, the authorization of the proposed modified risk marketing order could spur such a

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grassroots movement in the U.S., increasing public awareness and knowledge of snus through word of mouth. The Applicant further states, "Word-of-mouth sales have already contributed to the steady increase in snus sales in the United States, which are expected to continue to rise among current smokers if the snus products are permitted to be marketed as MRTPs."

Turning our focus to snus use in the U.S., recent convenience store sales data show that snus, as a portion of smokeless sales in the U.S., is low, representing approximately 5% of U.S. smokeless sales in 2014. Despite snus sales generally being dominated by other brands, sales of Swedish Match's General Snus brand has gained market share from 2010 to 2014, growing to 6% of U.S. snus sales in 2014.

In terms of prevalence, according to data from the 2012-2013 National Adult Tobacco Survey, a national random digital telephone survey funded by CTP in collaboration with the U.S. Centers for Disease Control and Prevention, just under 6% of adults have ever tried snus and less than 1% reported current daily or non-daily snus use. Sixty-nine percent of current snus users also reported current smoking, and males and young adults exhibited the highest prevalence of snus use.

Among youth, results from the 2013 National Youth Tobacco

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Survey indicates similarly that just over 4% of youth have ever used snus, and 1.3% of youth reported past month's snus use. A high proportion of past month's snus users, nearly 70%, reported past month's cigarette smoking. Again, snus use among males was more prevalent than females.

So, to summarize, differences in the sociocultural environment and consumer preferences, amongst other factors, may lead to differences in product uptake between countries.

The net population health impact of the modified risk marketing order depends on the likelihood that U.S. tobacco users and non-users will initiate use of the MRTPs.

Current U.S. warning labels, which Swedish Match North America proposes to change, are similar to those displayed in Sweden.

And modified risk messaging has not appeared on snus packaging in Sweden, which may limit the extent to which Swedish tobacco use behaviors might inform the likely impact of the proposed modified risk order in the U.S.

Thank you. And I will take any clarifying questions.

DR. HUANG: Okay, Dr. Novotny.

DR. NOVOTNY: So I'm interested in the sociocultural issues. In the United States we know that smoking prevalence

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is inversely related with socioeconomic status. We know that uptake is inversely related to socioeconomic status. We know that the ability to quit is inversely related to socioeconomic status.

Also if you compare the poverty rate in the U.S. and Sweden, we're about 55% greater in prevalence of poverty. If you use the Gini index of dispersion of income, it's about 51% difference greater. It seems to suggest that there's a health disparity in the uptake of cigarettes in the United States, and that disparity is not evident in Sweden. Should that be a consideration in the evaluation of this product?

DR. AMBROSE: So please let me try to repeat back what you said --

DR. NOVOTNY: Sure.

DR. AMBROSE: -- so I can figure out where the question is. Your question is obviously in the U.S. there is currently a health disparity in terms of exposure to cigarette smoking. We don't see that in Sweden. Should we -- can you repeat your question around what --

DR. NOVOTNY: I'm wondering if that renders making extrapolations from the Swedish smoking market to the United States smoking market challenged.

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DR. AMBROSE: And I think that's one of the points we would love the TPSAC to consider tomorrow, because I think that's a bigger question than I can answer at this moment, and it does get at what are the underlying factors causing the disparities in cigarette use in the U.S. and how might that continue to play out if Swedish snus were to become more popular and increase in use.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I have a question about the host-agent-vector-environment model. I'm interested in an agent factor and in a vector factor. The agent factor -- Dr. Bickel has me thinking about abuse liability, and I'm wondering a couple things. And I don't expect you to have the answer at this moment.

DR. AMBROSE: Thank you.

DR. GIOVINO: So please don't feel pressured. But I wonder maybe if this Committee should consider the abuse liability of cigarettes in Sweden and the United States as well as the abuse liability of smokeless tobacco products in Sweden and the United States, and if there's any difference in the abuse liability between cigarettes smoked in Sweden and cigarettes smoked in the United States, for one thing.

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The second thing I want to ask is, is there any difference in the abuse liability of the various snus products that you list on Slide 17?

So I'll stop there. I don't know if you have any answers to those or if that might be tomorrow.

DR. AMBROSE: I don't have any answers to that data. I mean, in terms of the current snus products on the U.S. market, all I can tell you is they're severely understudied. And yes, that type of research would be very welcome to better understand what's going on in terms of the current use of snus in the United States.

DR. GIOVINO: Okay. And my second question is on the vector. I'm wondering if Swedish Match is an independent company in Sweden and if it's an independent company in the United States. In other words, is it a subsidiary of another company in either of those countries, either here or in Sweden?

DR. AMBROSE: Could I deflect that question to Swedish Match?

(Laughter.)

DR. RUTQVIST: Swedish Match North America is a subsidiary of Swedish Match, the Swedish Match Group. Swedish Match is not owned by another company.

DR. HUANG: Dr. Choiniere.

DR. CHOINIERE: Yeah, I just wanted to follow up on Dr. Giovino's question. Your question about the abuse liability in Sweden and differences in abuse liability across snus products relates directly to one of our questions for you about the additional types of behavioral studies that we might want to see in an application, and whether or not there is sufficient information in this particular application. And so we would welcome more discussion about that point tomorrow.

DR. HUANG: Dr. Swauger.

DR. SWAUGER: Good afternoon. I just had a quick question. I actually was also interested in that same chart. I'm just sitting here kind of wondering, in a world in which, as near as I can tell, Swedish Match isn't going to advertise or make a claim or sort of highlight the fact that these labels potentially changed -- and I don't get the sense that FDA is going to advertise or put into place some migration strategy to drive people to it -- how do labeling and marketing actually impact this situation at all?

I mean, people are already aware of the warning labels. I'm not even sure what would influence them to read them again at that point. We're not going to talk about it. Do you

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understand my question?

DR. AMBROSE: So if I can repeat your question. Given the assumption that Swedish Match is not going to advertise at all in the United States, and that really the only modified risk messaging will be the warning label, why wouldn't we expect then -- why would marketing matter here? Why wouldn't we be able to just extrapolate the Swedish patterns of use to the U.S.?

And I think the question that we have is, could prior marketing that has happened in terms of suggestions to use smokeless tobacco as a product to bridge between smoking rather than completely switching -- this is just an example, but could that basically lead to a resulting pattern of use that's different in the U.S. compared to Sweden?

DR. SWAUGER: I'm not sure if you got it right or not. I'll just say what I'm thinking, which is I'm not sure if this is like a silent tree falling in the woods and nobody's talking about it. I just don't know whether the consumer would notice, that's all. And I don't know what to expect in the U.S. under those conditions.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Yeah, I was so unfamiliar with this product

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that I went online to look for it and see how it was sort of available. And it appears as though there's already advertising -- I don't know who's doing it or whether it's distributors or whatever -- that is implying, you know, the safety impact of it already, but also very much so emphasizing the fact that you can use the product when you can't smoke.

And so, you know, I guess the question is, has FDA looked at the sort of already kind of social media and kind of online messaging that's already been sort of out of the bag, and whether or not there's -- you know, what the impact will be of any sort of labeling that might need to be, you know, even corrected?

DR. AMBROSE: So is your question, have we gauged the existing --

DR. NOVOTNY: Yeah, the existing environment that's -- yeah.

DR. AMBROSE: -- sort of advertising environment and within that context thought about how the --

DR. NOVOTNY: The label would be affected, yeah.

DR. AMBROSE: -- label change would impact?

DR. NOVOTNY: Yeah.

DR. AMBROSE: At this moment in time I think it would be

only speculation to even try to gauge how that would impact. But it's absolutely, I think, something that we're concerned about in the sense that it could potentially lead to less desirable tobacco use patterns in the U.S. compared to what we've seen in Sweden.

DR. CHOINIERE: And if I can just follow up. There certainly would be concern for any tobacco product in relation to social media, and that is something that we -- it's not the industry necessarily that is engaged in social media, so therefore it's not something that we can regulate effectively.

DR. NOVOTNY: Unless the industry is --

DR. CHOINIERE: Unless the industry itself is doing it, yes.

DR. HUANG: We have Dr. Ribisl and Mr. Henton and Dr. Boffetta.

So Dr. Ribisl.

DR. RIBISL: I've got a comment and then two questions. So the comment is it seems like there's a very different pattern of dual use in the U.S. and in Sweden, and if I remember right from earlier this morning, the dual use rates are in the 6% to 8% for in Sweden. If I look at Slide 18, you have 68.9% of snus users are smokers.

So what we're seeing is a massive difference in the dual use rates, which would be somewhat alarming. But, again, if you don't promote -- I mean, I know some of the current products on the market have promoted dual use. But Swedish Match doesn't make cigarettes, so it seems like it might be less of an issue. But I'm still concerned about the dual use pattern differences.

Okay, my two questions are going to Slide 17. I would read the article by Delnevo, but I think a lot of the stuff I'm interested in is your internal analysis. So you're showing a really dramatic decline in Marlboro snus from 2010, like 28% down to 3%. Do you have any idea why that one -- why Marlboro snus is going down so much?

DR. AMBROSE: I do not.

DR. RIBISL: And if anyone knows and can comment on that by tomorrow --

(Off microphone comment.)

DR. RIBISL: Pardon me?

(Off microphone comment.)

DR. RIBISL: Okay. And then the other one is -- my final question has to do with the type of users who use General Snus both in Sweden or even in the U.S. Do we know that they --

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following up on Dr. Bickel's questions about SES and so forth, are they more health concerned? Are they higher SES?

I mean, we know, for instance, that people who use e-cigarettes appear to be maybe a little more health concerned than smokers, and maybe the General Snus users are either maybe a little more educated or a little more health concerned. And is it the different type demographic using this product?

DR. AMBROSE: I'm not aware of any research in the U.S. that has been able to look at the characteristics of General Snus users, or snus users in general, separate from other smokeless tobacco users. I can tell you that the information as presented in the application definitely describes the seeming phenomenon of the switch from smoking to snus being first taken up by perhaps a more educated population in Sweden. And as you know, diffusion of innovations tend to follow through then to the rest of the population that was -- generally, it sounds like the pattern -- and that there is literature regarding Swedish and Norwegian snus and tobacco use that does indicate that, for instance, immigrant populations are less likely to use snus in Sweden and perhaps other disadvantaged populations.

So that is a pattern that has to some extent been

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described, but we don't have that information for the U.S.

DR. HUANG: Mr. Henton.

MR. HENTON: It was on 11 and also 17. And it's maybe a question for tomorrow, but do you have thought that the products on this chart here are identical in types of tobacco, source of tobacco, how it's processed? Is it domestic? Is it grown in Kentucky, by chance?

DR. AMBROSE: I don't have -- that is not a part of the application that I reviewed. I believe it was the constituents were -- everything was provided, but that's not me.

DR. CHOINIERE: Are you asking about the General Snus in particular or all of the snus products?

MR. HENTON: The products that are listed here. There's some inference that these products are identical, Camel, Marlboro, Skoal, Triumph, and General, and I don't know if they're exactly the same product, if they come from the same source of tobacco -- with the tobacco market. I think of it in terms of the sourcing and the type and styles of tobacco. So my question is -- these are not all identical. As you might imagine, a Camel cigarette and a Marlboro may be different.

DR. CHOINIERE: My guess would be the same. And I don't think the information was meant to imply that we think that

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they are the same. It's just that they're all marketed as snus.

DR. HUANG: Okay, Dr. Boffetta.

DR. BOFFETTA: No, I can leave my question for tomorrow. That's okay.

DR. HUANG: Okay. Dr. Swauger.

DR. SWAUGER: Yeah, I just wanted to comment. You made the comment about different patterns of dual use in Sweden versus the U.S., and when you said it, my first thought was I don't find the fact that there's more dual use in the U.S. particularly shocking. Unless people are actually going to tell the consumer there's a reason to move to that category in isolation, I just -- meaning FDA at this point telling them that there's less risk associated with smokeless relative to cigarettes. I think it's how somebody actually communicates that. They've got no reason to move. I don't know if those numbers shock me at all.

DR. RIBISL: My question is, why is the magnitude almost 8 to 10 times greater in one country versus another? It's the magnitude difference.

DR. SWAUGER: At least for me, part of that answer is we're basically telling the consuming public that the risks are

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the same. Why would they move to sole category adoption?

DR. HUANG: Okay.

DR. AMBROSE: And Dr. Eissenberg, just to make one clarification. I think the 10% dual use rate -- I'm sorry.

(Off microphone comment.)

DR. AMBROSE: I'm sorry. I can't see your name tag. The 10% is a population-level rate, and the 70% is amongst snus users. So that is the difference in the data that we're presenting.

DR. RIBISL: Do you know what the rate among snus users is in Sweden then, who also smoke then?

DR. AMBROSE: So I would have to be quoting from specific studies. I don't know that off the top of my head.

DR. HUANG: Okay, Dr. Fagan.

DR. FAGAN: Just staying with this dual use issue, just going back to the youth data where the dual use is 69.3%. So do we know whether or not the youth are initiating with snus first or cigarettes first, and do we know anything about their transition? So are they still in the experimental phase of dual use or are they transitioning to become chronic dual users? Do we have any indications of any of those things?

DR. AMBROSE: No, we don't. This is from a cross-

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sectional study that did not -- that was not able to identify -- the question was not asked, in 2013, about which product did you use first? We also do not or did not, in 2013, ask about frequency of use.

So to sort of get at your question of whether or not these were experimental users who had just -- you know, kids who had tried maybe once or twice in the past month versus regularly using, we don't have that type of information. Clearly, cohort studies and more sort of directed recruitment type of studies would be helpful to sort of better understand these patterns.

DR. HUANG: All right, I think we'll move on to the next presentation. Thank you.

Dr. Johnson.

DR. JOHNSON: Hello. Good afternoon, my name is Dr. Sarah Johnson. I am a social scientist in the Office of Science at the Center for Tobacco Products, and in this presentation I will address consumer understanding and the implications of including modified risk information in the context of a warning label.

For background, I will begin by reviewing language from Section 911 that pertains to the topic of consumer understanding. Next, I will discuss information provided by

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the Applicant on this topic, in particular, provide just a high-level overview of the consumer perception study that's already been mentioned today. Then I will turn to the focus of this presentation, and that is to consider the implications for consumer understanding of the Applicant's request to include the modified risk statement in the warning label itself. And this is the subject of the questions to the Committee on this topic.

Section 911(h)(1) requires that any advertising or labeling concerning modified risk products enable the public to comprehend the information concerning modified risk, and to understand the relative significance of such information in the context of total health and in relation to all of the disease and health-related conditions associated with the use of tobacco products.

In support of these MRTPAs, as we've already heard today, Swedish Match conducted a study designed to address, in particular, the consumer perception topics outlined in FDA's draft guidance.

In brief, this was an online experimental study conducted with an Internet consumer panel. The total sample was just over 13,000 U.S. adults, and this included current users and

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non-users of tobacco.

Participants were randomly assigned to view one of six warning labels. These six conditions included the four warnings currently mandated for smokeless tobacco. One was the proposed modified risk label that's the subject of this application, and one was an alternate version of that label that omitted the word "substantially." As we heard, participants saw images of a set of product packages that displayed the warning label to which they were assigned.

And to summarize the design, this was a 2 x 6 between-subjects experimental design.

Per the applications, the study was intended to assess the effect of marketing the snus products with a modified warning label on the following populations and behaviors, including:

- Tobacco use behavior among current users;
- Tobacco use initiation behavior among non-users;
- Consumer understanding and perceptions of the product;
- and
- The population as a whole.

And I'll note here just for clarity, that behavior was not assessed or observed directly in this study. Thus, statements and findings regarding tobacco use behavior pertained to items

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that assessed participants' stated intention, such as reported likelihood to use or motivation to buy the product.

The results of the study were reported in an appendix to the applications, in the form of a PowerPoint slide deck containing over 500 slides. The findings were then summarized in the application across 13 pages. The summary results are not organized around a set of pre-specified hypotheses, but rather findings were reported by the topic areas I just mentioned for the total sample and then repeated for a number of subgroups identified by the Applicant.

So my next set of slides provide an overview of the primary conclusions drawn by the Applicant. Since we've already heard most of these from them earlier, in the interest of time I'm going to move through them. But just for reference, since you have the slides with you essentially, across their primary outcomes I quote the conclusions from the Applicant and then provide some indication of the findings that provide the basis for those conclusions.

So now I'd like to spend a little time addressing some of the high-level limitations with the study that FDA has identified.

First, there are a number of issues related to

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measurement, and these range from issues of conceptualization or construct validity, question wording, and response scales. And these issues compromise the validity of the data and/or complicate interpretation.

It should also be mentioned, as it has been discussed already, there were some inconsistencies between the wording of the modified risk statement that is in the application and the wording that appeared on the stimuli that participants viewed in the study. And, of course, this limits the applicability of the findings.

Finally, the Applicant did not provide a statistical analysis plan, a priori, to define an analytical approach and criteria for evaluating results and drawing conclusions, which leaves room for multiple different approaches to evaluating the data and drawing interpretation.

In conclusion, FDA is assessing what conclusions can be drawn from these data regarding consumer understanding of the proposed modified risk label, in light of the study limitations, some of which were discussed in this presentation.

So now putting aside the wording of the modified risk label per se, we'd like to think about the placement of that statement. So as I said, the Applicant's consumer perception

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study was designed to evaluate consumer perception based on the content of the modified risk information. However, it was not designed to assess a separate question, which is the impact of the context of that information in terms of whether it was presented in a warning label, as proposed in these applications, versus in a statement separate from but in addition to a warning label.

And so at hand for discussion is what additional questions may be raised by the context of that modified risk information, that is, including it within the warning label itself.

Active communication of modified risk information in the context of a government-mandated warning label may raise additional questions regarding consumer understanding of that information, their perceptions of the product, and more generally, there may be implications for their perceptions of government-mandated warnings on other regulated tobacco products.

To our knowledge, there is no study that directly examines the effect of the context of modified risk information, that is, comparing whether the information is presented in a warning label to the same information presented in a statement that is separate from but in addition to a warning label on a product

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package.

So in considering the implications for consumer understanding, we note first that information about the relative benefits of product use, that is, benefits to using a product relative to the use of another product -- here, the comparison to cigarettes -- is atypical for inclusion in a product warning label. This language would appear in a place where consumers typically see, and thus might expect to see, information about the potential risks of the product, which could be confusing.

Likewise, it is unclear if consumers would perceive the statement as a warning at all, and moreover unclear what the downstream consequences of this might be.

In conclusion, the Applicant conducted a consumer perception study to assess understanding of the modified risk information in the proposed modified label.

Methodological issues, some of which were described here briefly, limit the conclusions we can draw from the study data.

However, the context of the modified risk information requested by these applications, that is, that it's conveyed within the warning label, raises additional questions. In particular, it raises questions about the implications for

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consumer understanding of the information and also more broadly their perceptions and understanding of tobacco product warning labels. And consideration of these implications are the subject of FDA's questions to the Committee on this topic.

Thank you. And I'll take clarifying questions.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: I'm sorry, I hate to belabor this point, but now you've confused me further. Can you go back to your Slide 7? Okay, on this slide you say that the modified -- I'm looking at the one, two, third major bullet and then the second indented one inside that. The proposed modified risk label per the application was "Warning: No tobacco product is safe." Is that your understanding of what was tested? Because that was not my understanding of what was tested.

DR. JOHNSON: Yeah. No, you're correct. So here it does get confusing. I'm quoting the application. And so the way it's described in the application is that it was tested this way. And as we've made clear earlier, it was not, in fact, tested that way. And that's not how it appeared to participants, but it's described this way in the description of the study in the application.

DR. EISSENBERG: Is it? Okay. Well -- okay.

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DR. JOHNSON: That is the description of the study, and the narrative of the application does not match what was actually shown to participants. That was a discrepancy.

DR. EISSENBERG: Okay.

DR. HUANG: Dr. Bickel.

DR. BICKEL: Just to beat this again, right? So I think the data from the ITC that suggests that one's socioeconomic status impacts the ability to make appropriate perceptions and understanding of risk of such statements -- and it strikes me that -- this is more of a comment than a question. It strikes me that the same consideration of socioeconomic status is relevant again in understanding the differences in how people may perceive this.

DR. HUANG: Dr. Swauger.

DR. SWAUGER: Thank you. I just have a question kind of running through my mind.

Conrad, you said something this morning that hung with me a bit, and I guess what I'm struggling with is from a broader industry perspective. And I sort of have this sense that at least from what I read in terms of Swedish Match's stuff, that they sat down with CTP and they had more than a few discussions about study design.

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I'm kind of listening to the presentation and hearing a fair amount of -- well, criticism might be a strong word, but concern raised here and there, and I'm just trying to understand the disconnect. I mean, I'd like to think, you know -- and I'm pretty sure the rest of the industry would like to think if they were sitting down with CTP, that they're having discussions and they're walking out with, if not a handshake, some clarity in terms of what CTP is actually looking for. And it just seems like there's a disconnect here, and I'm just trying to understand that. Does that make sense?

DR. CHOINIERE: I can see why you think there may be a disconnect. Certainly, when we meet with applicants, we respond to the protocol letter provided, and we give the feedback that is requested. Certainly, we can't be expected to foresee all of the issues. Applicants take our feedback or don't. And so -- I lost my train of thought here.

(Laughter.)

DR. SWAUGER: That's all right. So is it fair that if an applicant or a company walked in and had the discussion and followed your advice, that they'd be fine? Or would we still --

DR. ASHLEY: Let me try to clarify a little bit what

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Conrad tried to say earlier today. We meet with tobacco companies, as you well know, and when we have meetings with tobacco companies, they come in with specific questions, and we try to provide them as much advice in response to those specific questions, or not.

We did not sit down with Swedish Match and go through and say, okay, let's work with you to design a study, et al. They came to us and they had specific questions. We responded to those questions as we could. And in certain cases we could not even give them the answers that maybe they were looking for, but we responded to questions as we could respond to questions, just like we do when you guys come in. And then they have the choice of going out and doing the study that they believe is the right study to do. And that's their decision and that's their choice.

And so again, I don't -- and Conrad tried to do this earlier today. You know, just to clarify, we did not sit down with them and develop a study design together. They came in with questions, and we answered those questions to the best of our ability.

DR. CHOINIERE: I also just want to add that a study can't obviously address every issue. So we have issues that we still

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need to resolve, and one of the ways we are trying to resolve this issue is to bring it forward to this Scientific Advisory Committee.

DR. HUANG: Okay, other clarifying questions?

(No response.)

DR. HUANG: Okay. All right then, I think we can move on to the last of the FDA presentations.

Dr. Apelberg.

DR. APELBERG: Good afternoon. My name is Dr. Benjamin Apelberg. I am the Epidemiology Branch Chief here in the Office of Science at FDA's Center for Tobacco Products, and today I'm going to be discussing some considerations in the design and conduct of postmarket surveillance and studies in the context of a modified risk tobacco product application.

So here is the first disclaimer, and there's the second disclaimer.

Okay, I'll start just with a brief introduction to the statute and where it describes the need for postmarket surveillance and studies. I'll then just provide a broad overview of Swedish Match North America's plan for postmarket surveillance and the studies as described in their applications, and then use that to lay out a few issues for

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consideration for postmarket surveillance and studies.

Section 911 of the Federal Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act, clearly lays out that an applicant that receives a market authorization order under Section 911 is required to conduct postmarket surveillance and studies. And, in particular, the Act specifies the purpose, to determine the impact of the order issuance on consumer perception, behavior, and health, to enable the Secretary to review the accuracy of the determinations upon which the order was based, and to provide information that the Secretary determines is otherwise necessary regarding the use or health risks involving the tobacco product.

The Act also goes on to discuss the timing of such requests, specifically that an applicant, once notified that they're required to conduct postmarket surveillance and studies, shall submit within 30 days a protocol for that required surveillance. In addition, the results of the postmarket surveillance and studies shall be submitted to FDA on an annual basis.

I did want to make it clear that, to date, no notification has been provided to the Applicant that such studies are

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required. However, in FDA's draft guidance on modified risk tobacco products, we did recommend that applicants submit a general plan, their thinking for postmarket surveillance and studies with their application. Swedish Match North America did submit some information to that effect, and that's what I'm just going to highlight now in order to use it as a basis for discussing some of the considerations around the design and conduct of such studies.

Okay. Great, okay. Swedish Match North America sets out their postmarket surveillance and studies plan in Chapter 9 of their applications, and this chapter is titled "Development of Swedish Match Postmarket Program." I will say that much of the information provided in this chapter of the application is commercially confidential. So I'm not going to be speaking about it in detail, but more just providing a general sense of the scope and framework of what's being proposed.

So the Applicant describes the objectives of such a program as twofold: one, to evaluate the benefit to the population as a whole of the labeling changes proposed in the MRTTP application, as well as to monitor and collect information regarding unanticipated and undesired events related to snus products and to contribute to the establishment of an adverse

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event reporting system.

And, broadly, the data sources the Applicant proposes to use include large-scale postmarket surveys to collect information on consumer perceptions and behavior, and the development of a system to monitor for unanticipated adverse events.

And, further, the Applicant goes on to note that the postmarket surveys will build on information gained from their premarket consumer perception study and will be used to generate data to inform the dynamic population model.

And so FDA's review of this material is focused, as I said, on Chapter 9. Included in the chapter is a draft preliminary outline of a postmarket survey protocol as well as an example of a questionnaire related to one of the surveys and an annual report in the form of results from one of their ongoing surveys.

As I mentioned, formal study protocols are not required until 30 days after receiving notice from FDA. Thus, the scope of our review to date has really focused on general considerations in the development of these types of studies.

So now I'll go on and touch on some aspects. So as Dr. Ambrose talked about, there is a range of factors to

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consider for assessing impact, and one of the determinations that FDA is required to make when reviewing and assessing protocols for postmarket surveillance and studies is whether the protocols will result in the collection of the data or information necessary to protect the public health.

So the factors that may impact the population as a whole include the inherent health risks associated with product use, as well as the behaviors that may result from modified risk marketing, which include, but are not limited to, the extent to which current tobacco users switch completely to the modified risk tobacco product or become dual users, the extent to which former tobacco users or never tobacco users initiate the product with or without going on to use other tobacco products. And I've also highlighted, as laid out in the statute, the need to collect information around consumer perceptions broadly, which may ultimately serve as an upstream measure of potential use and uptake of the product.

I also borrowed this slide from Dr. Ambrose to highlight the fact that not only is this host-agent-vector-environment model useful for thinking about the factors that influence tobacco use at a population level, but it's also been used as a model and framework for thinking about tobacco surveillance.

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And so that includes information about the behaviors themselves among individuals as well as perceptions, knowledge, attitudes, behaviors, and factors that might influence use.

To date, however, in tobacco surveillance, much of the focus has been on the use of large-scale national surveys to monitor tobacco use patterns over time in youth and adults, as well as determinants of tobacco use. These surveys typically focus on product categories or product classes as a whole, such as: cigarettes; cigars, which may or may not include subtypes of cigars; e-cigarettes; smokeless tobacco, which may or may not include a separate category for snus. And although some of these large-scale surveys collect information about brands, regular brands or favorite brands, most of them are not really designed to be able to drill down to the brand and the product-line level. But, of course, the modified risk tobacco product order is issued not for a class of products or category of products but a specific product or, in this case, set of -- in this application it would be for a set of 10 products.

So as I mentioned, the Applicant proposes to use postmarket surveys to collect information on consumer perceptions and behavior and describes them as large scale. And surveys that are national in scope, however, may really

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result in limited numbers of users at the level of detail needed to understand who's using a product that may have been authorized as a modified risk tobacco product user. And, of course, even smaller samples of users would be available to examine potentially susceptible subpopulations.

So just to kind of demonstrate this a little further, FDA does have experience in the conduct of national surveys on tobacco use. As Dr. Ambrose mentioned, we at CTP collaborate with the Centers for Disease Control and Prevention in the conduct of a National Adult Tobacco Survey and a National Youth Tobacco Survey. And these surveys provide really critical information for us at the national level, in terms of prevalence of use of a range of products, key indicators and determinants of use and how those are changing over time, both at the national level as well as within subgroups.

However, as demonstrated here, even a survey, you know, with the size of the National Adult Tobacco Survey, which is over 60,000 individuals at present, the ability to drill down to snus use and to use of a specific product and brand and product line would be limited.

Now, of course, the issue of an order might -- one would think, would contribute it to an increasing use of a product.

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But it still, I think, poses many challenges.

So, for example, currently, of the over 60,000 individuals in the 2012-13 national adult tobacco survey, 327 adults report current snus use. Only a small fraction of those are daily users. And as mentioned previously, presently General Snus is just a small fraction of the overall snus market. So we're talking about relatively small numbers here.

The same concern would be apparent if you looked at the national Youth Tobacco Survey in terms of being able to characterize who's using these products and what the characteristics of those individuals are. Of course, FDA is very much interested in the impact of a modified risk tobacco product order on youth, and so we'll look forward to any recommendations from the Committee about ways in which to collect such information.

I also just wanted to note, as I mentioned previously, that the Applicant does talk about the use of survey data to inform population modeling. And the Applicant's model relies on estimates, as described earlier, of product use transition such as rates of initiation, cessation, and switching.

And so one of the challenges is, is that cross-sectional surveys may be limited in the ability to measure some of these

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transitions, specifically at the level of the brand and the product line that would be necessary to really inform an order that was issued for a specific product.

In general, FDA agrees that the principle of linking real-world behavior data to population modeling in order to estimate long-term impacts is a good one. But we would like to see more information on how survey measures would be used to generate the needed inputs and how they would be derived and implemented in the model.

So, in summary, upon issuance of a risk modification order, an applicant would be required to conduct postmarket surveillance and studies to assess its impact on consumer perception, behavior, and health.

Some of the unique challenges to the conduct of postmarket surveillance and studies include the need to collect information at the product brand and product line level, specifically to understand who's using these products and what the characteristics of those users are.

Given these challenges, a postmarket surveillance and studies program would be strengthened by incorporating multiple lines of evidence to ensure that the order continues to benefit the population as a whole. And that may include the need to

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really conduct oversampling or targeted recruiting to identify those who are using the product as well as those who are at risk for use, in order to really characterize their patterns of use and behavior; the collection of a range of measures related to perception that might ultimately inform who might take up the product, as well as the ongoing collection and reporting of data such as product sales, information that, you know, can be used to monitor uptake of the product over time and place.

And, finally, FDA does agree that there's value in being able to link the real-world behavior data in a postmarket setting to population models that are developed to understand what those changes in behavior mean or likely mean for future health impacts.

So with that, I'll stop and take any clarifying questions.

DR. HUANG: Okay, clarifying questions?

Dr. Tomar.

DR. TOMAR: Yeah, this is a question -- I guess it's primarily for the Center, you know, just so I understand the regulatory framework. So say a year from now they conduct postmarket surveillance and in fact find that 90% of these products are used by current smokers as a bridge. So they're still smoking, and they're using this product. They wind up

with higher indications of nicotine addiction. What actions would the Agency take with that information?

DR. APELBERG: Yeah. So I mean, the statute does lay out some reasons for FDA to take action to withdraw a marketing authorization order, and that includes the results of postmarket surveillance and studies, if those suggest that, you know, the order no longer benefits the population as a whole. So the authority is there to do that, and we would have to make a determination based on the available evidence.

DR. HUANG: Okay, Dr. Novotny. Oh.

(Off microphone comment.)

DR. NOVOTNY: Okay.

DR. HUANG: Okay.

DR. ASHLEY: I just want to add a little bit more to Ben's answer, and that is modified risk is very interesting -- and this was mentioned early today, I believe, during Conrad's presentation, where he talked about the fact that these orders are time-limited. And so clearly we will look at the information from studies and surveillance that come in.

But also if the companies want to continue to market after that time has run out, they've got to come in and ask for permission to do that again. And so we will have a decision to

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make, and I'm sure a lot of that decision will be based on the real-world events that occur with that. So it's not just we don't have just the authority to pull it under certain circumstances, but the companies also have to come in to get a renewal of that order to continue.

DR. NOVOTNY: This is a comment and also a question. The use of social media and in particular big data to monitor the things you mentioned, product sales, but there's so much more that is actually being used. And I think public health in general is pretty much behind the curve on this, in terms of things like, you know, adverse events, that people go to the Internet to ask questions before they go anywhere else, and lots of information is generated as a result of these inquiries; and Twitter feeds and other kinds of social media, which would seem to be more rapid and more efficient in many ways than trying to mount surveys periodically, especially given the problems with the representation and the difficulties that there are, and they're costly as well. And you know, I wonder if there couldn't be a little bit more expanded thinking about this.

And also, you know, getting back to the adverse events. I mean, FDA is very involved in adverse event reporting for

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vaccines, et cetera, and whether or not there could be something connected to our surveillance systems and other kinds of ways of identifying risks that may not appear in surveys.

DR. APELBERG: Yes. I mean, I think those are all great points. And you know, honestly, the reason for bringing this to the Committee, hopefully there will be time tomorrow to have these discussions, if time permits, to get to the issue of postmarket surveillance and studies. But part of it really is to get feedback and insight from you all, in terms of innovative approaches that could be used to collect information that would inform ultimately decisions that would have to be made. So I mean, I completely agree with you.

You know, I guess just to clarify, this presentation was not really intended to sort of, you know, present an overview of all the factors that we think are important in the context of postmarket surveillance and studies. It's really to use the information that Swedish Match provided as a kind of jumping-off point to start having these discussions. But I think those are great points.

DR. HUANG: Okay, I think we're going to go ahead and take a break now, because we want to make sure and have time for the Open Public Hearing. I don't know if anyone has any other

clarifying questions for Dr. Apfelberg. So we can do it after -- okay. So I think we're through with that. So we will take a break until 4 o'clock, and then we would like to ask the public speakers to be ready to speak promptly at 4 o'clock, once we reconvene.

So, again, now Committee members, please remember there will be no discussion of the meeting topic either amongst yourselves, with the press, or with any member of the audience. So, again, we'll reconvene at four o'clock.

Thank you.

(Off the record at 3:49 p.m.)

(On the record at 4:01 p.m.)

DR. HUANG: Okay, it's 4:01. So we will get going with our Open Public Hearing.

Okay, before we get started with the Open Public Hearing, I need to read something, so if everyone could please be seated.

First of all, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making, so to ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the

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context of an individual's presentation. For this reason FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the Sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this Committee place great importance on the Open Public Hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when

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recognized by the Chair. Thank you for your cooperation.

And, also, we do have a timer. Each of the individuals who previously signed up have 7 minutes, and then if you came in late, then I think you have 3 minutes, so our last speaker has 3 minutes. And there is a light that starts out green; at 5 minutes it turns yellow, and then it turns red, so you need to stop when it turns red. Okay?

So our first speaker is Geoffrey Curtin with RAI Services Company.

DR. CURTIN: Good afternoon. I appreciate the opportunity to be able to speak with you this afternoon. My talk will be on smokeless tobacco and modified risk. I'm currently Senior Director of Regulatory Oversight at RAI Services Company, and I don't have any financial connections with Swedish Match North America.

This has been an information-filled day, so I'll try and keep my comments short, and a number of things have already been addressed by the Committee. Given that my role with the company is to do the type of studies that have been talked about today, consumer perception, comprehension, likelihoods of use, it's been very informative for me in terms of how Swedish Match or another tobacco company operates and why some of these

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measures -- and really, it's our first look into how FDA would evaluate these things and, you know, judge these things as well. So it's been very informative.

So, first off, RAIS believes that smokeless tobacco presents substantially lower risks to health than cigarettes. This is all smokeless tobacco, including snus. We put in a citizen petition back in July of 2011 that requested a rulemaking to modify the not-as-safe alternative warning label for smokeless tobacco products in an identical way to what was subsequently suggested by Swedish Match.

In that application, or in that citizen petition, we summarized the relative and absolute risks of smokeless tobacco, U.S. studies, Swedish studies. If anyone is interested, that's part of the comments that we provided.

We supplemented that petition in March 2013, summarizing about 50 tobacco use behavioral studies from the U.S. and Sweden, and also presented evidence on population modeling, which we think will be critical for, in this case, an MRTP, but that's not what we were doing at the time. But we looked at a number of what we considered worst-case scenarios and make the case that it's more likely than not that there would be a benefit for informing tobacco consumers on tobacco use

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behaviors.

So even though we agree on the basic premises of Swedish Match's application, we do believe that there are some methodological flaws in the consumer understanding and comprehension and likeliness of use studies that do raise some questions on whether Swedish Match actually met the evidence threshold per the draft guidance. I won't go into those in detail, we did talk about them in our comments, but I think Dr. Johnson with FDA CTP talked about a number of those a few minutes ago.

I guess our biggest concern is, this is TPSAC's first exposure to this proposition, that smokeless tobacco may present less risk or would be -- the evidence would be available to -- for an applicant to petition for a modified risk order. And our concern is even if the evidence is deemed, because of the flawed methodology, not sufficient to support the application, we wouldn't want that evidence to also be used to impact or negatively impact future submissions.

In terms of population modeling, we fully support the use of statistical modeling as a way to likely predict the effects of tobacco use behavior changes on population health. In our world, given that these products won't be on the market with

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modified risk messaging until they're approved, it really does become about prediction with consumer testing, comprehension perceptions, likelihood of use, and we really believe that the modeling is very important to take those possible changes in tobacco use behaviors and project what's going to happen in terms of population health.

We believe that this modeling is most informative when based on empirical evidence such as likelihoods of use studies with hypothetical inputs mostly used for sensitivity analysis, because obviously these are projections and there will have to be some exploration of, you know, some things that might happen, unintended consequences that may be worse than what the data show.

We do think that Swedish Match's use of the statistical modeling is lacking in at least two important areas, at least from our interactions or our read of the draft guidance interaction with FDA on this, and that is it fails to examine the net population level effect, taking all the adverse and all the beneficial transitions and putting them together. And even more importantly, there's no modeling in there that really looks at the primary drivers, and we submitted modeling to FDA CTP over the years.

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But really, as you might imagine, the two primary drivers for population mortality are MRTP initiation followed by gateway, because you're going from zero risk to 100% risk and then current smokers who would have continued to smoke, switching completely to a lower-risk product. And those are the type of things that need to be looked at in an application like this.

We also believe that the application includes unsupported and unrealistic use behaviors as inputs, and these give somewhat of a skewed perspective of what the likely impact is going to be, if it's going to be a net population benefit or a net population harm.

So, in summary, we think that in order to promote greater public understanding of the evidence-based risks associated with smokeless tobacco use, that the current warning labels should be revised for all smokeless tobacco products. This goes outside of what's being currently discussed as a warning label, but really is in line with our citizen's petition.

Again, we believe the epi supports it, not just for snus but for smokeless tobacco as a category, and that the flawed studies and analyses presented in Swedish Match's MRTPA should not be used to support or inform a conclusion against the

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likely potential of a population health benefit if, in fact, consumers are appropriately informed about the relative risks and absolute risks of smokeless tobacco compared to cigarettes.

I'd be happy to address any questions.

DR. HUANG: Thank you very much.

All right, our next speaker is Scott Ballin.

MR. BALLIN: I want to thank the FDA and TPSAC for allowing me the time to make a few comments today. I know a number of you on the Committee, and I've known you for many, many years, and I think we have a shared vision for reducing disease and death caused by the use of tobacco.

A little over a hundred years ago a technological invention changed the manner in which tobacco was used and created what can only be described as a global epidemic of disease and death. The technological invention was a cigarette manufacturing machine that made it possible to produce trillions of cigarettes at little expense. How the cigarette industry evolved and how it profited at the expense of the public health is well documented, and it should never be forgotten. But today, we, a century later, and with the FDA oversight of tobacco and nicotine, we are in a new era that requires new thinking, new ideas, and new leadership.

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While many unfortunately still seem to classify all tobacco products as being equally harmful, the reality is that there are major significant differences in the risks and relative risks of products from the deadly cigarette, as I mentioned, to NRT products at the other end. In between we have products like snus, tobacco-based lozenges and dissolvables, gums, and the broad spectrum of ENDS, which are getting so much attention these days.

To say that consumers and the general public are confused about these products and about the risks and relative risks of them would be an understatement. We need to recognize that it's not the tobacco per se that causes the harm, but rather how it is grown, cured, processed, manufactured, marketed, sold, and most importantly used that determines that harm.

I say all this because I think the time has come, and is long overdue, to develop a more rational approach as to how we, as a society, decide to regulate this growing spectrum of tobacco and nicotine products. The tobacco and nicotine alternative products environment has changed drastically just in the last couple years and it will continue to evolve. Unfortunately, it remains full of rhetoric, emotion, and information and disinformation that only confuses the consumer

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and the general public.

We need to look at the categories of the products, as well as the specific products within those categories and to begin to set workable and rational product standards that cut across the spectrum of all the products, and we set regulations based on risks, relative risks, and intended uses. The public and users of these products are entitled to have truthful, accurate, and relevant information about the products they use.

I am therefore here today not to talk so much about the application that has been filed but rather to encourage you to look at things differently, to look at how we should be regulating the growing spectrum of products, including snus, some of which -- some of the products which are far more hazardous than others. I do find it interesting that for about 15 years and ever since the landmark report of the IOM "Clearing the Smoke," we've recognized the potential of snus as possibly playing a role in reducing disease and death caused by the deadly toxic cigarette.

I want to commend CTP Director Zeller for his visionary view that we are in a new era or, as he has said, a new beginning, one in which we should be regulating tobacco and nicotine based on the continuum of risk. I think the Food and

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Drug Administration and TPSAC have important roles to play in helping shape the new policy and new regulatory directions that are urgently needed.

Regulating products based on the continuum of risk and providing the public and consumers with truthful information about those products needs to be a part of the overall tobacco control agenda. It has tremendous potential: Change the product and you can change the public health risk. Make science-based, clearly labeled, lower-risk, consumer-acceptable products available to users, and you can move the public away from the deadly combustible cigarette.

Director Zeller and others at the Center have also spoken about the need for stakeholder engagement and dialogue, and I encourage the Center and TPSAC to do more of it rather than less. There needs to be more civil engagement of all stakeholders, including researchers and scientists, NGOs, manufacturers, consumers, policy makers, regulators, growers, and the general public.

I strongly recommend that TPSAC embrace such a philosophy that allows for such interactions of interests. I believe that TPSAC should even consider making site visits to different companies and places that are producing products so you have a

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better understanding of what is happening in the marketplace and take it out into the environment.

In order to accomplish some of the things I'm suggesting, consideration should also be given to a number of interrelated factors which have been outlined in the set of core principles concerning the implementation of harm reduction strategies recently released by the University of Virginia. That is the basis of a series of dialogues that have been done by the university to try to promote a more constructive approach to harm reduction.

The document identifies a number of areas that includes the need for clearer definitions in terminologies that are being used today; the need for all tobacco and nicotine products to be regulated under a single umbrella and based on the continuum of risk; the need for transparent and collaborative research in both the public and private sectors; the need for innovation; the need to collectively, cooperatively monitor and provide surveillance of all products; and to involve consumers and to involve the agricultural sector and to encourage and promote civil dialogue in both the private and public sector.

Let me close by reminding ourselves that we live in a

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society where we are confronted with many dangers and risks: the automobiles, motorcycles, and bikes we drive and ride; the alcohol we drink; the food often high in fat, cholesterol, salt, sugar, caffeine, additives, and pesticides we eat and drink; the possession and use of firearms; unprotected sexual activity and unwanted pregnancies.

All of these are things that we have to confront on a daily basis. Tobacco and nicotine is no different. We do many things to minimize those risks in our society, but in a democratic society some risks will remain. Today, although we have challenges, we have opportunities to move in a new direction, as CTP Director Zeller has talked about. We can undo what occurred 100 years ago. The FDA can do more to educate the public.

And that's my time. Thank you.

DR. HUANG: Thank you.

Dr. Ribusl.

DR. RIBUSL: All the speakers are supposed to list any financial disclosures. Do you have any disclosures to make?

(Off microphone response.)

DR. RIBUSL: I said, all speakers are asked to make any financial disclosures related to this application or to the

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topic of discussion. Do you have any financial disclosures?

MR. BALLIN: I have no conflicts of interest. I am not being paid by any company or anything. I do consulting with the University of Virginia in trying to bring people together to talk about these important issues and to set a new agenda and course for the future.

DR. HUANG: Thank you.

Our next speaker -- okay.

Mr. Henton.

MR. HENTON: Mr. Ballin, you mentioned the agricultural sector, you mentioned growers, and you mentioned how tobacco is grown and cured. We don't hear much of that in this room. Do you have suggestions there?

MR. BALLIN: Mr. Henton, I go back a few years, and I think that the importance of involving the growers in the discussion, because so much can happen at the agricultural level, and I think farmers need to be a part of this discussion and dialogue. And as you said, you don't hear much of that. I brought it up in the past to several meetings at the FDA, and I know FDA does not have the regulatory authority over the agricultural sector. But when you're talking harm reduction, when you're talking about setting standards such as GOTHIA TEK

that was mentioned this morning that Swedish Match is doing, the growers need to be a part of the solution for moving forward in the future.

And I would encourage members of TPSAC to talk with Hoppy and talk with others of the grower leaders to see how there could be a more active, participative process to have them, again, be part of the solution rather than to be seen as part of the problem.

DR. HUANG: Okay, thank you.

The next speaker is Patricia Kovacevic.

MS. KOVACEVIC: Good afternoon, distinguished TPSAC members, distinguished CTP representatives, and audience. Thank you very much for this opportunity to present before this very unique TPSAC and during this very unique opportunity the first ever MRTP application to be considered by the FDA. My name is Patricia Kovacevic. I am a Director of Regulatory Affairs and Associate General Counsel for Lorillard Tobacco Company, and I have no affiliation with Swedish Match.

My comments are intended to make three points. First, the Swedish Match modified risk tobacco product application, which I shall continue to refer to as MRTPAs, appear to be supported by significant scientific evidence that is consistent with

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these smokeless products posing reduced risk to users and reduced harm to the population as a whole. Furthermore, based on the evidence suggesting reduced risk of disease, a modified risk claim for the respective Swedish Match products is certainly appropriate.

Second, there are impediments to implementing the request for action in Swedish Match's MRTPA, as requested. An MRTPA order under Section 911 of the Tobacco Control Act provides a mechanism by which a company may make certain claims in addition to and separate from the warning statements.

Swedish Match's MRTPAs seek a product-specific modification of health warning, that is, permission to remove two of the statutory warning statements for smokeless, as discussed earlier, and also Swedish Match requests FDA permission to revise one of the warning statements from "this product is not a safe alternative to cigarettes" to the following: "No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

Surprisingly, Swedish Match does not request permission from the FDA to make actual modified risk claims on its product for advertising. The FDCA, as amended by the Tobacco Control Act and specifically Section 205 of the Tobacco Control Act,

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expressly authorizes the Secretary of Health and Human Services to modify tobacco product warning statements through their rulemaking process and not through issuance of an MRTP order, which is under Section 911. Therefore, FDA should work with Swedish Match to ensure that appropriate modified risk claims are made on the respective products.

FDA has an opportunity to consider rulemaking for changing smokeless warnings for the entire smokeless category. There is great value in the scientific evidence submitted by Swedish Match and by other manufacturers of smokeless products with respect to the reduced risks of smokeless products compared to cigarettes.

Based on the best available science, FDA must ensure that all mandatory communications to the public, including tobacco product warnings, are truthful and not misleading and also that they do not violate the First Amendment. Such scientific evidence must be used by the FDA in a constructive manner which may include proper revision of the current smokeless warnings through rulemaking.

Third and last, but certainly not least, looking beyond the Swedish Match application itself, it is critical for FDA to recognize and communicate to the public that the data needed to

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support an MRTPA will inevitably vary according to the unique characteristics and circumstances of the product at issue. In particular, FDA should make clear that the Swedish Match MRTPA is not a benchmark or a standard against which all future MRTPAs will be assessed and certainly should not mandate the same amount or type of data that Swedish Match provided. The draft guidance on MRTPAs, in our opinion, has an opportunity to be also revised.

The data available for Swedish snus are unique due to the long history of marketing in Sweden and other markets. Thanks to this history, Swedish Match was able to amass a significant, impressive amount of epidemiological data. Although the data available is commendable and should support approval of an MRTPA for Swedish snus, FDA should not require the same amount of data for novel products that do not share the same history of use and market penetration.

In particular, for any MRTPA application review of electronic cigarettes or similar vapor products, to the extent they are deemed tobacco products, FDA should account for their relatively recent development and, as a result, the emerging nature of the evidence of long-term benefits and risks.

However, because the available scientific and biomedical

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literature on electronic cigarettes and related products is promising and shows a significant possibility of advancing public health, FDA should adopt a flexible approach to the level of evidence required for modified exposure and modified risk claims approval for electronic cigarettes and vapor products that is based on the best available science.

This concludes my comments. Thank you.

DR. HUANG: Thank you.

Our next speaker is Lars Ramstrom.

DR. RAMSTROM: Good afternoon, ladies and gentlemen. I'm Lars Ramstrom from Sweden without any connection to Swedish Match. I am free of any conflicts of interest. Thank you.

I shall speak about a study where I start on the background that in Swedish men born after 1949 -- 1940, there has been a considerable shift from smoking to snus use. Early published studies have concluded this shift has been the main reason why Swedish men have low all-cause mortality than men in any other European country.

The current study aims at investigating how the increasing snus use is associated with incidence of tobacco-related cancer. Comparisons have been made between cohorts born in successive 5-year periods around the years 1943, '48, '53, and

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'58. For each birth cohort, age-specific cancer incidence rates have been retrieved from the 2015 edition of the NORDCAN database, and tobacco use data have been retrieved from large nationwide representative surveys.

In this diagram, each bar represents one of the birth cohorts. The segments of each bar illustrate the proportion of cohort members whose first day of tobacco use was snus use (light blue segments) or smoking (red segments). When comparing the cohorts, we see that smoking as first day of tobacco use decreased from 55% in the earliest-born cohort to 38% in the latest-born -- while the proportion of men received snus as first tobacco product increased from 8% to 22%.

Further, among those with smoking as first tobacco use, increase in proportions who later quit smoking by switching to snus use by either on a long-term basis or as a transitional stage towards sustained abstention from all tobacco use, this has successfully increased the proportion of snus use versus smoking in later-born cohorts.

In this diagram there is, for each cohort, a vertical set of data points indicating lung cancer incidence rates at three age levels represented by different colors. Trend lines for each age level illustrate that incidence rates are successively

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decreasing from the earliest-born cohort to later-born ones. This downward trend in lung cancer incidence reflects a downward trend in smoking that we saw in the previous slide, and it appears that the concomitant increase of snus use has not upset the beneficial effects of the lower effects, lower levels of smoking.

This diagram shows the corresponding data for oral cavity cancer. In spite of the fact that the oral cavity is directly exposed to snus, the increase in snus use has not prevented cancer incidence from being lower in later-born cohorts. However, the downward trend is less pronounced than for lung cancer. The possibilities could be that the beneficial effects of decreasing smoking has, to some extent, been upset by the increase of alcohol consumption that has occurred.

If snus use had had a noticeably contributing factor to oral cavity cancer in Sweden, the comparison between cohorts would not have shown the actual downward trend. The trends for esophageal cancer are similar to those for oral cavity cancer, and similar comments would apply here as well. The increase in use of snus appears to have -- not to have contributed significantly to esophageal cancer either.

Some studies have found associations between snus use and

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pancreatic cancer, while other studies have not. This diagram shows pancreatic cancer, as well, and association between increase in snus use and low incidence rates in later-born cohorts. This lends support to those earlier studies that have found snus use not to be an appreciable risk factor for pancreatic cancer.

So, in summary, population effects of Swedish snus have been assessed by comparisons of age-specific cancer incidence rates in birth cohorts with different levels of smoking and snus use. Lower levels of smoking are consistently associated with lower cancer incidence rates despite concomitant higher levels of snus use. So, as conclusion, Swedish snus does not appear to be an appreciable risk factor for tobacco-related cancer.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Denny Henigan.

MR. HENIGAN: Mr. Chairman, members of the Committee, I have no financial relationship with Swedish Match. My name is Dennis Henigan. I'm Director of Legal and Policy Analysis at the Campaign for Tobacco-Free Kids, and on behalf of that organization, I'd like to thank FDA and TPSAC for the

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opportunity to address you today.

In our view, the risk profile of Swedish snus, compared to cigarettes, may well suggest that a properly supported modified risk application by Swedish Match would deserve serious consideration by FDA. However, the application submitted by Swedish Match is seriously flawed for several reasons.

First, there is a significant danger that revising the statutorily required warning labels in the manner advocated by Swedish Match will have adverse population-wide effects. Even though Swedish Match purports to seek a modified risk order under Section 911, it does not actually propose to make a modified risk claim. Instead, it seeks to have FDA revise the statutorily required warning labels for its products. These products -- these warnings exist separate and distinct from any claims the company may wish to make about its products.

Now, as we have argued in our written comments, there is a serious legal issue as to FDA's authority to alter the statutory warnings under Section 911. But there are important scientific and policy implications as well. Because Swedish Match proposes to introduce a reduced-risk message in the form of a government mandated warning, this message would appear generally on packages and advertising of these products with

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broad exposure to nonusers of tobacco, particularly youth.

Swedish Match has not proposed a modified risk claim that would be carefully targeted to existing smokers, nor has it proposed limitations or conditions that would minimize the risk of exposure of this message to nonusers of tobacco products, particularly young people, who may be persuaded by the message that use of the products involves a negligible health risk. Thus, the company's proposal to transform a warning label into a government-sponsored statement of reduced risk creates a special risk of adverse population-wide effects, including increased initiation of tobacco use by youth and former users. As noted, this is not really a warning; it is a recommendation for use.

Second, Swedish Match's reliance on the so-called Swedish experience, in our view, is misplaced and offers little assurance that it would be replicated in the United States. The Swedish market for tobacco products is radically different than the U.S. market. In Sweden, these products have long been the dominant smokeless tobacco products; they enjoy little popularity or market presence in this country. And in Sweden, they are marketed in an environment where there is no tobacco advertising; it is not permitted.

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In the U.S., tobacco companies spend over \$8 billion annually to market cigarettes through advertising, promotion, and price discounting. Given this pervasive cigarette marketing activity, it is far less likely that cigarette smokers will switch to snus in the U.S. than in Sweden, even with the proposed change in the warning labels for Swedish snus.

In fact, everything we know about the consumer use of smokeless tobacco in the U.S. suggests that it is unlikely that the proposed change in warning labels would lead U.S. consumers to switch from cigarettes to Swedish snus. Longitudinal studies show no strong evidence that U.S. cigarette smokers switch to smokeless products; in fact, the research shows that smokeless is a gateway to smoking, particularly among youth. And as noted by the Committee, the evidence also suggests that in the U.S., consumers use smokeless in conjunction with smoking, particularly in places where smoking is prohibited, rather than switching entirely. Thus, smokeless is used to maintain cigarette addiction among those who may otherwise have quit smoking.

Indeed, the marketing of smokeless in the United States expressly encourages this kind of dual use. And the issue of

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dual use is absolutely pivotal because even Swedish Match acknowledges, in its own application, "The health risks among dual users appear to be similar to those among exclusive smokers." Therefore, the company's reliance on the Swedish experience provides an insufficient basis to conclude that changing the warning labels as proposed would either significantly reduce the risk of disease to individual users or benefit the population as a whole.

And, finally, modifying the warning labels as proposed would mislead consumers as to the safety of Swedish snus. Granting this application would mean an absence of any warning of specific health risks of snus apart from addiction, even though the research discussed today has shown Swedish snus associated with an increased risk of heart disease and stroke, esophageal and pancreatic cancer, and adverse pregnancy outcomes. It is critical for TPSAC to consider these health risks and the public health implications of a complete absence of any specific disease warnings for these products. Moreover, the proposed language that this product presents substantially lower risk to health than cigarettes is itself misleading because it does not inform consumers that the health benefits of snus usage depends on switching completely from cigarettes

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to snus.

Swedish Match did not test alternative, less misleading messages, nor does its consumer perception survey test whether consumers would understand, from its proposed modified risk message, that the health benefits of snus depend on quitting cigarettes. Therefore, Swedish Match has not demonstrated in this application that its proposed change in the smokeless warning labels would significantly reduce the risk of disease by inducing U.S. smokers to switch to snus or that it would benefit the population as a whole.

DR. HUANG: Time's up.

MR. HENIGAN: We, therefore, urge TPSAC to recommend to FDA that this application be denied.

DR. HUANG: Thank you.

All right. And our final speaker has only 3 minutes, and this is Gal Cohen.

DR. COHEN: Members of the Committee, thank you for the opportunity to address you today. I am head of Scientific and Regulatory Affairs at PAX Labs. We are an independent vaporization company based in San Francisco. We have no financial affiliation with Swedish Match, but ideologically we support them in their vision, pursuit, and progress towards a

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smoke-free society. The morbidity and mortality associated with combusted tobacco is an epidemic and public health emergency. It is incumbent on TPSAC and FDA to define a path forward for modified risk products.

Under Section 911, it is clear that Congress intended that modified risk products can be approvable even based just on a modified exposure and reduced biomarker data and incomplete population and health data. The bar for that is clearly exceeded here in this application. We have a product that is safer than a cigarette, at least with respect to the important endpoints of lung cancer, COPD, and chronic lung disease. That's really significant.

Now, any modified risk application's claims should be tuned and consistent with evidence and the needs of the product. However, let's make sure that the details don't cause us to lose sight of the big picture here. Consumers and industry are looking to you, Committee and FDA, for guidance. Your recommendation here matters a lot. We hope that in the language of your recommendation to FDA you can support the concept of modified risk as an actionable and achievable pathway.

Please make sure that you clarify and don't cloud what

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that pathway is; there's already more than enough smoke in this industry. We're looking to you to articulate how we can best develop products that enable the vision of a smoke-free society to become a reality.

Thank you for your attention.

DR. HUANG: Thank you.

Okay, now the Open Public Hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

So the Committee will now turn its attention to address the task at hand: the careful consideration of the data before the Committee, as well as the public comments. So our schedule now -- we have until the end of the day, which I'm told could go as late as we want; that is for discussion at this point.

(Off microphone comment.)

DR. HUANG: Oh, okay. We will take, first, a 5-minute break and then reconvene. So we need to read that? All right, 5-minute break. Thank you.

(Off the record at 4:43 p.m.)

(On the record at 4:49 p.m.)

DR. HUANG: Go ahead and reconvene. We'll go ahead and reconvene. Okay. If everyone could please take their seats

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again.

So, again, Caryn has said we can stay until midnight if we wanted, but we wanted to put it out there to the Committee. I mean, you know, does anyone feel compelled to try to get through the first question and vote tonight or probably put that off until tomorrow? Does anyone want to proceed on that?

(No audible response.)

DR. HUANG: Okay. Seeing no one anxious to do that, we will not plan on having that accomplished today. So I think what we're thinking is to wrap up the day, just see if there's any discussion about what additional information or other things that we might want to have prepared for tomorrow so we can get started again bright and early.

So any thoughts on that from the Committee?

Yes, Dr. Ribisl.

DR. RIBISL: Yeah. So two things, and I think I'm speaking to FDA here. So one is, have you all performed a detailed legal analysis of whether what Swedish Match is proposing is allowable? And so in some ways I think you're conflicting with Section 201, which is related to warning labels? 205? 205, the warning label section, and that you could actually modify -- the MRTP one can kind of trump the

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warning label section. Is this even possible?

DR. ASHLEY: Let me just respond to that right away. There have been a number of people that made comments, and there were comments from the public, there were comments to the docket. It's a very good question; we've heard that question. That's not a scientific question. This is a scientific advisory committee, so we're not -- that's not -- that's out of the range of the discussion. Right now, we are having our deliberations based on the assumption that that is correct. It has not been decided, and clearly, we have heard what people have said.

DR. RIBISL: Right.

DR. ASHLEY: And so we're not going to go there in this advisory --

DR. RIBISL: Perfect, okay.

And my second question is a request. I thought through all the different unanswered questions from the day, but to me, the most important one for me is getting an apples-to-apples comparison on dual use in Sweden/Norway and the U.S. And so we had data presented on the percentage of U.S. adults, I believe, from the National Adult Tobacco Survey, who use snus who also smoke, and it was pretty high, I believe around 69%.

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Could we get similar data for Sweden and Norway so we can have a sense of how the dual use rates compare in both countries? If you could present -- if that could be presented by -- at some point tomorrow, that would be fantastic. Does that make -- is that -- did my question make sense?

DR. CHOINIERE: Yeah, I just want a caveat that we'll see what we can do, what is feasible and what's not, and then whatever is feasible we can provide tomorrow.

DR. HUANG: Dr. Moynihan.

DR. MOYNIHAN: This is just in response to that. It won't make much sense unless you can get data over a period of time. I don't think we can compare, when Swedish snus use in the United States is about 1% of the population, to the situation, when Swedish snus is a dominant tobacco product in Sweden. I think we need to know something about the historical data. I don't know if you'd be able to get that in that timeframe, but it would help.

DR. CHOINIERE: Might I also suggest that if Swedish Match has that information, they might be able to provide it tomorrow, as well?

DR. HUANG: Dr. Tomar.

DR. TOMAR: Just to speak to that question, actually, we

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published a paper a couple of years ago specific to the U.S. It really is -- so I guess the other caveat is it really needs to be age specific because it varies dramatically across the age spectrum.

DR. HUANG: Dr. Bickel.

DR. BICKEL: So information about the abuse liability of snus and also about the relative abuse liability of these 10 different products that Gary brought up. I think that's an important question. We don't know that the abuse liability doesn't vary as a function of these different products.

DR. HUANG: And Dr. Boffetta.

DR. BOFFETTA: Some of the information on the dual use is present in the studies that have been used to assess the risk of these products in Sweden and Norway. For example, in the Code of Construction Workers, you know, there are several papers that were discussed today. And many of these papers do present the data on how many snus users were exclusive snus users, current tobacco, former tobacco users, et cetera.

So this information -- one should consider whether it's more relevant to have the information about the situation in Sweden today or whether it is more relevant to have it relevant to the studies that were used to assess the health effect that

-- for the latter. I mean, there are some data in these studies.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I think it would be helpful, since we're going to be looking at population-based effects, and the population here in the U.S. is quite different. I know it was mentioned earlier that certain groups are included in the analyses, but if we want to know the effects on particular groups, women, people of low socioeconomic status, I understand that the racial diversity is not there. But for the data that do exist, we need to know subpopulation effects for some of these things. I think that would be extremely helpful, particularly as you're talking about these health effects and who the users are. And including the abuse liability component as well.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Yeah, I had a couple of requests, if possible. I wanted to go back to the question of specific organ types, cell types, on the cancer risk and specifically to see if we can't get information on oropharyngeal cancers, not just head and neck as sort of a wastebasket of all cancers. They can be thyroid or other kinds of things. But, you know,

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it seems, because of the physical contact that snus has with the oropharynx set, it would be the most likely one and should be separated out to be very, you know, more specific. If we can get any data on that.

Second, on the GOTIETEK [sic] -- how do you guys say that?

(Off microphone response.)

DR. NOVOTNY: GOTHIA TEK, okay. The GOTHIA TEK process. I want to know what it does actually measure. What is it that it's meant to do, you know, in terms of quality control or actual product stewardship? And along those lines, on product stewardship, I asked earlier about the environmental impact statement that may be necessary, and my understanding is that it is part of the application process.

And the reason I bring this up, and it may sound a little silly to begin with, but the most common picked-up item of trash in the world is a cigarette butt, and we are now talking about trying to convert people to getting what sounds like is a non-biodegradable pouch of tobacco. What do you do with it after you use it, and what kind of environmental impact may that have, because this contains, as we know, tobacco-specific nitrosamine and other kinds of things. You know, that all seems to me that at least it ought to be at least considered,

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you know, in terms of the environmental impact statement. Also, I understand that the pouches are marketed in or sold in plastic containers, which again is another issue.

And then the final thing is, because there's one loose tobacco product in this list of 10, I wonder if there isn't some sort of difference in either exposure or sort of impact that -- there was one implication of this that I think somebody made, but I just wondered if there has been any other sort of, you know, differences that we need to at least understand relative to the loose versus the pouch product.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: There are other Swedish Match product markets besides these 10 brands that we are discussing today, and the question is also whether they are made according to GOTHIA TEK's standards. And the issue is the status over risk perception, whether the consumer would be able to differentiate between the message which is put on these products that we are discussing now, modified risk tobacco products, or other Swedish Match products, because there will be then understanding by association.

If you change the label, "there are no risks for certain disease," does it apply then to all Swedish Match products?

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Because consumers would see Swedish Match products, you know, it must be then safer than other products. So we don't have those kind of risk perception studies which would show the understanding between two different types of products on the market.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I'll repeat, I had asked for consumption data more recent than 2007 or 2008, and one of the FDA people presented trend data that didn't show that huge drop in 2007 that was on the slide that Swedish Match presented, and I'd like to get that resolved, if possible.

The other issue is I'd really like to see if there are relative risks for smokers who have switched. Are there any studies that have looked at smokers who smoked 10 years and then switched to Swedish Match, 20 years and switched to Swedish Match products, 30 years and switched to Swedish Match products? I just don't know. And I'd like to see that, if possible.

DR. HUANG: Dr. Moynihan.

DR. MOYNIHAN: I believe, if you compare the two figures that were presented, one is labeled 1915 to 2010, and the other is labeled 1915 to 2008, but, in fact, I think the titles, I

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think, are reversed and the one that shows the downturn has a couple of years of additional data.

DR. GIOVINO: If we could clarify that and even get more recent data, that would be great. I mean, the difference between the two curves is how many years are included.

DR. HUANG: Okay. Mr. Henton.

MR. HENTON: So I assume that there will be an opportunity tomorrow to ask some questions directly of Swedish Match?

DR. HUANG: Yes.

DR. CHOINIERE: Dr. Huang, if I can just add something here?

So I hear these various things that people are wanting to hear about. I did want to advise you that as far as FDA knows, all of the studies related to snus are included in the application itself. So if there are additional studies on switching and age of switching, they should be in the application.

Also, information about organ/cell types, Dr. Novotny's question. Subpopulation effects, the abuse liability of snus. If there were abuse liability studies, they would be in that application. There's information about dual use between Sweden and Norway. I'm not sure if we would have that information.

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I'm not sure if it's in the application, but maybe Swedish Match can fill us in on that.

As far as the environmental impact statement, we can have someone here tomorrow to talk about what we typically have, would see in an environmental impact statement. But I believe that the types of information that you would want to see in an environmental impact statement that you just mentioned is exactly what we would be having in an environmental impact statement.

DR. HUANG: Okay. Any other requests, comments, clarifying questions?

(No response.)

DR. HUANG: Okay. So seeing none, I think, then, we can adjourn for the day, and then we are scheduled to reconvene at 8 o'clock tomorrow morning. Thank you very much.

(Whereupon, at 5:03 p.m., the meeting was continued, to resume the next day, Friday, April 10, 2015, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the
matter of:

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

April 9, 2015

Silver Spring, Maryland

were held as herein appears, and that this is the original
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TOM BOWMAN

Official Reporter

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