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

April 10, 2015
8:00 a.m.

FDA White Oak Conference Center
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10903 New Hampshire Avenue
Silver Spring, MD 20993

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M E E T I N G

(8:00 a.m.)

DR. HUANG: Good morning. I think it's 8 o'clock. So I'm Phil Huang. I'm the Acting Chair of the Tobacco Products Scientific Advisory Committee. We want to welcome everyone and thank you for joining us. Before we start, I want to make a few statements, and then we'll introduce the Committee again.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and 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 and the Government in the Sunshine Act, we ask the Advisory Committee members to 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 media until its

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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.

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 the 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 the 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, and 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 interests 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 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, Jeff Ventura and Tara Goodin. And if either of you are here, please stand up.

Thank you.

DR. HUANG: And now we'll go ahead and introduce our Committee members. And I am, again, Phil Huang. I'm the Medical Director and Health Authority with the City of Austin and Travis County Health and Human Services Department, serving as Acting Chair.

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

DR. ASHLEY: David Ashley, Director of the Office of Science, Center for Tobacco Products.

DR. CHOINIÈRE: Conrad Choiniere, Director of the Division of Population Health Science, Center for Tobacco Products.

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

DR. BOFFETTA: Paolo Boffetta, Mount Sinai School of Medicine in New York.

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DR. NOVOTNY: Tom Novotny, Professor of Public Health at San Diego State University and UC San Diego.

DR. BICKEL: Warren Bickel, Professor of Psychology, 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 of Community Health and Health Behavior, University of Buffalo.

DR. EISSENBERG: Tom Eissenberg, Professor of Psychology, Virginia Commonwealth University.

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

DR. DJORDJEVIC: Mirjana Djordjevic, Program Director at National Cancer Institute representing NIH.

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

MR. HENTON: Hampton Henton, tobacco grower.

DR. MOYNIHAN: Michael Moynihan, Vice President of

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Research, Goodrich Tobacco.

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

DR. HUANG: Again, welcome to everyone. And now I'm going to turn it over to Mitch Zeller.

MR. ZELLER: Thank you, Phil. And thank you, Committee, for the yeoman work on Day 1 and for the work ahead of you on Day 2. It's my privilege to introduce the Acting Commissioner of the Food and Drug Administration, Steve Ostroff. As everyone knows, Peggy Hamburg stepped down after 6 years as Commissioner, and Steve has thrown himself into the fire and has agreed to serve as Acting Commissioner of FDA and wanted to make some welcoming remarks of his own to TPSAC at this very important meeting.

Steve.

DR. OSTROFF: Well, the first thing I'll say is that I don't want to get you off schedule at all today, and I apologize for not being able to be here yesterday. I was all day down at the Department. But when I saw Mitch yesterday afternoon, I said to him that I really wanted to come down and at least listen to part of the discussions because this is a

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really challenging and important issue that you currently have before you.

This is actually the end of my first week serving as Acting Commissioner, and yes, I've thrown myself into the fire. But fortunately, at the end of the first week, I don't feel singed yet. And when I had the opportunity to become Acting Commissioner, I did have a month or so to be able to interact with Peggy Hamburg and discuss a number of the very important issues before FDA as she handed over the baton, and I can tell you that she consistently mentioned that the work that's going on at CTP is very, very important, not only for FDA but for public health.

As Mitch didn't mention, before I agreed to serve as the Acting Commissioner, for about the past year I've been serving at FDA as the Chief Scientist. One of Peggy Hamburg's mantras was that we base our decisions on science and what's best for public health, and that was certainly something that resonates for me, and I continue -- I will continue to have that perspective as we move forward. And so I'm very pleased to be able to spend some time listening to the work of the Committee this morning; I won't be able to stay that long. But what you're doing is very, very important, not only for us but for

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the health of the nation.

The last thing that I'll mention is that it's good to see an old friend of mine on the Committee, Tom Novotny, and one of the very first articles that I co-authored was with Tom back in the 1980s. I don't know if you remember, Tom, and it was on the cost of smoking in Washington State. So this is indeed a topic that I've been interested in for quite a long period of time.

So thanks to all of you again. I'm not going to take up any more of your time, but I'm going to sit and listen for a while.

So thanks again.

DR. HUANG: Thank you very much for being here.

Next -- oh. Also want to recognize Dr. Tim McAfee on the phone. Do you want to introduce yourself?

DR. McAFEE: Yes, thank you. This is Tim McAfee, and I'm the Senior Medical Officer of the Office on Smoking and Health at the Centers for Disease Control.

DR. HUANG: Great. Glad you could join us also.

Next, let me turn it over to Dr. Choiniere to sort of review our first day and introduce, again, the questions.

DR. CHOINIERE: Good morning and welcome back. I don't

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really want to spend a whole lot of time reviewing yesterday. I'm very excited about diving into the questions that we have before us. But I want to thank everyone for the very productive meeting we had.

We heard from Swedish Match as well as FDA scientists about these modified risk applications, the first ones filed by FDA. You also heard about a number of important issues to consider when looking at these products and the evidence supplied in these modified risk applications.

We identified a number of critical scientific questions for which we seek advice from this Committee.

At the end of the day yesterday we heard a lot of interest from members of the Committee about additional information that you would like to have. Many of those requests for information directly relate to the questions that we bring to you today, so I will defer to you, Dr. Huang.

But given the number of questions that we have to discuss today, I would recommend that in lieu of discussing all of those additional questions before we begin, that we dive right into the questions, and that when the particular issues that were identified at the end of the day appear to be relevant, that we get that information in the context of the discussion

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of the questions.

DR. HUANG: That sounds good. So the individual who proposed a particular question from yesterday might interject that at that point, then.

DR. CHOINIERE: Yes, I think that would be the most appropriate. Then Swedish Match can provide that information as it arises.

DR. HUANG: Great, thank you.

DR. CHOINIERE: So as a reminder, we posed several questions related to the evidence on the associations between the use of these products and the risk of certain diseases: gum disease, tooth loss, and oral cancer.

We also discussed the evidence on the comparative risk between the use of these products and cigarette smoking; the applicability of the data from Sweden to infer impacts on the U.S. population; the potential impacts of providing modified risk information in the context of a warning label; and the elements of Swedish Match North America's postmarket surveillance and studies program.

We have a lot to cover, we have a limited amount of time, and so I think I can just introduce the first question, if that's appropriate, Dr. Huang?

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DR. HUANG: Yes.

DR. CHOINIERE: So our first questions to the Committee deal with respect to the relative health risks to individual users of these snus products (i.e., the Swedish Match North America, Inc. snus tobacco products that are the subject of these applications).

We ask the Committee first to discuss the evidence regarding the association between the ten snus products and gum disease or tooth loss. In your discussion, 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 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 the

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number of snus users is not large. Many of the cross-sectional surveys in the application included fewer than 50 snus users.

And our first voting question after that discussion will be: Does the evidence support that these snus products pose risks of gum disease to individual users of these products?

DR. HUANG: Okay, so we have it now open for discussion, and I think, you know, we want to encourage active discussion, not just asking more questions at this point.

So Dr. Tomar. Oh.

DR. BICKEL: I just had a point.

DR. HUANG: Okay, Dr. Bickel.

DR. BICKEL: There's an assumption behind this, and I just want to know how we should deal with it. So the assumption is that these 10 products are substantially equivalent with respect to all these questions. Is that what we should assume?

DR. CHOINIERE: I would not assume that. If you feel that there are significant differences between the products, then that should be discussed.

DR. HUANG: And I think that that was one of the sort of clarifying questions early on yesterday that I had in terms of -- the question, as it is stated, does the evidence support

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that these snus products pose risks of gum disease to individual users of these products, that's not just based on there being science showing these particular 10 products have this health risk.

There is an assumption that, in the category of smokeless tobacco and what we know about the science of their association with some of these health risks, then I think that there's adequate information or that these studies show distinction from that, so it's more also like -- because the question, how it relates in a practical sense to what's been proposed, is there evidence, then, to support the removal of some of these warning labels for smokeless tobacco products and these health effects.

Dr. Tomar.

DR. TOMAR: I just wanted to get verification on some data that was presented yesterday. So in Dr. Day's presentation on reviewing the data on periodontal and gingival diseases associated with the use of snus, particularly in Slide 11 from her presentation, cites one study that examines the association between the use of snus and gingival recession. And I just wanted to verify that, in fact, that was the only study that was found in the literature. That was a study by Monten 2006.

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DR. DAY: Hannah Day, epidemiologist, Center for Tobacco Products. I would like to clarify on Slide 11, as I mentioned in Slide 10, FDA is evaluating these outcomes per the aims of the study, and we're doing that in order to really look at the studies as they were designed to evaluate each outcome.

In your backgrounder, it does include additional outcomes, if you look at the tables in the end. This table was really just meant to be a summary of the overall outcomes. Regarding the gingival recession, the Montan study actually was one of the four studies that did not have specific aims, but gingival recession was the only factor that was an outcome that was adjusted for.

In addition to the Montan study, there were several other studies that looked at gingival recession. Rolandsson stated that there were 7 out of 40 users who had gingival recessions. They did not state whether or not any nonusers had recession, so there's no statistical test in that one.

Andersson and Axell, again, they did not have any nonusers, so they just looked at gingival recessions in loose snus users compared to portion snus users, and they found that the loose snus users had higher risks of gingival recessions than portion snus users.

In addition, the Wickholm study looks at recessions in unadjusted analyses, and I can pull that study up very quickly, if you're interested in that.

So in unadjusted analyses, the Wickholm study did find there were significant differences between never users, ever smokers, ever snuff users, and ever mixed users. They give the percentage of recessions, and it looks like in never users they report 54.28%; in ever smokers, they report 63.09%; in ever snuff users, 62.96%; and in ever mixed users, 65.31%. And it appears that the p-value given for that is significant, 0.01, but it is not a pairwise comparison; it's just an overall p-value between the groups.

Does that answer your question?

Thank you.

DR. HUANG: Yes, Dr. Eissenberg.

DR. EISSENBERG: Wait, before you leave the microphone. Sorry. The Axell and Andersson study, was that a significant difference in gingival recession between the pouch products and the loose products?

DR. DAY: Yes. And if you wait one minute, I can get you the odds ratio for that.

So, again, this is Hannah Day.

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The odds ratio for Andersson and Axell, they stated it as a relative risk, but I think they mean odds ratio. I'd have to go back and verify it. It doesn't appear to be a cohort study. They state that the loose snuff compared to the portion bag snuff had a relative risk of 8.71 with a p-value of less than 0.01.

DR. EISSENBERG: So this is at the heart of Warren's question because, of course, we have 9 of the 10 products that are pouched; is that correct? And then one that's loose. And it's the pouch products that have, in that study, a higher incidence of gingival recession; is that correct?

DR. DAY: I'm sorry, the pouch products have the higher incidence or the loose?

DR. EISSENBERG: Well, I'm asking you.

DR. DAY: Oh, okay. The loose products --

DR. EISSENBERG: The loose products, okay.

DR. DAY: -- have the higher incidence of gingival recession --

DR. EISSENBERG: Okay.

DR. DAY: -- than the portion products.

DR. EISSENBERG: But the change in warning labels would be across the board for all 10 products?

DR. CHOINIERE: These are actually -- these are 10 individual applications.

DR. EISSENBERG: Okay.

DR. CHOINIERE: So there would be 10 individual decisions to be made here.

DR. EISSENBERG: Okay, good. Thank you for that.

DR. HUANG: Yes, Mr. Henton.

MR. HENTON: When you look at the discussion before the Committee and then the number (a), there's some discussion. Maybe this is a question for the Committee, but also for Swedish Match. We're talking about the products of Swedish Match, and we noticed earlier that there are a number of snus products, so this is just for Swedish Match. And my question is, are the products that are produced by Swedish Match significantly different than the other snus or snus-like products?

DR. HUANG: That's --

MR. HENTON: I think it's a question for them. I don't understand if there's -- is it a better product, a different product, different tobacco? So I'm confused as to -- because your question is, you know, these snus products, and I don't know if we're talking all snus or just -- is it different, is

it better?

DR. HUANG: And I think that is the fundamental question, and it is specifically for these 10 products, to say --

MR. HENTON: Is that something that Swedish Match could address?

DR. HUANG: And that's what I think we have to assess the evidence for there being that justification for these 10 products having that warning label removed, because they have to demonstrate that difference.

Yes, Dr. Swauger.

DR. SWAUGER: I think -- it's a really good question. I mean, it came up a couple times yesterday, at least three that I can think of, sort of people pointing at what they perceived to be differences between these 10 products and other products in the U.S. marketplace. And I wanted to ask several times and just let it go frankly, but I'm just curious why it is people naturally believe that. I mean, I think, at least thinking about it from a manufacturer's perspective, we've got -- well, I'll speak for myself.

I've got very limited knowledge of the actual process, the actual products that are produced by other manufacturers, but I think largely, we all believe that, to the extent we're talking

about snus, just for the day, that these products are all remarkably similar. I think if you spoke to manufacturers one by one, they would tell you they believe they're using -- they have knowledge of what's going on in Sweden; they're using very similar processes, if not the process that they brought over from that country. They're building products that basically use the same tobacco blends, they're processed the same way, and ultimately but for perhaps the flavor systems involved, my sense is they're all remarkably similar. I think they're all snus. So I sort of struggle with some of the conversation where we're trying to pick apart either the Swedish Match products and what's the rest of what's in the U.S. or frankly even within the context of just the 10 submissions. I just don't understand it, so if somebody can help me understand that, that would be a great start.

And then I guess the only comment I would make is, I think ultimately only CTP can be the arbiter of that. I think they're the only ones that probably have all that information in their hands. I mean, surely there's enough information in the ingredient submissions or under the 904(a)(1) for them to sort out how similar or different these products are.

DR. CHOINIERE: We're not here to determine whether or not

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these snus products differ from other snus products, that the question on the table is whether or not these snus products differ from smokeless tobacco products sufficiently enough to warrant the granting of the request to remove the warning, that these snus products differ from -- that don't pose risk of -- in this case, what we're talking about is gum disease or tooth loss. Now, if other snus products feel that they also have similar risk to the Swedish Match products, then those manufacturers can come in with modified risk tobacco product applications as well.

DR. SWAUGER: Conrad, I understand that. But the truth of the matter is, whether it's presentations by FDA or Swedish Match, there have been several instances in which those distinctions are being made, so it is part of this discussion. We can't really let go of them in the complete sense of the word, and you've got your own voting members asking questions about, sort of, what the relative differences are across products. You can't walk away from it; you've got to be able to talk about it.

DR. CHOINIERE: Well, the question I heard was the differences between pouched and loose, and the question on the table is the biological plausibility that these snus products

differ from smokeless tobacco products in the way that they may pose risk to gum disease or tooth loss. I think you can respond to that question without debating whether or not these snus products differ from other snus products.

DR. HUANG: All right.

Dr. Giovino.

DR. GIOVINO: Okay, I'll make two points.

One, the question was brought up yesterday was -- when the table of market share was brought up and it had to do with nicotine delivery, in my mind. You know, Warren talked about an assumption, and we have to make another assumption to process this, which is, well, maybe we don't have to make another assumption, but if we are going to proceed with any certainty, it's that these 10 products are like the products that were actually tested in Sweden, that were actually the subject of these epidemiological studies. And if we can't accept that, I'm willing to make that reasonable -- you know, I'm willing to accept that that's an assumption, and does FDA have any reason to believe that that's not true?

DR. ASHLEY: I actually think it may be best to direct that question to Swedish Match and let them talk about these 10 products in relation to their products that were the subject of

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most of the studies, and so let them talk about whether these 10 products -- how they bridge between these 10 products and the products that were the subject of most of the epidemiological studies that have been discussed.

Does that make sense?

DR. HUANG: So would we like to hear some -- from Swedish Match at this point? Okay. Yes.

Oh, Dr. Eissenberg.

DR. EISSENBERG: I'll just jump in because if we're going to hear from Swedish Match, I don't want to hear about the market share. I buy the market share argument. I want to hear about the differences between the products, if there are any, the 10 under consideration and those that dominated the market in Sweden during the times in which the data were collected.

DR. HUANG: Yes, yes.

DR. RUTQVIST: Thank you.

I appreciate the possibility to expand on the biologic rationale why these snus products are likely to have different effects on gum disease and tooth loss than most other smokeless products on the U.S. market, because there is a very clear and plausible biologic rationale for this. And that is included in Chapter 3 of our application where products' physical and

chemical properties are outlined.

And, to summarize, Swedish snus does not and has not ever historically included added sugars.

Secondly, the heat treatment process decreases the natural sugar content in the tobacco leaves.

And, thirdly, through the addition of a buffering agent, the pH of our products is among the highest among the smokeless products on the U.S. market.

And I'm sure you're well aware that both sugar, added sugar and pH are risk factors for both oral -- gum disease and tooth problems, caries and so on. So, yes, I realize now, after hearing these discussions, that we should probably have reiterated that rationale as an introduction to the section on where we review the evidence on gum disease and tooth loss.

But we also have some other comments on this issue.

Carol?

(Off microphone comment.)

DR. RUTQVIST: I think you should, because I think you have some interesting comments on this literature.

MS. COHEN: Can you please state your name for the record?

DR. WARD: Sure. I am Carol Ward, an epidemiologist with ENVIRON Corporation. We are consultants to Swedish Match.

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We reviewed the same set of literature and -- that FDA did, and we really have very little difference, the same set of studies. We also looked at the primary objectives, and I think we just interpreted them a little bit differently, a little wider, when the stated objective was to look at periodontal effects. It included some of the outcomes that are associated with that, not just frank periodontal disease, which I think we again are in agreement with FDA in terms of there are no positive associations.

We also agree with FDA, especially -- particularly this morning, that there are other studies of gingival recession that should be included when you examine that outcome, and in particular the Andersson and Axell study, where the prevalence of gingival recession was 2.9% in the pouched snus users compared to a prevalence of almost 24% in the loose snus users. And as FDA pointed out, that was statistically significant.

Does that answer your question?

DR. RUTQVIST: We also have prepared some extra slides that will elicit --

DR. HUANG: I'm sorry. Can you please state your name and --

DR. RUTQVIST: Oh, sorry. I'm Lars Rutqvist, Swedish

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Match.

We also have prepared some slides that will illustrate to you that essentially these products are identical in physical properties and therefore also in their likelihood to cause disease. And if the Committee so wishes, we can proceed in presenting those data.

DR. HUANG: Yes, Dr. Eissenberg.

DR. EISSENBERG: Before we do that, there are two questions I have. The question that brought you to the podium was the extent to which the products that are before us, the 10 products before us, are absolutely identical or in any way different from those that were in Sweden during the time that the data were collected, not whether -- so the question was not the extent to which they're different from products on the U.S. market, and so I don't -- wasn't sure I heard that. But even before you get to that, what I heard you say was that the sugars in all the products are low and the pH is high; is that correct?

DR. RUTQVIST: Yes.

DR. EISSENBERG: And so given that that's true for the 10 products that are before us, what causes, if not the sugar and the pH, the higher rates of gingival recession for the loose

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product in the Andersson and Axell study?

DR. RUTQVIST: I think that's not entirely clear, and no rationale has been provided in the literature for why there should be such an effect. Theoretically, it could be a local effect, a local irritating effect from loose snus. In the pouched products, the gums are protected from contact with the tobacco through the pouch material. That, theoretically, could be a possibility. But it's never really been fully elucidated.

DR. EISSENBERG: May I?

DR. HUANG: Yes.

DR. EISSENBERG: So given the results for the Andersson/Axell, and that we're considering the warning label change for each of the products separately, why is it that you're asking for the label to be changed for the loose snus product in this instance?

DR. RUTQVIST: Because we don't think that there is an evidence base to include this in the current warning for gum disease and tooth loss for any of the products. Yes, there are suggestive data from one study, but we don't feel that that is reasonable to use the results from one study without a verified biologic rationale to include a warning.

DR. HUANG: You know, I'm hesitant to get into another

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presentation at this point. I mean, is there anyone who would specifically like to see this additional presentation?

DR. GIOVINO: I don't know that we need a presentation, but I certainly would like the question answered.

DR. RUTQVIST: Excuse me, what was the question?

DR. HUANG: Would you like to restate the question?

DR. GIOVINO: Are the products -- are the 10 products that are on the U.S. market that the MRTP applications are being made about, how do they differ and -- are they -- how do they differ, if at all, from the products that were in Sweden that were subject to the epidemiologic and other studies?

DR. RUTQVIST: Well, as our presentation would show to you, they are lower in nitrosamines, they are lower in the number of HPHC levels. Because of the continual quality improvement work, these levels have gone down over the years. But the current products are no different from the products that are marketed in Sweden at the moment. In fact, these products are at the moment manufactured in Sweden and shipped here to the United States.

DR. HUANG: But, again, the question is how they relate to the products that were in use during the time of the epidemiologic studies.

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DR. RUTQVIST: I would say that they are of higher quality because they have lower levels of HPHCs. Nitrosamine levels, as I mentioned, have gone down, and a number of other potentially harmful constituents have also gone down. So, if anything, they should be less risky than the products that were on the market historically in Sweden.

DR. HUANG: Dr. Swauger.

DR. SWAUGER: I just wanted to say, I mean, it's a pretty weighty issue that's obviously a focal point of discussion, and if Swedish Match has taken the time to actually prepare some small deck that describes or answers these questions in some detail, I don't know why we won't spend the time actually letting them talk through it. I mean, it's been a focus of discussion since yesterday off and on, and doing this by bullets verbally just doesn't seem fair. I mean, why can't they have a chance to express themselves?

DR. HUANG: Sure. No, I mean, we certainly want to give them a chance to express themselves. I don't know how long a presentation -- I mean, is --

DR. RUTQVIST: It's short.

(Off microphone comment.)

DR. HUANG: Yes, Dr. Tomar.

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DR. TOMAR: I have another comment unrelated to the slides, but -- if that's okay?

DR. HUANG: Okay.

DR. TOMAR: So the sugars are certainly an established risk factor for dental caries, one of the disease endpoints looked at. I'm not aware of a single study that implicates sugar is a risk factor for gingival recession. Perhaps somebody at Swedish Match can point me to that literature, if you're aware of it?

DR. RUTQVIST: No, my comment was just that these factors that I mentioned, sugar content and pH, distinguishes Swedish Match snus products from a lot of other products on the U.S. market.

DR. TOMAR: I would argue that the gingival recession certainly would seem, in the U.S., it's unrelated as far as any evidence that I know of, unrelated to sugar content. One of the properties of tobacco is delayed soft tissue wound healing, so it actually impairs the ability of the periodontal tissues to repair themselves. That, combined with local irritation, is probably what accounts for a good portion of the gingival recession. And I would say even though that there's relatively little evidence that's been published, what is available that

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we just heard described by Dr. Day is actually pretty consistent with what we see with U.S. other types of smokeless tobacco products.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Just a minor point of clarification. You talked about the HPHCs and the nitrosamines. To what extent has this cellulose material itself changed over the last 20 years, the stuff that makes the pouch into which the tobacco is placed?

DR. RUTQVIST: Well, obviously HPHC levels are dependent on the tobacco recipe and type of raw tobacco, which also varies from season to season because this is a natural product. But generally the levels have gone down because of improved selection of the raw tobacco used for production.

DR. EISSENBERG: Yeah, I'm asking about the outside, the pouch --

DR. RUTQVIST: Oh.

DR. EISSENBERG: -- into which the tobacco -- has that changed or not changed over the last 20 years?

DR. RUTQVIST: It has not changed in any significant aspect. Obviously, we've changed the external producer of this product, but essentially, they've been the same since they were

introduced in the early '70s.

DR. HUANG: Dr. Choiniere.

DR. CHOINIERE: I was just going to recommend that if indeed the slide set is very brief, that it might be helpful for all of the discussion today for Swedish Match to present them.

DR. HUANG: Sure, okay. Go ahead. Proceed with that, then. And please state your name.

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

We prepared a presentation yesterday based on the different questions that we heard through the day. We heard a number of questions around GOTHIA TEK, and in this presentation I can weave in many of the additional questions that you had during the day.

So Swedish Match has a number of standards that we operate around. We are certified for ISO 9001, and we have the environmental standard ISO 1401, and we also have the testing laboratory accreditation for our chemical analysis. We didn't really feel that this was sufficient. There was nothing specific to our industry like there is in the electricity industry or in the car industry with car crash standards and so

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on, so we created our own standard. This was introduced in the year 2000. It is applicable to all Swedish Match snus products and has been since then. There is no difference there between, you know, products that are produced in -- sold in the U.S. and European products.

The volume of production that goes to the U.S. is only in the order of magnitude 2%, and we are producing on the same tobacco grades and the same manufacturing processes and everything being the same as the Swedish or the Scandinavian products.

We have the ambition here to continuously improve on our standard here. The GOTHIA TEK has a number of requirements. It has limits on the maximum allowable levels for NNN and NNK that are the two most important TSNA components, limits for B(a)P for heavy metals and so on. We also have an ambition of being very open to the public, so we declare all the contents on our home page, and this is every single substance that we add. We use, predominantly in Scandinavia, compounded flavors, which means, you know, it could be 20 different substances. They are all on our home page with CAS numbers and the CAS chemical name.

For all our products we also declare certain components,

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like nicotine, salt, water, humectants, pH, and so on, so that the public can see the complete composition of our products.

It has elements of manufacturing requirements. We adhere to food standard production, Swedish food production standard, but our standard goes beyond that.

We have raw materials standards, particularly how tobacco should be sourced and how we ensure that we have maximum levels of GMOs. Every ingredient is evaluated in terms of its health hazard, and if for some reason, you know, say in a compounded flavor that we find one single ingredient after maybe 20 that we say doesn't meet our standard, then it goes back to the flavor supplier for reformulation.

For packaging, we have food grade for everything and also food grade handling. We ordered the packaging company -- our packaging is a plastic material, but it is recyclable, and it is the same material that goes into plastic bags.

There was also a question yesterday on the pouches and the disposal of these. The package has -- or the cans have a disposal function, which means that the user can, you know, discreetly put back the pouch in that disposal function, and it has enough space to cover, you know, sufficient numbers of that when the consumer passes a trash bin that he can empty there.

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So it's a convenient way of disposing of the used pouches.

We have a heat treatment process in a closed system. This is very different to products in the U.S. that are not heat treated, and we think that the way that we heat treat on the pasteurization is quite efficient and doesn't generate any toxic compounds and, as we heard earlier, reduce the residual sugar content. And we consider that, you know, proprietary, the whole setup for that pasteurization process.

And there are also requirements on sanitation with street cleaning regimes.

I think I'll skip this slide here.

There was a question of what do we actually measure with GOTHIA TEK. We have maximum and lower levels for a number of components, NNN and NNK predominantly. We have a GOTHIA TEK limit of 1 ppm. This has just, in 2012, been reduced to be in line with the recommendation of an advisory group to WHO, the World Health Organization, on maximum levels for smoke-free tobacco products.

We have NDMA, which is another nitrosamine limit; nitrite; B(a)P. Also, that has been reduced in 2012 to also there be in line with the recommendation of the advisory group to the World Health Organization.

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And then we have maximum levels for various heavy metals and also for agrochemicals.

And as you see, we also announce the mean content for all our products during the course of the year. And there is quite a gap there between the mean content and the GOTHIA TEK limit, and this is to ensure that everything that we produce is within GOTHIA TEK limits.

This is also something that we publish every year on our home page.

There was a question on the difference between our products and other smoke-free tobacco products, and this is an example of the variety of smoke-free products. This is an example from -- these are examples from the European continent. There is also a variety of different types of smoke-free tobacco products in the U.S., and as you can see, they vary in appearance, they vary in use. And not to go through the second column there, they have different origins. Some come from India, others come from Bangladesh, and some from Africa and so on. But interestingly we can look at the right column there, which is the TSNA that has been measured in one particular study referenced at the bottom. And as you see, there is a significant variation in TSNA content that this researcher

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found.

At the bottom there are five samples of Swedish snus that were evaluated, everything below 1 ppm. And just going one step above, you'll see another product where four samples were analyzed where the range was between 295 and 992 ppm. So there's a factor of 1000 difference there. I'm not suggesting that there are all such differences in products in North America, but there can be substantial differences from one product to another. And with the methodology that Swedish Match applies, we can get to really low levels of the TSNA, and we continue to push these levels down.

Here are some examples of what we have accomplished over the time, applying the GOTHIA TEK principles of operating. These are B(a)P levels that have been reduced from raw to stay at the low levels now that where we are. Lead and cadmium are two other examples where we have made the same improvements over the course of time. And as you see for TSNA, we continue to push downwards. If you take something like cadmium in the levels there, the relative exposure to the population from the Swedish Match snus products is really small in comparison to the exposure that would be -- that you would get from other foodstuff like rice, for an example.

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So we are focusing on the most critical component of the smoke-free tobacco product, which is the TSNA. And as you see, the levels are continuing to go -- get lower and lower. So this is the whole purpose of GOTHIA TEK, and this is the way that we operate with a high degree of transparency and continuous improvement.

Then there are some slides here that my colleague will show which will explain or convince you hopefully that the products that we use today are in this context similar to the products or is the same as products that were used in -- during these studies.

There's one thing that I forgot to mention. Oh, I don't think so. That's all right.

So thank you.

DR. LINDHOLM: Johan Lindholm. I'm Director of R&D and responsible for analytical testing at Swedish Match. And I heard several questions here today regarding the HPHC levels in the product we have in Sweden compared to the products we have in the U.S.

And here, in this figure, this is also included in the MRTP application. We have a rich content of TSNA's for NNN and NNK and the total TSNA's based on the dry weight.

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And this picture is for all snus products, including Swedish Match chemical testing program. And these products cover the products both in Sweden, Norway, and in U.S. And you also have the 95% confidence interval, and you see that the interval is very narrow, so all the products are very similar.

And if we compare the products here with the products in Sweden, for example, if you look into year 2011, could see the NNN and NNK and the TSNAs for the products to the left in Sweden, and to the right, that is the levels for the products, the similar products that we manufacture and sell in the U.S. And if you look into the last decade, to the levels, you'll see that there is no difference between the products we have in Sweden or the products we sell here in the U.S. That's due to what Thord was talking about earlier, that the manufacturing process is exactly the same and the products are manufactured in Sweden. So there are no significant differences in the nitrosamine levels between the products in Sweden and in the U.S. products.

And if you continue to look into the benzo[a]pyrene, for example, you have also, for the last decade, show that there are very low levels. And also if you look into the same type of picture for -- where we compare the products in Sweden

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compared to the products/brands we have in the U.S., for example, in 2011, the left bar is for the benzo[a]pyrene for the products in Sweden, and the right bar is for the products in the U.S. And if you look into the 10 years there, you can see that there are no significant differences between the products in Sweden compared to the U.S. products.

Now, this could show for all the different HPHC; for example, for nitrite there are no significant differences between the products in Sweden and U.S. products. And the same for the metals, for the arsenic, the lead, the cadmium, the chromium, and the nickel. There is no difference either. And if you look into the nitrosodimethylamine, there is no difference either between the products. And if you look into the level of nicotine for the products in Sweden compared to the U.S. products, the levels are also the same.

And if you look into the pH, it is, as Dr. Rutqvist mentioned earlier here, we have quite high pH in our products. But it's the same pH in the Swedish products compared to the products we have in the U.S. market.

And I don't know if I should respond to this question now, but yesterday I heard a lot of questions about product stability and some claims that TSNA was increasing -- during

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shelf life storage. And we have done testing, and this feature, this slide is from the MRTP application, it's Table 343, and it's analytical results from different years. So for example, for General Loose, we have compared batches from different years, from 2007 until 2011. And we compared the levels of TSNA's for 3-week samples and also when we have stored samples, 14 weeks at ambient temperature and the best before date for General Loose is 14 weeks. And you can see there is no increase in the TSNA levels.

And for the portion product, the General Portion Original Large products, the best before date is 20 weeks, so that have been shelf life studies for 20 weeks, and you can't see any increase in TSNA either. And also for General Portion White Large, we have showed the same thing. It's no increase in TSNA's.

And also another table from the MRTP application. It's analytical results for proposed MRTP products, showing the content of TSNA products in the U.S., and it's stored both in refrigerator and at ambient temperature. And you can see here that for some products, we have stored them up to 30 weeks, and there are no differences in TSNA levels.

And in addition to this, we have also done studies where

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we have stored the product at increased, at elevated, ambient temperature, and those tests we don't see any increase in TSNA levels either.

DR. HUANG: In interest of time, how much longer are you thinking?

DR. LINDHOLM: I could stop now, if you would like to.

DR. HUANG: Pardon?

DR. LINDHOLM: I could stop now, if you would like.

DR. HUANG: Okay. Yeah, I think let's move on. Was there anything else important that we needed to present at this time? Any questions about that? Okay.

Yes, Dr. Djordjevic.

DR. DJORDJEVIC: I just have one question. On Slide 7 and the following slides, did you include Swedish Match products in U.S., Timberwolf and Longhorn Fine Cut?

DR. RUTQVIST: Our applications only relate to our snus products, and we have not included any American snuff products.

DR. HUANG: Please state your name first.

DR. RUTQVIST: Sorry. Lars Rutqvist, Swedish Match.

Our applications only include the Swedish snus products and not any of our American moist snuff products, so we have not included data on those.

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DR. DJORDJEVIC: I understand that, but on that particular slide you contrasted to many other products from all over the world and -- but there is no contrast to Swedish Match products.

DR. RUTQVIST: That is true, and I should say that you know very well that American moist snuff is a completely different product. The manufacturing process is totally different, the raw tobacco is different, but I can assure you that over the years we are working to improve the quality also of our American moist snuff products, and for most of the components included, for most of the constituents included in the GOTHIA TEK limit, most of our American products do meet those maximum limits. There are a few exceptions, but we are continually working towards being able to introduce also a product standard for those products, and we're almost there.

DR. HUANG: All right, thank you.

Let me bring us back to the questions at hand, and specifically, it's been mentioned -- the question that we're going to vote on initially is: Does the evidence support that these snus products pose risks of gum disease to individual users of these products?

And I'd like to also sort of bring in, we had introduced

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that question. But then part (b) of it was also: Does the evidence support that these snus products pose risks of tooth loss to individual users of these products? And I think the discussion that we've had thus far is relevant to both, so I think, as we go back to the points also that we are looking at discussing, keep these in mind; again, the biologic plausibility that gum disease or tooth loss in snus users would differ from those in users of other smokeless tobacco products.

But confidence in the information from the studies that only include young adults under the age of 25, given that the prevalence of periodontal disease increases with age, and I think what, you know, FDA had presented of the 12 studies, I think six of the studies were in adolescents or adults under age 25. So, again, this is another issue that we need to have some discussion regarding.

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 again, the sufficiency of the information from studies where the number of snus users in many of the cross-sectional surveys was fewer than 50, and I think, of the 12 studies, only three studies included more than 50

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users.

So, again, we're looking at the sufficiency of the evidence and the studies to make a determination regarding snus, these snus products in particular with respect to gum disease and tooth loss, and what we can say how they are differentiated from what we already know about smokeless tobacco.

So, again, other discussion points regarding this?

Yes, Dr. Eissenberg.

DR. EISSENBERG: So I have a question for FDA that goes directly to the issue in vote question (a). Does FDA have a position on the extent to which snuff dipper's lesion is a disease?

DR. CHOINIERE: Snuff? I'm sorry, what --

DR. EISSENBERG: Snuff dipper's lesion.

DR. CHOINIERE: We look at tobacco-related health outcomes and disease. So, yes, if that's -- that would be considered a health-related -- tobacco-related health outcome.

DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Yes. Well, I was not very familiar with this literature, so I went back and reviewed some of the original studies, you know, last night, and I have to say that

I'm not very impressed by the evidence. I mean, we heard yesterday, through the FDA presentation, about some of the limitations of the studies. I think there are more limitations than what was discussed. Obviously, there was initial time, et cetera. Just to give you a few examples. I mean, the Andersson and Axell study, the participation rate was less than 50% in that study. These are the same construction workers of this large cohort that had been studied in a number of other investigations, and they were invited to come for oral examination at about less than 50%. And, for example, in older snuff users, there was a higher prevalence of former smokers, and they didn't adjust for that. So, I mean, there are all these sort of issues in these studies.

The Mod  er study, which is one of the positive studies for Gingival Index, all these snuff users were boys. This is one of the adolescent studies. And they didn't adjust for site cycling, and if I understand, it's a bit difficult, the way it's described, but -- so, I mean, I found many issues within this data, and so just to stress this. I mean, we may not have time to go into the detail of each study, but clearly these studies had a number of limitations.

DR. HUANG: Well, that's certainly a key point because

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we're looking at the sufficiency of the evidence to say, then -- and to remove these warnings regarding the association with gum disease and tooth loss.

Yes, Mr. Henton.

DR. SWAUGER: I was just kind of interested in Dr. Boffetta's comment. I'm just wondering -- I mean, I also am not very familiar --

DR. HUANG: Henton.

DR. SWAUGER: Sorry.

DR. HUANG: Mr. Henton.

DR. SWAUGER: Pardon me?

DR. HUANG: Henton.

DR. SWAUGER: Wrong guy.

DR. HUANG: Sorry.

MR. HENTON: I was looking at your -- the way the question is before the Committee, and it seems odd the way you phrased the question: "Does the evidence support that these products pose" -- I'm not sure how -- what -- it seems that you're -- it's a positive/negative issue there. It would seem that "the evidence support the fact that they do not" would be a way to phrase it. The way you phrase this is -- I'm not sure what you're asking in the voting. This is odd the way it's phrased,

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and I thought maybe you might have some clarification on what you're voting on there; that's all.

DR. HUANG: Okay. And yeah, again, I think that's sort of that underlying issue that we've discussed in the past, and I had some questions about that, also, from the very first -- of reading it. Because I'd see it, it's in the context of what -- we're not asking for just scientific evidence to prove that these 10 products -- the study showed their posed risks of gum disease, but in the context of what we know about other smokeless tobacco products, because we're really being asked are these -- do we have enough evidence to show that they're different, that these warning labels would be removed regarding that.

Dr. Swauger.

DR. SWAUGER: Yeah, I just have a quick comment. I was listening to Dr. Boffetta and sitting here wondering, at least as I think about it, I've had a fair amount of time to look at, at least, the redacted version of Swedish Match's submission over time, and I've had a team of people helping me do that. I don't know that I could have done it over 2 days. I'm sort of -- I'm sitting here overwhelmed, just looking at -- just the dataset tied to this particular topic. And I'm wondering, at

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the end of the day, is it true, does this committee actually think that it's had enough time to digest all this material to actually make an informed recommendation? I'm not making a statement; I'm just asking a question.

And I heard Dr. Boffetta's comment maybe a little bit differently than you restated it. I mean, I thought -- he was obviously pointing at study limitations, but it sounded like he was also suggesting there wasn't a lot of time to review this data, and at the end of the day, we -- you're talking about one question. You haven't even gotten the first voting question in the morning, and it's 9 o'clock. I just wonder if a day is enough time to actually do this. That's all I'm asking.

DR. HUANG: Anyone want to comment on that? Dr. Choiniere or --

DR. CHOINIÈRE: I think that's a question for the Committee. If the Committee feels --

DR. HUANG: Well, again, I think that that's -- from a macro level, you know, I mean, we're looking at the number of studies. You can look at who was participants in the studies. There's the issue -- and I think that's where some of these issues that are raised that we're supposed to have discussion on. I mean, you know, let's see. How many of the studies --

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again, only 6 of the 12 studies were in adolescents or adults under age 25, and Dr. Boffetta mentioned specifically the Mod  er, you know, is age 13 to 14, you know. What is the applicability of these studies? Because we're looking for, is there sufficient evidence that says then we should remove this warning, or that is the question that's --

DR. CHOINIERE: And I also wanted to point out, maybe perhaps members of the public don't understand this, but the Committee has had more than 2 days with this material. The Committee has had access to the full application for some time.

DR. SWAUGER: I mean, I'm just thinking about sort of the range of questions. We're really down in the weeds over a lot of this. It's just not obvious that everybody is that conversant on it. Maybe they are. I'm just asking a question. I mean, at some level, you said it yourself, we're talking about a change to a warning label. I haven't got the foggiest idea how long the discussion went on to put the warning label on in the first place. I imagine it was months of discussion.

DR. HUANG: And I'm saying, you know, again, we've been asked to speak to the science and the evidence. It's in the context of this application, which is asking for the warning label. But I'm --

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DR. SWAUGER: But it's ultimately got to be an informed recommendation, whatever it is.

DR. HUANG: Sure.

DR. SWAUGER: That's all I'm asking.

DR. HUANG: Exactly. And so I think that this Committee is charged with looking at the science and the evidence that's presented and assessing the quality of the evidence and sufficiency to make, you know, a decision that would ultimately -- the decision is, would that warning label be taken off?

DR. SWAUGER: And I'm just looking for confidence that it's an informed recommendation.

DR. HUANG: Yes, Dr. Ashley.

DR. ASHLEY: And one of the reasons we have phrased the questions the way we have is to help the Committee focus in on specific issues that FDA wants their advice. We're not asking the Committee to make broad determinations. FDA will do that; that's our job. So that's why the questions -- they may sound strange, but that's the way they are phrased the way they are, to allow the Committee to focus in on specific aspects.

DR. HUANG: And so again, so as we continue, some of the comments and discussion regarding this, if you can focus on some of these specific sort of questions or issues, you know,

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the biologic plausibility, the confidence in the information from these studies that only include young adults under the age of 25, given that the prevalence of periodontal disease increases with age, does that -- these are what the studies that we have available to look and make a decision are. What is your, you know, comments regarding the sufficiency of that, the limitations perhaps?

Dr. Tomar.

DR. TOMAR: As I had mentioned yesterday, the primary gingival disease that is seen in smokeless tobacco users is localized gingival recession, and that will show up relatively young, you know, as it has and, you know, I agree that these studies, like many others, have limitations. But with the limitations of what we have, the data are consistent on there being an increased risk for gingival recession among users of snus, similar to what's seen in U.S. forms of smokeless tobacco. I'm not aware of any biologic plausibility that would suggest that differences in sugar content, as was said by one of the speakers, there's no evidence that that would change that risk for gingival recession. I'm not aware of any evidence that sugar is a risk factor for gingival recession, so I wouldn't expect a difference in sugar composition to affect

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that outcome.

DR. HUANG: So that sort of -- all available evidence would still support that these particular snus products would pose, continue to pose risks for gum disease or tooth loss.

DR. TOMAR: I would say, based on the available evidence, and granted, it's limited, but if we're being asked to remove a warning, I'd want to see evidence suggesting that -- I mean, obviously, there was a body of evidence that was reviewed in determining the applicability of that warning label in the first place. So now we're saying all right, is there sufficient evidence that this product is sufficiently different and consistently doesn't show an increased risk for gingival recession? And I'd say that that's not the case. The limited evidence we have suggests the same, or at least on that outcome, the same outcome that we see with other forms of smokeless.

DR. HUANG: And tooth losses.

DR. TOMAR: Tooth loss can be an endpoint for -- advanced gingival recession can result in tooth loss. Yet, again, there was no evidence presented showing -- that wasn't presented as an outcome for any of these. And, again, I'd want to see evidence that, you know, this has been examined, and no, it's

not a risk factor if we're talking about removing an existing warning label.

DR. HUANG: Mitch.

MR. ZELLER: Scott and others on the Committee, but I'll start with Scott, so you've made a general statement. I'd ask you and others to now address that and drill down to the second, third, and fourth bullets that we have up there because we're looking for feedback. Those are not votes, but we are looking for feedback on the four bullets. But given what you just said, generally I'd like you and welcome comments from any members of the Committee on the second, third, and fourth bullets that we've put up there.

DR. TOMAR: And, again, I would say, in terms of gingival recession, that is an outcome that can manifest before age 25. We talked about peritonitis; that was one of the disease points that was looked at, but there really isn't -- there's only one or two studies that I know of that have found peritonitis as a significant association with even U.S. forms of smokeless tobacco. So, again, I think, at least to me, we're looking at primarily gingival recession and the fact that that's been looked at in young cohorts.

If anything speaks to a stronger level of evidence that it

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is, in fact, causing deleterious effect on periodontal tissues, it's showing up relatively young, as I said, you know. Two thoughts. It's hard to comment because there isn't -- although that can be an endpoint for advanced gingival recession, there weren't studies that specifically looked at that as an endpoint.

And, again, you know, I have to think that when the warning labels were created, that the body of evidence was reviewed, and it was determined there was sufficient evidence to include that in the original warning label, so I'm not seeing evidence that would suggest that these products are different and that that part should be removed from the warning label.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: There's a couple of points. One, that we're not being asked to assert causality according to the criteria, you know, the Bradford Hill criteria; that has been used by the Surgeon General on, you know, the relationship between risk factors and disease outcomes. But we're asked to see whether or not there's sufficient evidence to say that there is, you know, no risk from these activities.

And I don't think that the studies that we have been able

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to see, nor the interpretation that was provided earlier on these studies, gives us confidence in the information that we have to say that there's no risk. It doesn't mean to say that we're saying there's a causal relationship, because I don't think we have that evidence either.

And, in fact, the question is asking us whether we know that these things pose risks, and we don't really have sufficient evidence on that they don't pose a risk. But we do have, as Scott has pointed out, sufficient evidence to be suspicious of the risk and not be confident that there is no risk. So it's not causal relationship that we're after; it's the perception of risk, and the studies don't rule that out.

DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Well, yes. This was exactly the point I wanted to raise. I think there is a very different type of evidence that need to be provided if you want to prove that there is a risk or whether you want to exclude it. There may be a risk based on other considerations, and I think we've been sort of going a little bit back and forth between these two aspects.

DR. HUANG: And that was, again, my point, that we're not trying to prove the risk based on this evidence, but we have

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the evidence. And the decision has already been identified before of the association with smokeless tobacco in general and these outcomes, and so is there evidence to show that these particular products are not in that category.

DR. BOFFETTA: Can I? But if you read the two questions posed by FDA, they talk about the presence of the risks, so they seem to go -- so just to -- we need to make --

DR. HUANG: Right. And, again, that is that same point.

Yes, Dr. Novotny.

DR. NOVOTNY: One other brief comment is that it was very helpful -- and I thank Swedish Match for providing that great presentation about GOTHIA TEK and the assessment of the product as it goes through the production process; that was very helpful. But the difference that we, I think, need to keep our focus on is that product and health outcomes in human beings is -- you know, may or may not be related.

And what we really have to look at is what is it that we see in human beings and the health outcomes. And though the product has all sorts of describable characteristics, it's the same kind of thing that we looked at with light and low tar. Yeah, you can measure these things in a machine, but what really is important is what the health outcomes are.

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DR. HUANG: And, again, going back to the actual public law, you know, with respect to an application submitted under Section -- modified risk product may be commercially marketed only if the Secretary determines the applicant has demonstrated that such product, as it's actually used by the consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and that it benefits the health of the population as a whole, taking into account both users and persons who do not currently use -- so yeah, it is that.

Dr. Giovino, did you have something?

DR. GIOVINO: Well, so let me just raise an issue for the Committee to consider, because I'm concerned that we're mixing what the policy implication is from what the science is. And I think, as Dr. Ashley said yesterday, we're here to talk about the science. And when I do that, I default to the Surgeon General's criteria, which are, I think, identical or at least a lot like our criteria, which is the evidence is sufficient to infer causal relationship; the evidence is suggestive but not sufficient; the evidence is inadequate to infer the presence or absence of a causal relationship, for example, the evidence is sparse or of poor quality or conflicting; and then the evidence

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is suggestive of no causal relationship.

And, you know, to be totally transparent, right now I'm thinking Level 3, the evidence is insufficient. And I know we're not supposed -- you know, one comment was made about causality, but do I think these things might cause risk based on the evidence? Absolutely. But it doesn't say do I think they might pose risks, and that's where I'm a little, sort of, hung up in the gray zone, I guess.

DR. HUANG: And I guess -- I mean, are you starting out with the premise that it's a given that smokeless tobacco products pose those risks?

DR. GIOVINO: I'm not factoring that in, other than the reality of what Dr. Tomar said about the biological mechanism of irritation. There's no reason to believe that that's any different, because the product has that physical property, so that's, to me, evidence enough for that issue.

DR. HUANG: And going back again to what Mitch mentioned, the other points that haven't had much discussion about, you know, the cross-sectional study design that, I guess, 11 of the 12 studies were cross-sectional and that -- in terms of the sample, number of snus users being, in many of the cross-sectional surveys, was fewer than 50.

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Are there any comments regarding that aspect? Those are specific things we've been asked to comment on.

DR. GIOVINO: That's why I think the evidence is sparse, of poor quality, or at times conflicting. There is clearly some evidence showing a risk, and then there's some evidence showing no increased risk. There's no evidence showing a benefit.

DR. HUANG: Dr. Ashley.

DR. ASHLEY: Yeah, I just want to try to respond to Dr. Giovino's question a little bit and to realize what the actual wording of the current warning is. It says, "Warning: This product can cause gum disease and tooth loss." It doesn't say, just for clarification, it doesn't say, "This product has been shown to be an" -- you know, it's "can cause," and so that's the wording, and so that's the warning we're talking about removing.

DR. GIOVINO: And as a scientist, I would process the evidence and think of it in terms of the Surgeon General's categories. And if I come to the conclusion that it's Level 3, I don't think -- then it's another question of should that warning label be changed? But you're asking us to vote on the science, not the warning label.

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DR. HUANG: And I guess we did not review all of the science regarding smokeless tobacco and gum disease and tooth loss. So I do have a problem with the way the question is worded a little bit, and I know it changed over time, that --

DR. CHOINIERE: I think that, as the Chair, you have the prerogative here to work with the question and phrase it in a manner that you think is appropriate for this Committee to respond to.

DR. HUANG: And I mean, again, I think part of what we are being charged with is assessing the science that, whether these 10 snus products, there is sufficient science to -- and I know it ties into the policy implication, but we are -- the whole question, the whole reason for us being -- what's been proposed is to remove these warnings regarding this specifically related to gum disease and tooth loss in this question. So is there sufficient evidence to support that these products -- I mean, it's essentially removing the warning label. But the warning label, as it states now, can you repeat that?

DR. ASHLEY: Can --

DR. HUANG: Can cause --

DR. ASHLEY: Can cause gum disease and tooth loss.

DR. HUANG: It's almost like, is there sufficient evidence

to say that for these 10 snus products, the statement that these products can cause gum disease or tooth loss is not supported.

DR. ASHLEY: And I think that's the nexus with the question is -- we have no pride of authorship here. If you want to change the question, as Conrad said, that's your prerogative. But I hope everyone can see the nexus between how we phrase this question and the request on the table.

DR. HUANG: Dr. Tomar.

DR. TOMAR: Yeah, I just wanted to speak to Dr. Giovino's comment, and I absolutely agree. I mean, what we're being asked here is to really just take a subset of the body of evidence, so only the evidence that specifically relates to Swedish product, which again we assume is the same as the products that are being considered, and to say, all right, you know, is there enough evidence that this is truly different in terms of this particular outcome to change the warning label?

And while I recognize that we're really supposed to be focusing on the science, I would say, you know, based on what we know about the factors that probably lead to gingival recession, I have not seen evidence suggesting that these should be treated differently, and so, you know, I don't know

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that we can make -- you know, truly draw a causal conclusion looking at just a piece of the fuller body of evidence.

DR. HUANG: I mean, because if we were presented with no studies, you know, on -- specifically with snus, and then we're only to limit our discussion or our assessment of answering this question based on no studies, does the evidence support that these snus products pose risks of gum disease to users of these products, we wouldn't be able to say anything, so that's --

DR. GIOVINO: I totally understand that, and I totally agree with that. I'm just getting hung up on the wording of the question.

DR. HUANG: Yeah. And I -- actually, Dr. McAfee is on the line. Do you have a question? Tim? Tim, are you on the line?

DR. McAFEE: Yeah, sorry about that. I was just un-muting. The conversation has progressed since I was -- I essentially wanted to make some of the same points that have been made about Dr. Giovino's concern. I think, again, just to reinforce, the situation is the Surgeon General's criteria had been met at the total population level for the larger class of smokeless products, and what is essentially being asked by Swedish Match is to remove them from this finding.

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And I think that's a very different question and one where the simple fact that there's not enough power, which is one possible explanation, should give us pause because really any other manufacturer could bring forth a product, you could take an American smokeless brand, and basically they could say, well, look, there have been no studies that have been done of our specific brand to show that this larger finding around smokeless applies to our brand, so therefore we want to remove the label. So it's actually setting a bar that's saying that the FDA has to prove, for each specific brand or product subcategory, you have to go through the Bradford Hill criteria, which doesn't seem reasonable.

So, actually, probably the data that we've seen so far from Swedish Match is going to be of higher quality than it would be for many other subcategories of the brands. So I think basically that letting go of the current wording and addressing it as it's been rephrased will make it a much more fruitful discussion.

DR. HUANG: Okay.

Dr. Novotny.

DR. NOVOTNY: I was wondering if we could offer -- the question it seems like we're being asked is rather than does

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the evidence support that these snus products pose risk is that does the evidence support that these products do not pose risk. Is that not really what we're being asked?

DR. HUANG: Sure.

DR. NOVOTNY: Or pose a different risk.

DR. HUANG: That seems -- so the question would be reworded: Does the evidence support that these snus products do not pose risks of gum disease to individual users of these products and similarly for tooth loss? Does that seem -- anyone have any comment on that?

Yes, Mr. Henton.

MR. HENTON: It would seem that you're right about changing the word "pose," but it seems what they're trying to say in the application is it shows reduced risk, not no risk. I think the absolutes here is where the problem is. So if it read, "The products show reduced risk," you might well vote no on that, but I think the point is does it show reduced, modified risk. That's the level -- it's not no risk or all risk.

DR. HUANG: But the current warning says "can" and so it's not -- so to say take off the warning that says "can" would require no risk.

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Dr. Swauger.

MR. HENTON: I think --

DR. HUANG: Let me go back to Dr. Swauger.

DR. SWAUGER: I'm just listening to the conversation and you say "can." I hear "may". And what I'm struggling with is I'm not seeing anything yet, lots of discussion around the table, anybody around the table is actually even clear what that evidence base is. It's supportive of -- in the first place. No disrespect to Dr. Tomar, but I'd like to be convinced that the folks around the table actually understand that dataset too. I mean, the warning doesn't say it does or it will. It says it may, can. All right, well, I'd like to understand what that evidence base is, and I'd like to believe you folks will understand it too, before you vote.

DR. HUANG: Again, I mean, I think that's, in terms of the scope of what we've been charged with, we -- there has been another process where the original warnings were placed, and so we were only -- we are not assessing the relationship between smokeless tobacco and gum disease and tooth loss, but we are --

DR. SWAUGER: Yeah, fair enough.

DR. HUANG: -- assessing specifically for these 10 products if there is sufficient evidence to show that these do

not pose risks. I think that that's a reasonable, you know, alternative way of phrasing the question.

DR. CHOINIERE: Yes, I think you need to keep in mind what has been requested by the Applicant.

DR. HUANG: Dr. Giovino? Okay.

Okay, I mean -- pardon?

MS. COHEN: Would you like me to --

DR. HUANG: Yeah, okay. Here's the proposed revision to the question.

MS. COHEN: Please dictate --

DR. HUANG: Oh, okay. Does the evidence support that these snus products -- what was it, pose? Do not pose risks of gum disease to individual users of these products.

MR. ZELLER: And then the same for tooth loss.

DR. HUANG: Same for tooth loss.

Do you have to go through a process to vote to change these? Anyone have any problem with changing that question to the question that we vote on?

(No response.)

DR. HUANG: Seeing none, I'll just assume it's like a vote to make the change.

(Off microphone comment.)

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DR. HUANG: Okay, yes. Dr. Novotny.

DR. NOVOTNY: Could we have the question one more time?

DR. HUANG: Does the evidence support that these snus products do not pose risks of gum disease to individual users of these products?

And then it would be similar: Does the evidence support that these snus products do not pose risks of tooth loss to individual users of these products? Okay?

(No response.)

DR. HUANG: All right, so we've revised the questions. Is there additional comment on the other issues that we've been asked to speak on? Again, not a lot of discussion regarding the cross-sectional study design or the sample sizes and number of snus users in these studies? I mean, do people feel we're ready to vote? Yes.

DR. RIBISL: Yeah. I mean, I'll just state the obvious, that when you have this many studies that have sample sizes that low, they're just underpowered to detect an effect. It would have to be a massive, massive effect, and this is just basic statistical power. And the same thing with cross-sectional studies to look at tooth loss; tooth loss is a longitudinal process. And enough said there.

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DR. HUANG: Is there any additional discussion before we bring this to a vote?

(No response.)

DR. HUANG: Okay. Are we -- oh, yes.

Dr. Boffetta.

DR. BOFFETTA: Just one small point. I mean, it was mentioned before that there were no studies on tooth loss but, in fact, in the Hirsch paper there are results on tooth loss and snuff use. It's a small study; it's not adjusted for -- I mean, the results are basically presented as unadjusted, but there are results, and they're basically negative except for one of the many comparisons they made for age 17. I was just checking the paper because it's not available online unfortunately. So there is one study which is basically negative for tooth loss and snus use --

DR. HUANG: Okay. All right, any comments on that? Again, we have one study, but that's the only one that had that as an outcome measure.

Dr. Tomar.

DR. TOMAR: I would just say that, again, tooth loss is -- it's a relatively rare outcome in the young population with pretty good access to dental care.

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DR. HUANG: And that is, perhaps, there would be more implications of having the studies primarily in the younger population more so than gum disease. Okay.

All right, so are we ready to call a vote? Start, try this process one time, and hopefully we'll get used to it and the hang of it as we go forward.

So, okay. Regarding the vote, we will be following the 2008 guidance for FDA advisory committee members and FDA staff voting procedures for advisory committee members. A robust discussion should take place before the vote, which we hope people feel has occurred. Nonvoting members can participate at this point, during the discussion, but then -- so we're going to use an electronic voting system and only the voting members can vote. Then a slide with the results will be displayed. The voting members then will state their name, their vote, and add any comments or rationale. The nonvoting members cannot participate at this point.

Okay, so here we're ready to go through this. So we will be using an electronic voting system for this meeting. Those of you here in the meeting room have voting buttons on your microphone: yes, no, and abstain. Once we begin the vote, please press the button that corresponds to your vote. After

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everyone has completed their vote, the local votes will be locked in. The final vote result will then be displayed on the screen. I will read the vote from the screen into the record. Next, we'll go around the table, and each individual who voted will state their name and vote into the record, as well as any additional comments or rationale for why they voted as they did.

So, okay. So we'll do -- what we're going to do is Question 1a, correct. So we will now begin the voting process for Question 1a. So the question is, again, the revised question that we're voting on: Does the evidence support that these snus products do not pose risks of gum disease to individual users of these products? So, okay.

So, again, sort of a negative. We have to make sure we understand what this means.

Does the evidence support -- is there sufficient evidence that these snus products do not pose risks of gum disease to individual users of these products?

Yes.

MR. ZELLER: It's why we phrased it the other way, but you could -- change is fine.

(Laughter.)

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DR. HUANG: Yeah, I know.

MR. ZELLER: So if you believe that it poses risk, then you have to answer no.

DR. HUANG: If you think that there is evidence to support that these pose risks --

MR. ZELLER: Then you have --

DR. HUANG: Then you vote --

MR. ZELLER: Then the answer should be no.

DR. HUANG: No.

MR. ZELLER: It's why we thought our phrasing --

DR. HUANG: Right, I --

MR. ZELLER: -- was simpler.

DR. HUANG: Yeah, I know. There's always a reason for something.

MR. ZELLER: But the Committee has a life of its own.

DR. HUANG: If you think that there is not sufficient evidence to support --

(Laughter.)

DR. HUANG: Whew, it is complicated.

UNIDENTIFIED SPEAKER: Let's vote on the question --

DR. HUANG: Okay. Does the evidence support that these do not -- I'm trying to think through this. Does the evidence

support that these snus products do not pose risks of gum disease to individual --

DR. CHOINIERE: So if you think the evidence conclusively shows that they do not pose risks to gum disease, then you should vote yes.

DR. HUANG: Say that again?

(Laughter.)

DR. CHOINIERE: If you believe that these products do not pose risks, then you should vote yes.

DR. HUANG: Oh, okay. And if you think that there is, perhaps, some question remaining, you --

DR. CHOINIERE: It's about posing risks. If you believe that they pose risks for these specific conditions, then the correct answer would be no.

DR. HUANG: Okay. Does everyone have that? Okay. Okay, so please press the button on your microphone that corresponds to your vote.

(Vote.)

DR. HUANG: Has everyone voted? Everyone has voted, okay.

Okay, everyone has now voted. The vote is now complete and locked in.

Well, what is that?

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(Off microphone response.)

DR. HUANG: What does that mean?

MS. COHEN: Red is no.

DR. HUANG: Okay.

MS. COHEN: Green would be yes.

DR. HUANG: Okay, so red is no.

So I am -- there are -- let's see, 1, 2, 3, 4, 5, 6, 7, 8
-- 8 no votes. So I will read the record from the screen:
Dr. Ribisl, no; Dr. Eissenberg, no; Dr. Giovino, no; I voted
no; Dr. Fagan voted no; Dr. O'Connor voted no; Dr. Bickel voted
no; and Dr. Novotny voted no. Okay.

Now the vote is complete. We'll go around the table and
have everyone who voted state their name, their vote, and any
comments or rationale regarding your vote.

So you want to start, Dr. Novotny?

DR. NOVOTNY: I voted no because I don't think there's
sufficient evidence to exclude the risks for gum disease in
human studies and that we need more evidence on that.

DR. HUANG: Dr. Bickel.

DR. BICKEL: It's biologically plausible, and there is
insufficient evidence.

DR. HUANG: Pardon?

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(Off microphone comment.)

DR. BICKEL: I voted no.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: I voted no for lack of robust evidence to the contrary.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I voted no because of the lack of sufficient evidence.

DR. HUANG: This is Phil Huang. I voted no, again, similarly because I do not feel there was sufficient evidence.

DR. GIOVINO: Gary Giovino. I voted no because I did not feel there was sufficient evidence.

DR. EISSENBERG: Tom Eissenberg. I voted no; there was not sufficient evidence.

DR. RIBISL: Kurt Ribisl. I voted no because there was not sufficient evidence.

DR. HUANG: Okay, great.

Now we can move on to the revised second question, 1b. So similarly: Does the evidence support that these snus products do not pose risk of tooth loss to individual users of these products?

So please press the button on your microphone that

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corresponds to your vote. And now it's turned on, okay.

(Vote.)

DR. HUANG: Has everyone completed their vote?

(Pause.)

DR. HUANG: Okay. Everyone has now voted; the vote is now complete and locked in. So the vote is again, 2, 4, 6, 8 -- 8 votes no.

Dr. Ribisl, no; Dr. Eissenberg, no; Dr. Giovino, no; Dr. Huang, no; Dr. Fagan, no; Dr. O'Connor, no; Dr. Bickel, no; and Dr. Novotny, no.

So now that the vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and any comment or rationale.

So Dr. Novotny.

DR. NOVOTNY: Tom Novotny. I voted no because there is essentially insufficient evidence, almost no evidence, regarding this issue.

DR. HUANG: Dr. Bickel.

DR. BICKEL: Warren Bickel. I voted no, insufficient evidence.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Dr. O'Connor. I voted no for insufficient

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evidence.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Pebbles Fagan. I voted no for insufficient evidence.

DR. HUANG: This is Phil Huang. I voted no, because I felt there was insufficient evidence.

Dr. Giovino.

DR. GIOVINO: Gary Giovino. I voted no because of insufficient evidence.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Tom Eissenberg. I voted no; there was not sufficient evidence.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Kurt Ribisl. I voted no because there was not adequate evidence.

DR. HUANG: Okay. So we have now completed our first question. Should we take a break? Yeah, let's take a 10-minute break. Okay, reconvene at like 10 until 10:00? Thank you.

(Off the record at 9:41 a.m.)

(On the record.)

DR. HUANG: Okay, we'll try to reconvene now. If we could

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please have everyone take their seats. Okay, we are moving on. We're moving on now.

Our second question that we're going to be addressing today, we recognize we're probably going to have to make a similar wording change. So if everyone is okay, we will change the wording of the second question to now: Does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products? And that would be what the discussion is regarding that question.

So, again, does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products?

So now we open the discussion to the evidence regarding the association between these 10 snus products and oral cancer. Anyone that would like to open that discussion?

DR. EISSENBERG: Yes.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: I need some help understanding a discrepancy between the Lewin et al. 1998 paper and FDA's interpretation of it. So I'm looking at a conclusion from that paper. Again, it's Lewin et al. 1998. In our study, relative risks were usually close to 1, something about some controls,

and then they cite some of the risks: 1.7 for cancer of the oral cavity with a confidence interval of 0.8 to 3.9, so a pretty wide confidence interval. I go to the briefing document and I read, "Lewin et al. found a significantly positive association between snus and head and neck cancer which includes oral cancer." This is the bottom of page 20 in the briefing document. So I didn't understand the discrepancy between those two statements.

DR. HUANG: Dr. Chang.

DR. CHANG: Thank you for your question. I'm --

DR. HUANG: If you could please introduce yourself.

DR. CHANG: Dr. Cindy Chang. So the discrepancy is that what was stated, what you quoted from the paper describes the main findings, which is primarily the smoking adjusted estimates. And so what we quoted was a subset of the findings, the never smoker estimate.

DR. EISSENBERG: And on how many people is that never smoking estimate based?

DR. CHANG: It's actually in my slide set. Let me just pull it up here. So the 4.7 odds ratio was based on nine exposed head and neck cancer cases. Does that help?

DR. EISSENBERG: It helps. I guess I'm hoping you can

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understand. I mean, we were just a second ago -- I realize a different question, different studies, but we were struggling with 50 being too small. I'm wondering how much weight I can put behind these nine.

DR. CHANG: I agree, it's not large and -- but the confidence interval did not include one. However, I agree. You know, it's not a very precise estimate.

DR. EISSENBERG: Okay, thanks.

DR. HUANG: Yes, Dr. Boffetta.

DR. BOFFETTA: I have two comments with respect to this. First is that the number 50 was mentioned in the previous discussion as a total number of snus users, not the snus users with the outcome of interest. Here we're talking about cases of cancer who were snus users. I mean, there were many more snus users in the study.

And the second point, which refers really to -- I think yesterday there was a bit of confusion in the discussion of this paper. This paper presents both results for head and neck combined, all the sites, including oropharynx, larynx, and esophagus, so it's even more than head and neck; it's upper aerodigestive. And then it presents some results for oral cancer specifically. And the results that were identified by

FDA as statistically significant refer to the entire site of head and neck plus esophagus. The results for oral cancer, they're all negative, and this is why the authors of the paper conclude the way you see.

It is true, however, that they do not present results for oral cancer in never smokers, probably because there were too few cases. There were only nine cases overall, so it was restricted to oral cavity; probably they were just a fraction of these nine. But the results for oral cavity are reported in Table 5, and they were reported also in the summary tables shown by FDA yesterday. They tend to be negative; for example, for current user, there the risk is 1.0.

DR. EISSENBERG: So I'm trying to put this information -- I'm not arguing with anybody, I'm just trying to put it in the context of this question, which is about oral cancer. So you're saying, Dr. Boffetta, that the Lewin et al. paper shows no risk, no increased risk for oral cancer in snus users?

DR. BOFFETTA: Well, the results for ever use, the risk is 1.4, non-significant. For current use is 1.0, so obviously it's not significant by definition. And for former use is 1.8, non-significant. So there is a small increase, non-significant overall, which is only in the former users, not in the current

users. That's what it shows for oral cancer specifically.

DR. HUANG: Other comments?

(No response.)

DR. HUANG: And, again, the question is: Does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products?

Dr. Tomar.

DR. TOMAR: Just for the record, on the Schildt case control study, while it found no statistically significant association between snus and oral cancer in their multivariate analysis, that study also found no significant association with cigarette smoking in its multivariate analysis, suggesting that there might be some, maybe some measurement issues.

DR. HUANG: Other comments?

(No response.)

(Pause.)

DR. HUANG: And, again, I guess there were six identified studies, three prospective cohort, three population-based case controls.

(Pause.)

DR. HUANG: Clarifying questions?

Yes, Dr. Eissenberg.

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DR. EISSENBERG: No, I don't have any clarifying questions, but I'm hoping we're going to get a little more discussion on this issue.

DR. HUANG: Yes, I think so.

(Laughter.)

DR. EISSENBERG: I don't think just sitting here quietly is going to help us very much.

DR. HUANG: I think people are shifting gears from our prior discussion, but -- yes, Dr. Choiniere.

DR. CHOINIERE: If I can suggest a starting point for your discussion, perhaps you can look at some of the issues that we had discussed in Question 1, such as biological plausibility or the strength of the evidence itself.

DR. HUANG: Okay. Any comments regarding biologic plausibility? Again, we're not dealing with a large number of studies.

Yes, Dr. O'Connor.

DR. O'CONNOR: I guess, sort of looking at the evidence that was presented both by Swedish Match and by FDA, we've got a lot of -- they've got, sort of, a number of studies all of which float around 1, and we have, sort of, to address the issues of biological plausibility. We got data from Swedish

Match from their trend lines on their products, at least back to 1990, that they presented where the constituents that one would reasonably expect are related to oral cancer are substantially reduced relative to where they were 20 years ago, so that would tend to be consistent with the epidemiological evidence that you're seeing, but I would put that to the Committee of what they think of that evidence.

DR. HUANG: Okay. And, again, there are some issues that have been identified, you know, definitions of the exposure varied among the studies, regular current use, and current snuff use. And for all the three cohort studies, exposure was only assessed at baseline only. Again, some limitations.

Other comments?

Yes, Dr. Swauger.

DR. SWAUGER: I just want to remind people from yesterday, I mean, I made the comment that I think you can step back, I think you can look at the broader evidence base. I can't remember the year it was published, but that Lee and Hamling document that looked at 15 studies, most recent 15 studies, that were adjusted for alcohol and smoking product looking at the association between smokeless use and mouth cancer in North America and Europe, and I don't think, from what I remember of

that study, there was no association that was observed. I know we're laser-like focused in on these six, but it's almost like we're fishing, looking for a weakness that would push us off of that perspective. I just don't see evidence to suggest that there's a relationship between these products and oral cancer or for that matter, smokeless more broadly. At least in those more recent studies.

DR. HUANG: And, again, I guess our starting place is sort of the warning label. The process for assessing the risk between smokeless tobacco and oral cancer has sort of been established. We are assessing what is the data for these particular 10 products to see if there's indication that they do not show that risk.

DR. SWAUGER: And I recognize that, and a moment ago people were asking for more discussion. I'm just trying to throw some things on the table for you to think about.

DR. HUANG: Sure.

Again, another issue I know that's been brought up, the definitions of the outcome also varied. Some were squamous cell oral cancers, head and neck cancer consisting of squamous cell -- oral cavity, hypopharynx, larynx, and esophagus, again, different definition.

Yes, Dr. Ashley.

DR. ASHLEY: I know the Committee is wanting to talk, they're having a hard time talking, so I'm going to make just a suggestion; let me throw it out there. The slides from yesterday from Cindy Chang, slide number 25 provided FDA's summary, preliminary summary of findings. I don't know if it would be worthwhile for the Committee to look at what those are and comment on whether they agree or disagree with those as a way to try to get the conversation going.

DR. HUANG: Sure, sure. I mean, I think -- yeah, a review of the studies that were seen, there was not a strong consistent association. But two of the studies did observe positive association, and so we're trying to say, decide is there evidence that there is not a correlation.

Yeah, Dr. Eissenberg.

DR. EISSENBERG: I mean, I want to qualify your statement, Dr. Huang, that two of the studies did because there's one where it's head and neck cancer, and we just decided a second ago that it wasn't oral cancer, so it's one, and that's the one that I'm staring at, at my screen. And then I see this other one -- I don't know how to pronounce it, Luo et al. 2007 where the confidence interval -- where the risk estimate was less

than 1, and it looks like the confidence interval doesn't cover 1, and I'm trying to -- I mean, those -- all the other evidence suggests no risk of oral cancer except for the Roosaar and the Luo, and the Luo seems protective. And so I'm trying to reconcile these results. It's the only thing that --

DR. HUANG: Sure.

DR. EISSENBERG: Maybe it's the way the confidence interval is drawn. I'm looking at one of the figures from the application.

DR. SWAUGER: And I believe -- I'm sorry. May I speak?

DR. HUANG: Yes, Dr. Swauger.

DR. SWAUGER: I believe the Roosaar study is, you know, ICD 140 to 148 so it's not specific to oral cancer.

DR. HUANG: And, again, there are these limitations to these studies obviously.

Yes, Dr. Boffetta.

DR. BOFFETTA: Well, to address this issue that there are some, at least one study which has a significant negative association -- and I'm one of the coauthors of this study, so I know the study quite well -- I think, well, the confidence interval is not an absolute sort of gatekeeper or -- I mean, it simply says that the likelihood that the results are due to

chance is less than a given level of probability, so it's not surprising that among many results, occasionally there are results that are significant one way or the other. So I think it needs to be put in the context of the entire body of evidence.

DR. EISSENBERG: Yeah. And I agree -- may I?

DR. HUANG: Yes, Dr. Eissenberg.

DR. EISSENBERG: Yeah, I agree with that completely, and that's why I'm trying to balance it against the other studies that showed no effect and then the one study that shows a positive effect. If we follow the logic that you just put forward, with which I agree completely, we must also apply that same logic to the Roosaar et al. study.

DR. HUANG: Yes, Dr. Bickel.

DR. BICKEL: One way I try to evaluate different studies with effect size and that -- if it's a very small effect size, right, then the chance that one study is going to find it and another one's not going to find it is high. If there's a large effect size, that's less likely to occur. Is there any translation of these studies into effect size?

DR. HUANG: Dr. Chang or --

DR. CHANG: Sorry, I couldn't hear the question. Can you

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repeat it?

DR. BICKEL: I just want to know if these studies, the effect size of these studies have been estimated.

DR. CHANG: The effect sizes of the studies. You mean power calculations?

DR. BICKEL: Cohen's d.

DR. CHANG: I'm sorry, I'm not following.

DR. BICKEL: So Cohen's d is a measure of the effect size of different -- that a study can report, and it's often used to allow us to understand the relative power, the relative contribution of the phenomena; weak effect size, small effect size are less likely to be replicated. It would be variable.

DR. CHANG: So, yeah. I didn't do power calculations, but in Dr. Boffetta's analysis, the number of oral cancer cases that he had in his study allowed for a minimally detectable risk ratio of 1.8. So that suggests that his study was relatively underpowered.

DR. HUANG: Okay, Dr. Eissenberg. Oh.

Okay. I mean, again, you know, what we're being asked is the strength of the body of evidence related to oral cancer, and I think, you know, it's been pointed out.

Yes?

DR. SWAUGER: I was listening to the conversation. I was just kind of wondering -- we're picking individual studies or at least we're discussing them. I'm just wondering, I mean, I don't know the literature all that well related to the meta-analyses that have been done, but I'm sitting here thinking Dr. Boffetta probably does. I just -- my first assumption is a meta-analysis is probably a little bit stronger way to look at this. I'm just kind of curious what his views are. Can he comment just in general? I mean, what is your view of the subject sort of in a general way?

DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Well, I would be hesitant to go for a meta-analysis because -- at least a meta-analysis for oral cancer because of this issue that many of the studies did not present results for oral cancer. We could probably do a meta-analysis combining head and neck cancer and/or cancer results. At least it would not be very -- well, we have the issue that, you know, we would not focus on oral cancer. By the way, the code by Luo is the only one which reported results for oral cancer specifically among the three cohort studies, as is shown in Cindy's slide.

DR. HUANG: Dr. Tomar.

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DR. TOMAR: In terms of the FDA's interpretation of the data, I mean, I would agree with it, that the first statement is "Based on the available evidence, there does not appear to be a strong, consistent association between snus and oral cancer." And I think that that's -- I think that's a valid assessment of what we have. But similar to the discussion we had on the previous question, well then, how do we weigh that in the context of the broader issue of separating this out as a class of -- or not even a class, but as a specific manufacturer's products within this broader class? And that one I don't know how to address.

DR. HUANG: Right. I mean, yeah, again, there's gaps in the information that we have, so is there sufficient information to make -- you know, to say that the warning label should be removed?

Dr. Fagan.

DR. FAGAN: Yes, I just want to make a point. I just looked at the Luo study, and it's all men enrolled in the final analyses. And I'm looking at the Roosaar study, as well, and this was also a cohort of men. And so I just want to make sure we take into consideration we're looking at the risk of oral cancer. If I am looking at the studies correctly, the

conclusions are based upon all male samples, which means that we don't know what the issues are associated with women who are users of snus.

DR. HUANG: Yeah, Mitch.

MR. ZELLER: I just wanted to respond, and I'm not trying to make a joke here. I want to respond to Scott's last comment. We never said this was going to be easy in what we've asked you to do. But the Acting Chairman's point about how the scientific question reworded has been put to you has a nexus, and I said this about Question 1, with the request. There's an existing warning that talks about "can cause," and now we've shifted to mouth cancer, "can cause." And, ultimately, how you answer this question is going to relate to the Agency's consideration of that request in the application.

We are not asking you to go to the ultimate question of should the warning be removed or not, but we are asking you a challenging, scientific question, and there is an obvious nexus between the question that we have reworded that has been posed to you and the ultimate decision that is ours to make.

It is not an easy question that we have put to you, but we do need you to grapple with it and ultimately render a vote. But don't lose sight of the frame. The frame is there as an

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existing warning that says "can cause," and ultimately we are going to have to decide whether, for these products before us in these applications, that warning should be removed.

DR. CHANG: This is Dr. Cindy Chang. If this will be helpful at all, I've heard the word meta-analysis a few times, and just so you know, there are two meta-analyses that have been published on -- that include the Swedish studies of snus and oral cancer. And the Boffetta -- one is by Lee, and one is by Boffetta et al. And, however, the Boffetta meta-analysis, from what I recall, and please correct me if I'm wrong, does not include the Roosaar study, the Roosaar 2008, which was published after your meta-analysis.

DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Yeah, this is correct because the study was not available when we did the meta-analysis. But our meta-analysis was not restricted to the Swedish study; it was a meta-analysis of all studies of smokeless tobacco. Well, the other studies are from the U.S. basically. There are no other studies. We dropped the Eton (ph.) study because the products are really very different -- and Sudal (ph.), et cetera. So our meta-analysis comprised both North American and Nordic studies.

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DR. HUANG: Yes, Dr. Swauger.

DR. SWAUGER: I just wondered, Dr. Boffetta, can you remember what the outcome of that analysis was?

DR. BOFFETTA: Well, I'm afraid I need to go back to the paper because I don't recall whether we presented separate results for oral cancer separate from head and neck, and that would be the range. If you want --

DR. SWAUGER: I would just think that --

DR. BOFFETTA: I can get the paper.

DR. HUANG: Oh, Dr. Giovino might have it.

DR. BOFFETTA: It seems to me it goes a little bit beyond our discussion today.

DR. HUANG: Sure, right.

DR. BOFFETTA: Because of the North American studies --

DR. HUANG: And, again, that's where -- we're starting with sort of some given association, but yeah, if Dr. Giovino can locate that, then we'll try to add that to the discussion.

But Mitch's points, again, are well taken. I mean, I think yeah, a lot of this -- the difficulty is, I mean, there is not a lot of -- I mean, you know, we're looking at the available evidence. There is not a lot of evidence, there's not a strong consistent association in some of the evidence,

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there are limitations to the studies that we have. So, again, the question that we have rephrased and posed is: Does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products? We'll let Dr. Boffetta -- any other comments?

Yes, Dr. Swauger.

DR. SWAUGER: I'm just still struggling with the notion of framing it the way it's framed. It's not my decision. I just think you're setting up a standard that's probably impossible to meet. I mean, at the end of the day you're asking people to prove a negative, and that just doesn't seem right. And I don't -- I mean, I'm sitting here thinking about epidemiology, and somebody else said, I think it might have been Dr. Eissenberg, but -- I may be wrong, but what are the odds of putting six or seven epidemiology studies on the table and you're not going to see some spurious result that pops up?

DR. HUANG: Right. And that's where, I mean, looking at the weight of the evidence -- I mean, their criteria for determining causality.

Yes?

(Off microphone comment.)

DR. HUANG: So -- and, again, it's difficult, and that's

where we're getting -- that's the purpose of this group, is to sort of digest this and to review what information we have.

Any further comments?

Yes, Dr. Ribisl.

DR. RIBISL: Yeah, I sort of favor going back to the wording of just "pose risks" to oral cancer than "do not," but --

(Off microphone comment.)

DR. HUANG: Well, actually -- and this is slightly worded different -- well, hold on.

DR. CHOINIERE: Dr. Huang, I think what would be helpful here is no matter how you word the question, that we would also really like to hear your thinking about your answer to the question, as well as if you have other -- I mean, if this issue of which question is being asked is not the one you're comfortable answering and you, in your explanation, want to talk about what question you think should be answered, that would be helpful as well.

DR. HUANG: Okay.

Yes, Dr. Swauger.

DR. SWAUGER: Just one more tidbit. I'm at least -- since you're sort of talking about focusing on the evidence you have

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in front of you and on the --

DR. HUANG: Please speak into the microphone, yeah.

DR. SWAUGER: You really can't hear me?

DR. HUANG: Yeah.

DR. SWAUGER: Sorry.

All right, so my thought was basically this: You said a moment ago, you were sort of talking to me, and you said we're supposed to focus on the evidence before us and these six isolated studies. I keep trying to broaden it because I have an interest in broadening it, and I think that data is relevant. But I'm at least aware to the extent we're talking about meta-analysis, and in addition to Dr. Boffetta's work, I think Lee actually presented a separate analysis, meta-analysis on these datasets too. I don't remember what the results were, but to the extent you want to focus on isolation, that seems relevant too. Maybe somebody knows what that analysis reported.

DR. HUANG: Well, again, and that's why -- what we're -- the issue we're dealing with are these 10 specific products, and we're supposed to make some sort of assessment of the data for those related, that are specifically related to these 10 products. But there is a given, sort of, established

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association between smokeless tobacco products in general and these outcomes.

DR. SWAUGER: What I'm suggesting is that the Lee analysis actually does isolate and present, I believe, a separate meta-analysis on these data. If that's true, it ought to be considered, and maybe it would take some of this discussion off the table in terms of the individual studies.

DR. HUANG: Yes, Dr. Tomar.

DR. TOMAR: Just try to move this along, you know. Again, a similar thinking process to what we went through on the previous questions. So the body of literature was reviewed, and when they developed the original warning labels, the determination was that there was sufficient evidence to include the warning that it can cause oral cancer. And so to me, the question is, you know, is there enough evidence before us to say no, these particular products cannot cause oral cancer? I'd say, given the limitations that we've discussed and -- you know.

And frankly, even the chemistry of it, while TSNAs are lower in these products than in others, compared to other consumer products, these are still pretty high nitrosamine levels, so there's certainly still a biologic plausibility for

these being carcinogenic products. And so I don't know that there's sufficient evidence to warrant removal of the existing wording.

DR. HUANG: Okay.

Yes, Dr. Eissenberg.

DR. EISSENBERG: So at the risk of stealing Dr. Boffetta's thunder, it's his paper, I'm going to address Dr. Tomar's comment. So Dr. Boffetta did a meta-analysis on oral cancer in a variety of countries; this is caused by smokeless tobacco use. So in the U.S., the relative risk is 2.6 with a confidence interval of 1.3 to 5.2 supporting, of course, the current labeling of U.S. products.

In Nordic countries, there were -- the relative risk was 1.0 with a confidence interval of 0.7 to 1.3, suggesting that, based on the data that he had reviewed at the time, there was no risk of oral cancer for these products. It seems pretty clear to me, and I'm having difficulty understanding why it is not clear, based on the results of that meta-analysis. U.S. smokeless tobacco users have an increased risk of oral cancer; those in Nordic countries do not.

DR. GIOVINO: The only -- well, I'm sorry.

DR. HUANG: Yeah.

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DR. GIOVINO: As you said, there was another study, Roosaar, that came out later.

Where is Dr. Chang?

DR. HUANG: Okay, Dr. Boffetta.

DR. BOFFETTA: Yeah, we did not include the Roosaar study because it was published --

DR. HUANG: Right.

DR. BOFFETTA: Right. More or less the same time our meta-analysis was published. Given the small number of cases, however, I don't think this would make a major difference in our results frankly. The other estimate for the Nordic study would remain very close to 1.0, I suppose. Yeah. This is work. It's obvious epidemiologists cannot prove the negative.

I mean, it can only accumulate evidence which goes in one direction or the other, and I think in our interpretation of the data, at the time we wrote this review meta-analysis, we clearly stress this difference between the results for the American products and the Nordic -- I mean, the American studies and the Nordic studies in terms of risk of oral cancer.

DR. HUANG: Again, is there an assessment of the adequacy of the evidence to then remove the warning label on that? I mean, is --

DR. EISSENBERG: Well, now that's not fair because that's not the question asked. The question isn't asking -- I understand what you're saying, nexus, Mitch. But the question is not asking is there evidence to remove the warning label.

DR. HUANG: Right. But that's how the information -- I mean, that's the task that FDA has to decide on. Our information should help with their decision.

Yes, Dr. Swauger.

DR. SWAUGER: I'm just wondering if somebody can -- so picking up on Dr. Eissenberg's thread from a few moments ago, can somebody actually give us the number out of the Lee analysis that was conducted on these studies? Somebody sitting around here. Surely Swedish Match knows that number.

DR. HUANG: Can you speak --

DR. SWAUGER: Sorry. I mean, all I'm saying is surely to the extent there are two meta-analyses that are available -- Dr. Eissenberg just pointed you to one of them a moment ago. I probably am sharing some of his -- well, what I perceive as frustration. But there's another one sitting out there that's relevant, too, that Lee published that isolated these studies. I'm just wondering if somebody can share that analysis with us. I think Swedish Match has it in their hand. It would be

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interesting if you could get them.

DR. HUANG: Is there someone from Swedish Match that would like to respond to that?

(Off microphone response.)

DR. HUANG: Okay. And please state your name.

DR. WARD: Carol Ward from ENVIRON International. I do have a slide on this matter. I don't know if that could be brought up. So this is the table that comes out of the Lee meta-analysis. I know you probably cannot read it, but the point was to show that there were two analyses. One was on the whole population, but then there also is a separate analysis of never smokers.

The next slide shows the results of the meta-analyses. Dr. Boffetta, we just heard about his, which was specific to Nordic countries, and then Lee and Hamling also is specific to snus. There are different numbers because the updated information; overall, there was no statistically significant association when you combine these studies, which, when you look for heterogeneity, in fact, there was significant heterogeneity when the whole population was examined. But when you look at never smokers, then the heterogeneity went away, which, you know, helps understand whether or not it's valid to

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combine these studies.

And those are the results that were presented in the Lee meta-analysis. I might also add that in that never smoking alcohol-adjusted, it's kind of a difficult -- there were only two studies that contributed to that number.

DR. HUANG: Yes, Dr. Novotny.

DR. NOVOTNY: One other piece of information that might be at least worth considering, in one of the public comments, Greg Connolly submitted some information about the carcinogenicity of the chemical components of snuff and quantified it according to EPA kind of recommended levels of exposure and, you know, it was significant. And I just wondered -- that, I think, was published 2011, so it's relative to rather more distant data. And I just wondered if some of the data that were presented this morning about the chemical components had been compared to the exposure recommendations that EPA has worked out on some of these carcinogens. That may be too much for this consideration, but it's -- you know, the carcinogenicity has been quantified in the past and whether or not it can be quantified just in terms of an exposure risk.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I just want to make the point again, I

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just checked a couple of the other studies; again, the samples are men, and so if there is a vote, I think the conclusion or the voting should be very specific to males. I don't want us to make the same mistakes that we made before with cigarette smoking when it was 20 years later before we had the SGR report on the relationship between cigarette smoking and cancer in women and we set down some different outcomes there. And so if there is a vote, I would like to suggest that the vote be very specific to males who were included in these studies.

DR. HUANG: Okay.

Yes, Dr. Boffetta.

DR. BOFFETTA: I understand this point, Dr. Fagan, but for other types of smokeless tobacco products, such as those consumed in the U.S. and those consumed in India, there are studies including both men and women, and the effects are very similar in the two genders. I mean, there are no difference for oral cancer risk in the two groups. So it is unfortunate that there are no large populations of women using smokeless tobacco, at least in the previous generation, which could have been studied in Sweden and Norway. And I understand we don't have results in those, that for what we know in terms of the risk from other types of smokeless tobacco, there doesn't seem

to be a difference in gender in the effect.

DR. FAGAN: There is one recent study, it's not included, but I was just doing some reading yesterday, a study that was just published in 2014 among women athletes. And I can't remember if it's Sweden or Norway. And basically that study found that about 20% of those women were snus users. And so I don't know if that means that the use is increasing there or that we really haven't adequately assessed snus use among women. But I would just -- really, I'm relying on the studies that were presented here to us and the evidence base that's embedded there.

DR. HUANG: Dr. Boffetta?

DR. BOFFETTA: No.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: No, I just want to reinforce Dr. Fagan's point. I agree completely. I don't -- I am considerably swayed by Dr. Boffetta's meta-analysis. I don't see a risk here for oral cancer, but I agree that the data are exclusively limited to men, and this presages a point I was going to make later on about pregnancy outcomes in women. There are serious issues to be worried about here. And so I think it's a good idea to limit the vote to what the evidence speaks to, and the

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evidence speaks to men.

DR. HUANG: Dr. Swauger? Okay.

Any other comments regarding some of the other identified issues? You know, all three of the cohort studies, exposure was only assessed at baseline only. I mean, there are methodologic limitations to many of these studies.

DR. RIBISL: Yeah, I would say every single study is flawed, if you ever read --

DR. HUANG: Right, sure.

DR. RIBISL: -- the tradeoffs of internal and external validity; that's a given. But the key is to look at the body of evidence and the weight of evidence, and I think that's what should drive our decision making --

DR. HUANG: Sure.

DR. RIBISL: -- similar to what the FDA Acting Director talked about with Hamburg saying let's let the science drive it, but it's got to be the bulk of the evidence, and there are occasionally Type 1 errors. There's a fluke here or there. But if you look at the body of evidence, and if you're looking for dose response and we fail to see any kind of consistent dose response and other stuff, I think there is a clear signal.

DR. HUANG: And, again, is there -- the body of evidence,

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is it strong enough to make that conclusion.

DR. RIBISL: Yeah, just on that, if you look at the sample sizes in a number of these studies we're talking of, I mean, thousands and thousands of people in multiple studies and then you pool it and you get even a bigger sample size. So I feel there's an apples-and-oranges comparison between the oral cancer stuff -- I mean, sorry. Between the oral cancer stuff and some of the gum disease and tooth loss that we looked at. These are, I think, very different literatures.

DR. EISSENBERG: Even within Dr. Boffetta's meta-analysis, the same studies that were used to show relative risk of 1.0 for oral cancer in Nordic countries were used to show that there was a relative risk of 1.6 with a confidence interval of 1.1 to 2.4 for esophageal cancer, so there's clearly -- I mean, speaking to Warren's issue for power, that's not an effect size, but it shows the sensitivity within those same studies for other cancer outcomes. Again, I remain convinced.

(Pause.)

DR. HUANG: Other comments?

(Off microphone comment.)

DR. HUANG: Okay. All right, does everyone feel ready to vote? Yes.

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DR. FAGAN: So my vote is going to be different depending upon whether these conclusions or the vote is related specific to men. And so, as it stands, my vote would go one way as it's worded here; but if it were specific to men, my vote would go in another direction. So I'd like to know how we exactly are going to vote.

UNIDENTIFIED SPEAKER: Can you vote both ways?

DR. HUANG: Yes, Dr. Boffetta.

DR. BOFFETTA: Can I offer a suggestion --

DR. HUANG: Sure.

DR. BOFFETTA: -- even if I do not vote?

DR. HUANG: Sure.

DR. BOFFETTA: Maybe we can add a qualification after the question stating that the evidence on oral cancer is primarily coming from studies of men. It's not true that there are no studies of women. Three of the studies include women, but the number of snus users was low in women; this is true absolutely. So maybe it's easier, rather than having two questions, is to say that the available evidence is based on studies including primarily male snus users or something like that.

DR. HUANG: Okay. What's that?

(Off microphone comment.)

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DR. HUANG: Yeah, okay. So how would you phrase this, then?

(Pause.)

DR. HUANG: Yes, Dr. Choiniere.

DR. CHOINIERE: If it would be easier, you could maintain the question as is --

DR. HUANG: Um-hum.

DR. CHOINIERE: -- and in our explanation, in your explanations of your votes, explain why you voted that way and if you would have voted differently if it were a different question. That's one option.

DR. HUANG: Sure.

DR. CHOINIERE: That's a suggestion.

DR. HUANG: Okay.

Yes, Dr. O'Connor.

DR. O'CONNOR: Yeah, I was going to make the suggestion to not embed this issue within the question but rather to let -- similar to Conrad's suggestion, to let people explain the basis for their vote.

DR. HUANG: Okay. All right, does everyone feel prepared to vote on this issue?

(No audible response.)

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DR. HUANG: Okay, go back to the -- so we will be using electronic voting system for this meeting. Let's see, where is -- we will now begin the voting process. This is Question 2a. So please press the button on your microphone that corresponds to your vote.

Does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products?

(Vote.)

DR. HUANG: Has everyone voted?

(Pause.)

DR. HUANG: Yes? Okay. Hold on.

No, everyone hasn't -- oh. Okay.

UNIDENTIFIED SPEAKER: White means abstain.

DR. HUANG: White means abstain, okay.

All right, so the vote is 3 no; 3 red -- 3 yes. And 2 abstain.

Okay, so it's Dr. Ribisl voted yes; Dr. Eissenberg voted yes; Dr. Giovino voted abstain; Dr. Huang voted no; Dr. Fagan voted no; Dr. O'Connor voted yes; Dr. Bickel voted no; Dr. Novotny abstained.

Okay, let's see. So now we'll go around the table and

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have everyone that voted state their name and any comments or rationale.

DR. NOVOTNY: This is Tom Novotny. I abstained because part of Dr. Fagan's comments about women, that we don't have any information about the risk, so it's a little hard to say that there's no risk. But on the other hand, there's certainly a lot of discussion that we had today that shows that the risk for oral cancer alone is around 1.0 in most of the studies and meta-analyses. The other part of the discussion, which we didn't get into, was the risk of other kinds of head and neck cancers, which there was some evidence for. So I just didn't feel like I could vote either way on this.

DR. HUANG: Dr. Bickel.

DR. BICKEL: Warren Bickel. I voted no on the basis of the relative absence of information about women. I thought the data regarding men were more conclusive.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: I voted yes. I thought the evidence was sufficient to argue there was no robust effect.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yes, I voted no based on the evidence set of these, the larger cohort studies that were presented. The

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larger studies presented did not include women, and the one study on Schildt just had one woman moist snuff user, so that's pretty important up there.

DR. HUANG: Phil Huang. I voted no. I think, again, looking at the strength of the body of evidence, I still was not convinced that it was sufficient for saying that there was not the association. I think the points about women not being included in the study is also relevant, and again, I think that some of the other, I guess, problems, methodological problems with some of the studies does not give me sufficient evidence to say that there was not association.

DR. GIOVINO: My name is Gary Giovino. I'm at a higher level of uncertainty with this one. However, I think, you know, the relative risk of 1 is pretty consistent. I voted abstain, meaning more like a Level 3 on the Surgeon General's, where I think the data are tending towards no risk but I'm not quite ready to go there. No increased risk, I'm sorry. I'm not quite ready to go there yet.

DR. EISSENBERG: I'm Tom Eissenberg. I voted yes. The data before me convinced me that there is no meaningful risk of oral cancer in snus users among those who use it. I agree completely with Dr. Fagan that the vast majority of people who

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use it are men. I wouldn't have any data to be able to make a conclusion about women.

DR. RIBISL: I'm Kurt Ribisl, and I voted yes. I do believe that evidence is pretty consistent. There's variable ways of measuring exposures. It was robust across different types of measurement: different studies, different countries. I feel like it lined up in terms of the meta-analysis, so I feel that it's pretty clear that there's very little risk of this type of cancer for this, in this particular case.

DR. HUANG: All right. Let's see.

Okay, we've gotten through Question 2.

Yes, Dr. Tomar.

DR. TOMAR: I don't know if it's appropriate to ask a question after the vote's been taken. But I just wonder, I mean, it seems like it's sort of a deadlock. But I wonder if the question had been phrased, you know, instead of -- you know, including the "do not" part, if that would have changed the conclusions, how people would have voted.

DR. HUANG: Any comments?

(No response.)

DR. HUANG: Okay. I think we've been instructed. We'll move on after when we take these votes. The votes close out

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these issues.

Okay, moving on. Should we take a break, or are we good to keep going? Keep going, keep going. All right. We're on a roll.

Question No. 3: Discuss the evidence regarding the association between the ten snus products and overall risks to health as compared to cigarettes.

- a. Should the comparison focus on (A) the major smoking-related diseases according to population burden or (B) assess all relevant health outcomes?

So, open for discussion on this topic. I mean -- yes, Dr. Eissenberg.

DR. EISSENBERG: That's a good start.

DR. HUANG: Okay, Dr. O'Connor.

DR. O'CONNOR: So I guess the fundamental issue here is "discuss the evidence and the association between snus products and overall risks to health as compared to cigarettes." And so if you're comparing something to the risks of cigarettes, then the body of literature on the health risks of cigarette use becomes most relevant.

And then a sub-question to that is: Are there any risks associated with snus that are unique to snus that aren't

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represented by risks of cigarettes? And if there are, then they sort of add on to the list. But, otherwise, it's really a question of the relative risk of Disease X in smokers versus snus users. So I'm not sure that those are mutually exclusive. I guess that's my point, is that (B) includes (A).

DR. HUANG: Right, right.

DR. O'CONNOR: And it's -- so I don't see how that's an either/or point.

DR. HUANG: Are they saying -- I think (A) without including (B) is the option. So they're saying should we not assess all relevant health outcomes but only the major smoking-related diseases according to population burden. Or because -- yeah, include them all. Is there a reason that we wouldn't look at all relevant health outcomes and only look at the major smoking-related diseases?

DR. O'CONNOR: I guess that's the question of what does relevant mean.

DR. HUANG: And there were --

DR. O'CONNOR: Are we talking (A) is smoking-related mortality and (B) is all-cause mortality? Or are we talking, in (B), this includes other diseases that are not known to be associated with smoking? I'm just -- I'm trying to understand

exactly what we're trying to vote on.

DR. HUANG: And maybe some clarification from someone at FDA?

DR. CALLAHAN-LYON: Priscilla Callahan, FDA. What I have is an annual cigarette smoking-related mortality in the United States from 2005 to 2009, and it does break it down by disease category, so that might help you a little bit. Number one is cancer. If you separate out lung cancer, that's 127,700. And the total number of deaths was 480,317, so it's about a quarter. If you add lung cancer and respiratory disease together in the causes of death, it comes out to about 50% of the total deaths in that time period. If you add cardiovascular disease and metabolic, it goes up to over 80%. And I've got a whole bunch of other numbers, if you're interested.

DR. HUANG: Thank you.

Yeah, Dr. Ashley.

DR. ASHLEY: So I think the way we tried to phrase the question is, in essence, should we only consider those three outcomes or should we consider all diseases that result from cigarette smoking in comparison to smokeless tobacco?

DR. HUANG: Or is it all diseases that are associated with

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smokeless tobacco?

DR. ASHLEY: Yeah, all diseases for cigarettes and smokeless tobacco.

DR. HUANG: Smokeless tobacco, right.

DR. ASHLEY: Yes. Or is it just those three that should be considered?

DR. HUANG: Yeah. And I mean --

DR. ASHLEY: And I also --

DR. HUANG: Okay, it seems -- Dr. Eissenberg.

DR. EISSENBERG: No, actually Gary was --

DR. HUANG: Oh, Gary. Okay.

DR. GIOVINO: I think -- maybe I was.

DR. HUANG: Okay. Dr. Giovino.

DR. GIOVINO: I think we should focus on everything, because if we don't, we haven't done our job. And, you know, theoretically, if there's a disease that smokeless causes that kills 100,000 people, then we would pay attention to it. There might be a disease that smokeless causes that just grinds their teeth a bit. But, you know, we're scientists; we should be thorough. That's my opinion.

DR. HUANG: Dr. McAfee on the phone.

DR. McAFEE: Yes. So I want to reinforce what Gary was

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just saying, but perhaps from a different perspective. I think what we need to be -- this is in the context of a modified risk application. And because there's the unusual approach -- I guess nothing is unusual yet because this is the first time, but of approaching the modified risk concept from the idea of removing or modifying a warning label, particularly if we are trying to make some global statement about the relevant advantage of snus compared to cigarettes. You can't just look at the big numbers because we also have to look at critical subpopulations that we are very concerned about, and if we only look at those big numbers, we will miss two groups, just as an example that are -- I think, we in general, put more emphasis on.

The first would be women of childbearing age and pregnant women, and since this is an area that was not covered in the Swedish Match proposal because of this very concept of, well, it's not 100,000 negative effects, but there are substantial acknowledged concerns around the role of snus which are far more similar to the effects of cigarettes in terms of pregnancy effects and almost any other condition. So I think we would be remiss to not consider pregnancy effect.

The other one that has not been talked about at all has

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been related to the relatively recent findings in the last 5 to 10 years mostly from animal studies associated with adolescent brain development and nicotine exposure. And although this has not been studied, almost -- really, any other consumer product that had as much animal data that was suggestive of deleterious effect on adolescent brain development, this would not just be ignored because it didn't involve 100,000 people or 100,000 adults with a hard marker, so I would agree.

I'm not sure everything from soup to nuts needs to be considered, but certainly anything for subpopulations it might affect and should be included in the consideration of the impact of "overall" effect on health. You can't just do that based on hundreds -- when you have, in effect, 100,000 deaths. That's misleading.

DR. HUANG: Okay.

Dr. Ribisl.

DR. RIBISL: Yeah, I think this is the easiest question we probably have before us. I hear a number of people saying you want to give way, you want to focus on all of the health outcomes for either cigarettes or snus, and so I feel like that's kind of a no-brainer.

I do think we need to not just focus on mortality, the

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body count. We have to focus on morbidity, as well, because it's really -- I can't remember if Andy Hyland's study showed 16 people are sick with pretty serious illnesses, COPD and others, for every one person that dies with tobacco-related illness. So I think we really have to keep morbidity/mortality in the picture here.

Final point, I do think, with a little bit of a nod to what's in (A), we do need to give the greatest weight to the most dangerous and disabling conditions, and those are the ones that were mentioned with, you know, cardiovascular, cancer, and expiratory problems.

Thanks.

DR. HUANG: Okay, Dr. Swauger.

DR. SWAUGER: I just want to agree with something that was just said down the bench here. I mean, I also think that the greatest weight should be placed on those conditions that are associated fractionally with the most risk tied to cigarettes. I guess what's in my mind is if there are specific concerns related to risks related to smokeless, whether it's -- some of the comments were made about pregnant women and other sorts of conditions. Couldn't those concerns be dealt with separately? There was some comment, there's always the opportunity to come

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back with a little more specific warning on smokeless that addresses those concerns.

DR. HUANG: Okay. Other comments?

Dr. Bickel.

DR. BICKEL: I just want to also note, because I'm not familiar enough with the literature, but the absence of certain racial groups in Sweden and the health risks associated with them are unclear to me, and that's just, I think, from looking at all causes, we should take that into account.

DR. HUANG: All right, is this -- this is probably our easiest question. Should we go ahead and vote on this? Just A or B.

Oh, we have a B, okay. A is yes, B is no.

DR. GIOVINO: A is the plus sign, B is --

DR. HUANG: All right, should we --

(Off microphone comments.)

DR. HUANG: Okay, so clarify. A is plus, B is minus.

Huh? Okay.

UNIDENTIFIED SPEAKER: On your voting machine.

DR. FAGAN: Oh.

(Laughter.)

(Off microphone comments.)

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DR. HUANG: Okay. So we'll now begin the voting process for Question 3a. Please press the button on your microphone that corresponds to your vote.

(Vote.)

DR. HUANG: Has everyone voted?

(Pause.)

DR. HUANG: Yeah, all right. Everyone has now voted. The vote is now complete and locked in.

The results: Dr. Ribisl voted B; Dr. Eissenberg voted B; Dr. Giovino voted B; Dr. Huang voted B; Dr. Fagan voted B; Dr. O'Connor voted B; Dr. Bickel voted B; and Dr. Novotny voted B. All right. So it's unanimous.

Now we'll go around the table and ask everyone who voted to state their name, their vote, and any comment or rationale.

Dr. Novotny.

DR. NOVOTNY: Tom Novotny. I voted B because I do believe we should consider all relevant health outcomes.

DR. BICKEL: Warren Bickel. I voted B because I think we should consider the broad range of health effects of both conventional cigarettes and snus.

DR. O'CONNOR: I voted B. Richard O'Connor, I voted B. I would -- a caveat, that I would place great weight on lung

cancer and respiratory disease outcomes.

DR. FAGAN: I voted B because I want to make sure we consider all the health outcomes.

DR. HUANG: This is Phil Huang. I voted B, again, for looking at overall health risks. I think we need to look at all relevant health outcomes.

DR. GIOVINO: Gary Giovino. I voted B for the same reasons. We need to look at all relevant health outcomes and be aware of the smoking attributable mortality estimates.

DR. EISSENBERG: This is Tom Eissenberg. I voted B. I think, in the context of the applications and specifically the change in warning labels that are requested, we are demanded to look at the wider range of health risks and not just those attributable to cigarettes.

DR. RIBISL: I'm Kurt Ribisl, and I voted B. And I do think we need to take a look at the wide range of health risks while still giving weight to the major causes of death and disability in this country related to these products.

DR. HUANG: Okay, all right.

Now move on to the next question, 3b: 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?

So discussion.

Yes, Dr. Giovino.

DR. GIOVINO: I think the health risks to individual users from using these products are a lot lower than the risks from smoking cigarettes. I was one of the experts who contributed to the Levy paper about 90% lower risk. I don't have huge reason to change my thinking. Obviously, I believe the respiratory diseases are relevant. From what I've read, I haven't seen any deposition of carcinogens in the lungs of smokeless users. Certainly, the chronic obstructive pulmonary disease effects seem nonexistent.

All that said, there are some diseases like pregnancy concerns and like nicotine in the brain that are relevant, but I do think the risks are a lot lower, and whether or not "substantially" depends on what the definition of "substantially" is. I did wonder why they didn't just pick the word "much" because "much" is one syllable versus four and it might have been easier to understand, but -- so I'll stop there.

DR. HUANG: Okay.

Other -- yes, Dr. Novotny.

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DR. NOVOTNY: I actually want to drift over into (c) a little bit on this just because, as we were instructed earlier, we need to consider the evidence about the statement, but we're then being asked to address the warning, which I thought you said we shouldn't do to begin with. But I would like to say that on (b), the word "substantially" seems superfluous. In other words, I think it's very difficult for us to say how much is substantial versus less than substantial versus excessive versus a little bit, let alone the people to whom this statement is directed, which is the general public.

And so I would have objections to using the word "substantially" in any form on this statement, and I don't think it's necessary. I think if we say that there are lower risks, that will be more than sufficient to describe the evidence that Gary and others and the Levy paper had lined up, but "substantially" just seems like it's unnecessary. But I do want to get some clarification that you are asking us to address the warning statement specifically in (c).

DR. HUANG: I do have a question. Would that -- including the word "substantially" change your vote? Would including the word "substantially" change your vote?

DR. NOVOTNY: Excluding it?

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DR. HUANG: Including it versus excluding it.

DR. NOVOTNY: Including it would affect my vote, but I have not yet voted, have I?

MR. ZELLER: Just a point of clarification. The question is worded this way because that's the nature of the request before the Agency in this application. This is an instance where we would ask you not to change the wording because you're going to further complicate an already complicated situation. We specifically worded this question this way and Dr. Novotny makes a fair point of FDA consistency between -- especially when we get into (b) and (c) together, where we're asking you to wade into, more directly, into the warning.

But consistency issues aside, I'd ask the Committee to consider what's in the quotes. If you want to talk about changing the wording outside of the quotes, that's a separate issue. But those words were chosen and the question was phrased this way for a specific reason because that's the nature of the issue before the Agency.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Yeah, I appreciate why "substantially lower" is there; I have no interest in changing it. I think it's a problematic adverb, and my graduate students would tell

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you I dislike adverbs at the best of times, and this is not a good time to be using one. I would also add that given that we know that there are very problematic pregnancy risks, a company that's interested in product stewardship and who also knows that their market base among women is especially low should have no problems of adding a warning label for pregnancy. And right now, I have to include pregnancy within my assessment of lower risk and especially substantially lower health risks.

DR. HUANG: Yes, Dr. Bickel.

DR. BICKEL: So I'd be interested in changing some portion of the rest of the statement because pulmonary and cardiovascular effects and their potential decrease on morbidity and mortality in the United States is of real importance. But I don't want to mislead the public and say, you know, or mislead anybody by saying everything is good. So I think having specificity helps. I think people understand that a little better. So if we could talk about substantially lower of the 50% of morbidity and mortality that was identified as contributing from conventional cigarette smoke that this might reduce, I would be very interested in that.

DR. HUANG: Dr. Ashley.

DR. ASHLEY: I'm going to kind of repeat what Mitch said

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in response to your answer, or your response, in that we're not asking you how the warning label should be changed. We're asking you specifically about this statement and your response to this statement. I think it gets to your question when you start looking at (c) and says, well, people understand that. And so try not to put those together too much.

DR. BICKEL: If I could just -- Mitch said we could consider changing the rest of the statement, so that was what I was trying to do.

DR. ASHLEY: Yeah, I think what Mitch said was if you wanted to change a "do" to a "do not" or those kinds of changes, not specifically changing the warning label in asking this question.

DR. BICKEL: Well, let Mitch speak for Mitch.

(Laughter.)

DR. BICKEL: All due respect.

MR. ZELLER: Dr. Bickel, the challenge that you would be adding onto the table by rewording the entire question the way you have, I would suggest to the Committee, though this is entirely the Committee's decision, might turn out to be less helpful rather than more helpful. You can always, as we said with the previous question, when the vote is called, each

member can always -- and we pay very close attention to the transcripts afterwards. You can go on at any length that you want to explain condition and qualify the answer that you gave, but you would -- a suggested change like that is significant to the issues before all of us, and I'd ask the Committee just to take that perspective into consideration.

DR. HUANG: Dr. Choiniere.

DR. CHOINIERE: Yeah. And I wanted to just add on to that, that your recommendations are not just the votes. Everything that you are discussing today -- so if you want to discuss what Dr. Bickel has suggested leading up to the vote, so we can hear more details about what your thinking is, then that would all be considered when we make a final determination.

DR. O'CONNOR: Dr. O'Connor.

DR. O'CONNOR: So going to -- I think where differences arise is, of this nature, the substantially lower overall health risks compared to cigarettes, and I would pose, almost as a devil's advocate kind of question, is for the other things that we're concerned about like pregnancy outcomes, like nicotine effects on adolescent brain development, do we have concerns that those effects are different for cigarettes versus

snus? Because if they are, then that suggests an additional risk of snus. If we think that they're not, then it's sort of a wash in terms of comparing the risks of cigarettes to those of snus. So I put that out there as a consideration in thinking about the overall weight of evidence.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Keeping the recommendation or exclusion of the warning separate from this statement, the statement says something that I think most of us would agree is that there is substantially less risk because of the cardiovascular and cancer risks that are associated with smoking, but would I be comfortable with this being on a label. That's another question.

UNIDENTIFIED SPEAKER: That's (c), isn't it?

DR. NOVOTNY: And that's (c). And so maybe we could go ahead and get --

(Off microphone comment.)

DR. NOVOTNY: Yeah. I don't know. I have a hard time separating them. I know they're asking us to do that, but it's really difficult for me to do that. I just think that, you know, it's easier to talk about the statement as a statement, but not as a warning label.

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DR. HUANG: Right.

DR. NOVOTNY: Because it's not a warning label.

DR. HUANG: Sure. We have Dr. McAfee on the line.

Dr. McAfee?

DR. McAFEE: I just want to amplify on this issue of actually the very specific wording in this, which says health risks to individual users are "substantially lower" than health risks from smoking cigarettes. And I think the issue is that that is not an accurate -- it's an accurate statement for adult cigarette users who would switch completely, but how this could be misleading as a statement with a caveat is that if the product, unless it is used as a complete substitute, the risks are not substantially lower. If you use -- half of your tobacco input is snus and half of it is cigarettes, you have not substantially lowered your risk, and since we know that is the majority pattern of smokeless use and of snus use in the United States, this has the potential to mislead. It also clearly would have the potential to mislead pregnant women or women who are of childbearing age, and if they could read this and think that their risks during pregnancy are substantially lower using snus -- and they may be lower, but there's no evidence that they're substantially lower.

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And I actually think, for adolescents who are contemplating whether to use nothing, cigarettes, or snus, it is misleading to them in terms of what are the risks that are directly attributable to them in the next, say, 5 years of their life. They would be lowering the risk of COPD and lung cancer, undoubtedly, but in terms of adolescent brain development, which is the primary immediate effect of any tobacco product, they would not be substantially lowering it. So I think caution, at least in terms of caveat, needs to be exercised.

DR. HUANG: Okay, thank you.

Dr. Fagan.

DR. FAGAN: I think Tim said it best. I mean, I'm looking at the statement here. Substantial accurately reflects the extent of risk reduction that actually occurs with a switch from cigarettes, and so I think that's the context in which this is being used and which we should also be considering as well.

DR. HUANG: Although we've been asked -- I mean, the statement stands as it is, so --

DR. FAGAN: Um-hum.

DR. HUANG: Dr. Giovino.

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DR. GIOVINO: When we wrote the work with Levy, the Delphi process, it was considered a lifelong user of snus and a lifelong smoker. The risks are very different. Well, actually, we don't really know precisely what the relative risks are for somebody who smokes Marlboros or Camel or Newport or whatever 10 years and then switched, or 20 years and switched. And that is a very good -- those are excellent points.

When I was looking at this label, and I will give some thoughts I had, and I'm looking forward to our discussion, but I'm much more comfortable with a warning label that says something -- well, first of all, one that says you only really get the health effects if you don't smoke and use this at the same time are the best way to get the health effects; and another one that would say, well, the risks for lung cancer and bronchitis and emphysema are a whole lot less if you use this product than if you smoke, I felt much more comfortable with that warning label. That said, I'd like us, before we vote, to have a sense of what are we voting on, lifelong use or a switching process here? And then if it's a switching process, are we assuming a process where they switch completely?

DR. HUANG: Dr. Tomar.

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DR. TOMAR: Although the caveat I would add to Dr. Giovino's comment is that, again, as we discussed yesterday, all the health outcomes we've looked at, you know, by necessity, we've tried to isolate them from the effects of smoking. So we looked at the exposure among either never smokers or current nonsmokers, but if we're talking about a product that's going to be primarily promoted as a switching -- as a way to quit smoking and move to this product, we don't have cohort data on health outcomes among those who, you know, smoke for 10, 20 years and then switched. Because, again, you're leaving people that have had long-term exposure to toxins and carcinogens and then move to a product that again still leaves them exposed to high levels of some carcinogens, we don't know that that's necessarily the same as a lifelong exclusive snus user.

DR. HUANG: Dr. Moynihan.

DR. MOYNIHAN: Michael Moynihan, Goodrich Tobacco. While I agree that there are concerns about the impact of dual use, I don't see anything in this statement that says to the user that mixing the two products together is better than anything else. The statement says, you know, the health risks to individual users for using these products are "substantially lower" than

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health risks from smoking cigarettes.

That's still true whether he's smoking the cigarettes or using this product or using them interchangeably. You know, the statement is saying that smoking cigarettes is worse than using these products; that's still true. The statement is still true whether it's not as good as stopping smoking completely, but it's still true that smoking the cigarettes in the dual use is what's causing the problem.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Yeah, I just wanted to respond to Gary's statement because he used a word in there that I think we need to be careful of, use the health effects of using snuff or snus. There are no health effects; it's not a health food. It's a less severe risk from a product that's addictive and carcinogenic. I know you didn't mean to say that there were health benefits, but I think --

DR. GIOVINO: I didn't say health benefits.

DR. NOVOTNY: No, you said health effects.

DR. GIOVINO: Yeah, well, that's -- I use that all the time.

DR. NOVOTNY: Well, but there are no health effects.

DR. GIOVINO: There are deleterious health effects, and

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there are good health effects.

DR. NOVOTNY: Okay. As long as we're clear on that.

DR. GIOVINO: Just for the record, I'm not claiming it's a healthy product.

(Laughter.)

DR. GIOVINO: In fact --

DR. NOVOTNY: I just wanted to be very precise on that because --

DR. GIOVINO: Okay, you know what? I'll use an adverb.

(Laughter.)

DR. GIOVINO: Or no, it's actually an adjective. Deleterious.

DR. NOVOTNY: I think it was an adjective anyway.

DR. GIOVINO: I said that.

DR. NOVOTNY: But the other part of this is, you know, putting the word "exclusive" use of snus products, would that make it any more appropriate to say that instead of exclusive use of cigarettes?

DR. HUANG: Exclusive?

Yes, Dr. Choiniere.

DR. CHOINIERE: I just wanted to make a clarifying point. I've heard a lot of comments and I don't know if, especially

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when Dr. Giovino was speaking, talking about more comfortable with this warning label versus that warning label, and that's not what the vote is on. The vote is just about the statement itself. As you noticed, the questions have been breaking the bigger question down into smaller chunks that we can then all put it together at the end. So discussion about whether it should be in a warning label comes later.

DR. HUANG: So it sounds like, I mean, we will vote on this question as it stands, but all the comments and discussion will be taken into account regarding concerns or better ways that it might be framed.

Mr. Henton.

MR. HENTON: Well, it's certainly justified. I think the prejudice on any tobacco use is showing up in this discussion. This focus is really on these products and the modified risk issue of these products. So I think sometimes we get all confused about any tobacco product, but I think we have to look at what the question is; it's focusing on the Swedish Match products, and that's the issue we're talking about here, not just tobacco use in general.

DR. HUANG: Yeah, Dr. Ribisl.

DR. RIBISL: Yeah, I want to support the Giovino-Novotny

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amendment that we add the word from "exclusively" using these snus products, because I think that's poor wording the way it is right now, and I think that would really tighten this up, make it easier.

DR. HUANG: Is that permissible or is that still not -- that is? Exclusively. So where -- how would it --

(Off microphone comment.)

DR. HUANG: Say that again?

MR. ZELLER: What I'm hearing is add the word "exclusively" between the words "from using" in the question, not in the setup, "from exclusively using."

DR. HUANG: "From exclusively using these snus products."

MR. ZELLER: Is that consistent with what you're suggesting?

DR. CHOINIERE: What I heard was, "Does the evidence support the statement that health risks to individual users that use snus products exclusively are 'substantially lower' than the health risks from those that smoke cigarettes exclusively?"

DR. RIBISL: Has to be "these snus products."

DR. CHOINIERE: "These snus products exclusively." Is that the amendment or a version of the amendment?

DR. HUANG: Yes, Dr. Fagan.

DR. FAGAN: I just want to clarify, again, we can't change the word "substantial"?

MR. ZELLER: Right.

DR. FAGAN: Okay.

DR. HUANG: Yeah, I know. Because that's the issue. That's the word I have a hang-up with.

MR. ZELLER: It's our plea with you for the sake of being able to move forward directionally, given the request that's before the Agency.

DR. HUANG: Okay. So, again, yeah. I have that concern with "substantially."

Yeah, Dr. Giovino.

DR. GIOVINO: I did have my hand up, but I want to defer to Dr. Boffetta.

DR. HUANG: Okay, Dr. Boffetta.

DR. BOFFETTA: Just to go back to what Dr. Giovino said earlier. Did you imply that there are no data on switchers from tobacco to snus? Because there are about five or six studies that provided risk estimates for a variety of conditions, mainly --

DR. GIOVINO: Switching?

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DR. BOFFETTA: Yeah, yeah.

DR. GIOVINO: Decade of switching?

DR. BOFFETTA: No. I mean, comparing those who continue smoking and those who switched in the same study.

DR. GIOVINO: And do they give relative --

DR. BOFFETTA: Yeah.

DR. GIOVINO: Do they give relative risk for --

DR. BOFFETTA: And roughly speaking, the relative risk is about half. I mean -- and then there are other studies, including some of the same studies that provide also comparison with those who stopped smoking completely and clearly, the risk for switchers is a bit higher than those who quit, for most of the outcomes, particularly cardiovascular disease. The relative risk is in the order of 1.1 or 1.2, I mean -- but compared to those who kept smoking, the relative risk is in the order of 0.5.

DR. GIOVINO: Thank you, thank you.

DR. HUANG: Yes, Mitch.

MR. ZELLER: Just a request. So if the Committee agrees with this rewording, and I'll just put this consideration on the table, each voting member can make a decision for him or herself. If you accept this change, then we would ask you to

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consider, in the comments that you provide when you explain your vote, to address the issue of nonexclusive use. Just in your comment, okay? We know that it seems to be the will of the Committee that the vote wants to be on exclusive use, but we would ask each member to consider addressing the issue of non-exclusive use in the context of this question, just in your comments accompanying your vote.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Yeah, I just -- I guess I could make this clear after we vote, but I just want to make it clear now that I very much like the inclusion of the word "exclusively." The problems for me with -- that would not make me accept the statement or vote yes to the statement is the word "substantially" and the fact that we're including all health risks. I'm not objecting to those things. I'm just telling you what the problems are for me, and I would point out that we're not the only group to consider the word "substantially."

There was this European group, I don't know how to pronounce the acronym, S-C-E-N-I-H-R, in 2008, and I'm quoting now, "Overall, therefore, in relation to the risks of the above major smoking-related diseases and with the exception of pregnancy," -- which I think is really important -- "smokeless

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tobacco products are clearly less hazardous, and in relation to respiratory and cardiovascular disease, substantially less hazardous." So I take that to mean when they say clearly less hazardous, there's less risk; but for only these two conditions, respiratory and cardiovascular disease, is it substantially less risk. That's very meaningful for me.

DR. HUANG: Yes, Mitch.

MR. ZELLER: Very fair point. And I think that that will very quickly get us into the next question, because I think so much of the comments that have been raised here take us into a discussion of (c). So I would suggest that we try to resolve (b) and then get on to (c).

DR. HUANG: Okay. And, again, I would just reiterate what Dr. Eissenberg said. I mean, I've got the issues with the term "substantially" without any more specificity regarding specific health outcomes.

Okay, Dr. Ribisl, and then we'll vote.

DR. RIBISL: Yeah, just to be clear. They didn't -- did they look at lung cancer, the primary cancer, and they didn't say substantially lower risk of lung cancer?

DR. EISSENBERG: No, I think that was included within respiratory disease.

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DR. RIBISL: Okay.

DR. EISSENBERG: So there's a group of respiratory diseases --

DR. RIBISL: Okay.

DR. EISSENBERG: -- and a group of cardiovascular diseases, but there were other risks.

DR. RIBISL: Yeah, so there's going to be lung cancer, COPD, a whole series of other -- I just want to make sure that they're not excluding cancers.

DR. HUANG: Okay. So are we ready to vote?

We're going to vote on Question 3b: Does the evidence support the statement that health risks to individual users from using these snus products exclusively are "substantially lower" than the health risks from smoking cigarettes?

Please press the button on your microphone. Again, yes or no or abstain.

(Vote.)

DR. HUANG: Good? Okay. Everyone has now voted. The vote is now complete. The vote is 4 no and 4 yes.

Okay, Dr. Ribisl voted yes; Dr. Eissenberg voted no; Dr. Giovino voted yes; Dr. Huang voted no; Dr. Fagan voted no; Dr. O'Connor voted yes; Dr. Bickel voted yes; Dr. Novotny voted

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no. Okay.

So now we'll go around the table and have everyone who voted state their name, their vote, and any comment or rationale.

Dr. Novotny.

DR. NOVOTNY: I voted no because of our consideration of all health effects, and I just didn't feel comfortable with the word "substantially" put in there, even if it's exclusive use, either way.

(Off microphone comment.)

DR. NOVOTNY: That was Tom Novotny.

DR. BICKEL: Hi, I'm Warren Bickel. I voted yes because of the opportunity to actually potentially impact major sources of morbidity and mortality in the U.S. population by the exclusive use of this product. I think I'm concerned about dual use consequences, which we don't really know about, as well as pregnancy and developmental consequences, as well as perhaps unknown consequences in other racial groups, which there is precious little data about.

DR. O'CONNOR: Richard O'Connor. I voted yes. I thought the evidence, particularly for the major smoking-related diseases, is enough to support that statement. With regard to

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mixed use or partial substitution of cigarettes, I think the evidence is less clear. But based on the exclusive wording, I would vote yes.

DR. FAGAN: Pebbles Fagan. I voted no because I also have a problem with the word "substantially lower" as it relates to all health risks and doesn't appear to be any evidence that suggests that the pregnancy outcomes related to snus would be any different from any other tobacco-related outcomes.

DR. HUANG: This is Phil Huang. I voted no primarily because of the inclusion of the word "substantially" and no specificity regarding specific health effects and having it apply generally to health risks.

DR. GIOVINO: This is Gary Giovino. I voted yes because, on the weight of the evidence, the weight of the public health impact, I do think it would be substantially lower for individual users who exclusively use this. That said, my caveat is that there needs to be sufficient warning about some potentially very deleterious health effects.

DR. EISSENBERG: This is Tom Eissenberg. I voted no because the word "substantially" is applied to overall health effects, in my view, and is not applied to specific health effects. You take lung cancer, for example. I think

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"substantially" is absolutely the right word. You take some other health outcomes, and it's not. And a responsible company, I think, would isolate pregnancy and have a health warning about it.

DR. RIBISL: Hi. My name is Kurt Ribisl, and I voted yes. And I want to make -- just in general, I do think that the evidence is pretty clear that they present overall substantially lower risk. I want to make three points.

Number one, as I showed yesterday, the reading level, reading grade level, is extremely -- is way too high for the proposed warning. I think FDA should not allow any warning that's over an eighth grade reading level because literacy issues are real. And I don't know if it's too late in the process that you could reject it and ask them to resubmit with a different wording, possibly even "much," but the warning label is not adequate.

Number two, the broader set of warning labels used for smokeless products are completely inadequate, and I know we'll get to it next, but they need to be pictorial, need to depict a much wider array of health effects. You have the authority to do this at FDA, and you should exercise it.

Number three, I think you can still care about the wide

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array of health effects and still endorse the idea that there is a substantial reduction in risk. The number -- you know, cancer and heart disease are the top, top killers of women in this country, and I think you can -- and the risks are substantially lower using these products exclusively compared to exclusively smoking cigarettes, and that's my main reason for acknowledging that.

Thank you.

DR. HUANG: All right.

Okay, we'll move on to the next question, 3c, which is: Does the proposed warning statement adequately communicate the potential health risks to individual users of these snus products?

And the proposed warning statement is "Warning: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

Dr. Giovino.

DR. GIOVINO: Well, I have several issues with this statement. First is one for our government. I think our government has the statement on cigarettes wrong when it says warning, quitting smoking now greatly reduces serious risks to your health. It should say good news, or it should say, hey,

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look up, heads up or something, but not warning. Likewise, I think the word "warning" on this may be misappropriated. That said, I think the way it's worded is too dismissive of the health risks. You know, "No tobacco product is safe, but" and any time I read a "but" statement, it always negates the first half of the statement. So I think this statement is far too dismissive in and of itself of the health risks.

I think I would agree with what's been said, that a statement saying substantially lowers the risk of lung cancer, other respiratory diseases, and whatever else we want to add to the list. And I do think that this statement fails to communicate that if you do this and continue to smoke, you aren't doing yourself much good. And I think it clearly fails to communicate concerns about pregnancy and issues like that.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: As I suggested earlier, I don't think that this is a warning. I actually think it's an advisory, and it's probably not what is intended. A warning should reflect the risks that, you know, it needs the specificity Gary described. But if anything, I think there needs to be more specific warning risks on the package than this change.

DR. HUANG: Yes, Dr. Eissenberg.

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DR. EISSENBERG: While we're rewording questions, I object to the way this is worded because it says, "Does the proposed warning statement," blah, blah, blah. It doesn't say does the evidence support, which would be critical. It doesn't really matter what I think about the proposed warning statement; it matters what the evidence is. And unfortunately, because of the flaw I pointed out yesterday in the absence of the word "warning" prior to the stimulus that was presented in the perception study, we don't have any evidence about the proposed warning statement. So the answer, therefore, must be no. There is no other answer. The evidence doesn't support whether or not the warning statement adequately communicates.

DR. HUANG: Would that be an acceptable modification that perhaps the question does include "the evidence"? "Does the evidence support that the proposed warning statement adequately communicates the potential risks to individual users of these snus products?"

Would that address your --

DR. CHOINIERE: Well, you could change the question in that manner, or you can provide an explanation in your vote. I don't think the question was related to the evidence that was provided in terms of what consumer understanding was. The

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question is more, does this warning and the warnings that would exist on these products convey the risks associated with the use of this product.

DR. EISSENBERG: But on what basis are we supposed to answer that question?

DR. CHOINIERE: Well, we know that --

DR. EISSENBERG: We're scientists, so clearly the answer is evidence.

DR. CHOINIERE: Well, from your perspective, you would say no, it doesn't, because they haven't provided evidence, correct? I don't want to put words in your mouth.

DR. EISSENBERG: Well, but to the question "Does the evidence support," I could answer no. To this question, this is a non-question for a scientist. Does the -- I don't know. Based on what, would be my response.

DR. HUANG: It actually might add more strength to the question if we put --

DR. CHOINIERE: Yeah, I defer to the Committee for wording the question. I didn't mean to --

DR. HUANG: Sure. Is that -- what you're saying, that that might be acceptable?

MR. ZELLER: This is the Committee's decision, not FDA's.

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So if you're asking for just a simple, an advisory view from the Center, I think we would be fine with it.

DR. HUANG: Again, it might provide more --

MR. ZELLER: Does the evidence --

DR. HUANG: Support --

MR. ZELLER: -- support --

DR. HUANG: -- the proposed warning.

MR. ZELLER: -- that the proposed --

DR. HUANG: Proposed warning, yeah.

MR. ZELLER: -- statement adequately communicates.

DR. HUANG: Um-hum.

Yes, Dr. Moynihan.

MR. ZELLER: Tom, how about "does the available evidence"?

DR. HUANG: Okay. So does the available evidence, or does available --

(Off microphone comments.)

DR. HUANG: Okay.

MR. ZELLER: Okay, okay. Then just the evidence.

DR. HUANG: Just the evidence.

Okay, Dr. Moynihan.

DR. MOYNIHAN: Fortunately, I don't have to vote on this question because one of the -- my first reaction to this

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statement was that this is asking a question which is very different than what is used in all the other systems of warnings on tobacco products in that we don't rely on any single statement on a tobacco product to adequately communicate the potential health risks to users of those products. And we have multiple warnings and rotations of warnings, and we don't have a comprehensive, you know, warning that appears as one single statement.

DR. HUANG: Dr. Choiniere.

DR. CHOINIERE: I can clarify the rationale behind this question gets at, I think, Dr. Giovino's point where the warning does have some information about risk. It says, "No tobacco product is safe, but." And so our question is does that statement convey to -- that there are risks associated with the use of snus products?

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Yeah. I would second that, but also point out that that's the point that many have made is, this is the only -- well, addiction is a health risk, but this is the only risk statement that this company has come forward with, and as Dr. Eissenberg said earlier, and as Dr. McAfee said, there are at least two other major concerns, one being pregnancy and one

being telling people that if they really want to get the benefits, they need to just get off cigarettes.

DR. HUANG: Dr. McAfee on the phone, do you have a comment, a question?

DR. McAFEE: Yeah, just a quick addition on these lines. I tried to make this point yesterday, but I don't think it was communicated adequately. It was that in the study that Swedish Match did, what they inventoried when they asked people their take-away from this message was simply a subjective measure of whether they thought they understood it. And what that doesn't tell us is whether -- what specific influence this warning statement had on their actual understanding.

And I think you would have to ask -- and it wasn't a qualitative -- a quantitative issue. It's -- you would have to ask people, for instance, if we were worried of this having some negative effect on people feeling like dual use was fine and that that would lower their risk. You'd have to ask them -- of course, people that saw this statement or didn't see the statement, you know, if you're a user, how do you feel about -- what do you think would happen to your risk if you stopped using half the cigarettes and used snus instead, what effect would that have on your use, and give people a choice.

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And you could ask women of childbearing age questions about, after reading this statement, what do you think would happen to your risk during pregnancy. Or you could ask adolescents or young adults who are nonusers, how do you think this affects your risk over your lifetime of using snus. And so the survey only is a subjective inventory of people's own self-assessment of whether they understood it or not.

DR. HUANG: All right, thanks.

Dr. Bickel.

DR. BICKEL: So it strikes me that when we're adding a product or having a product out there that has definitive risk -- and we've talked about that -- but less risk, clarity is of key. And I think it's the obligation frankly of the manufacturer to be very clear. And I think I would like to see some sort of statement, label, whatever you want to call it, that if someone read it, they'd say, I want to decrease my chance of cardiovascular disease and pulmonary disease if I use it exclusively, but if -- you know, they'd be able to, after they read that material, endorse a statement that I recognized I would be not at reduced risk for those things if I smoke or if I was pregnant or if I was -- and let's not forget about addiction as one key health outcome that's highly negative,

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that allows people to keep on being stuck in this habit.

So I really think it's really incumbent upon the company to be clear, because if it's just a general health warning, I know how many people in America will respond to it. Good times, right? I'm going to use this while I'm smoking or when I can't smoke, when I'm pregnant. A young person, not going to worry about the adverse consequences of being addicted to nicotine for a substantial portion of their lives.

So I really think that we really have to ask the companies -- you know, they talked about stewardship of the product yesterday. I think that's what I'm talking about, stewardship of the product. And the only way that can really be done is if it's a central part of their product that they make people clear of what the concrete risks are and what -- you know, how they're reducing some risk if they use this exclusively.

DR. HUANG: Okay. Do you think we're ready to vote? And maybe any other comments might come out during the explanations of the vote. Anyone opposed to going forward with that now?

(No response.)

DR. HUANG: Okay. So we'll now begin the voting process for Question No. 3c: Does the evidence support that the proposed warning statement adequately communicates the

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potential health risks to individual users of these snus products?

Press the button on your microphone that corresponds to your vote.

(Vote.)

DR. HUANG: Okay.

Everyone has now voted; the vote is now complete and locked in. The record, it's 8 noes. Dr. Ribisl, no; Dr. Eissenberg, no; Dr. Giovino, no; Dr. Huang, no; Dr. Fagan, no; Dr. O'Connor, no; Dr. Bickel, no; and Dr. Novotny, no.

Now that the vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and any comments or rationale.

DR. NOVOTNY: This is Tom Novotny. I voted no because I don't think that the warning, as stated, communicates the potential health risks. I agree with Dr. Bickel that a very clear set of warnings are really necessary, and this is inadequate.

DR. BICKEL: I voted no because it was inadequate in describing the risks. We don't have evidence of how those warnings will be able to be interpreted. And I think that for stewardship of the product, the company should be very concrete

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about the potential risks in any such statement.

DR. O'CONNOR: Richard O'Connor. I voted no because the proposed wording was not clear about the specific risks of that product.

DR. FAGAN: I voted no, one, because the evidence presented did not include adolescents in the study. The warning statement was not tested as proposed. And then I think they really should be specific to the various health outcomes. And then the other component is that this message is -- will be problematic for dual users.

Pebbles Fagan.

DR. HUANG: This is Phil Huang. I voted no. Similarly, I didn't think the warning was clear. It does not adequately convey the actual risks for the specific health conditions that are relevant. I also have a problem with "substantially" also.

DR. GIOVINO: This is Gary Giovino. I voted no for several reasons. I think the product, or the statement, is dismissive of the health risks. I do think it wasn't tested with the word "warning" and that could theoretically very easily change the dynamic. As Dr. Fagan pointed out, it wasn't tested among adolescents, and there are many other concerns that the consumer needs to be made aware of.

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DR. EISSENBERG: This is Tom Eissenberg. I voted no because the study that provided the data that addressed this point was fatally flawed because of the stimuli that were presented, the populations that were tested, and the outcomes that were measured.

DR. RIBISL: This is Kurt Ribisl. I voted no. I have two comments. One, I mainly said this because the warnings needed more -- specifically address the specific health risks, and this was too general. Number two, I agree with Dr. Eissenberg that the consumer perception study was flawed, it should be rejected, and I think Swedish Match needs and any other future applicant really needs to use data on the actual exact wording that they're proposing for either a message or a warning revision going forward.

DR. HUANG: All right. Okay. We're finished now through Question 3. We had hoped to finish through Question 4 before lunch. Are people okay moving forward or want to get -- yeah, Dr. Novotny.

DR. NOVOTNY: Yeah, this is a leftover question from yesterday, and it was briefly addressed in the earlier presentation by Swedish Match today and it has to do with the environmental impact statement. I had asked for this, and I

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understood that this was perhaps coming today in some way before we go on to this last question and wrap up, would be --

DR. CHOINIERE: We can have someone discuss the environmental impact statement process.

DR. NOVOTNY: Uh-huh.

DR. CHOINIERE: I don't know for sure that -- is Kim on the phone? Okay, we have Dr. Kim Benson on the phone who can talk briefly about this.

DR. NOVOTNY: Okay.

DR. BENSON: Yeah, hi. Yeah, this is Kim Benson. So if I heard correctly, after -- I had to leave yesterday. What you had brought up was concern about the throwing away of the pouch of the product and what might happen to that. And I guess the easiest way to say it is that the environmental assessment is considered, for lack of a better word, a cradle-to-the-grave document. So it will address everything from the manufacture of the product, the use of the product, and then the disposal from use of the product. And then that will address what we believe might happen to it being either recycled or thrown out. Or I heard Swedish Match say today that the tin is intended to take the used sachets, to be put in there, and then the tin itself would be thrown away, so we will address all of that in

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the EA.

DR. CHOINIERE: Dr. Novotny, did you have specific questions about the EA? The EA is the responsibility of -- well, Kim, can you describe whose responsibility the environmental assessment --

DR. BENSON: Right. At present, within CTP, the EA is actually the responsibility of CTP. NEPA itself puts that responsibility on the federal government. The federal government should look at the environmental impact of their actions. The FDA has gone a little further in 21 C.F.R. 2540; we actually put the onus back on the regulated industries. We say you come to us, asking us to take an action; we therefore say to you, you have to include an environmental assessment in your request for our action. At present, though, CTP tobacco products are not within 2540. We have a draft roll-out that puts us in there, and once that's finalized, it will then be -- the onus will be on the industry. So until that time, the onus is actually on us to do that, although I think I said yesterday that Swedish Match did include an environmental assessment in their application. We are just taking that information and our own research and our own information and writing the environmental assessment ourselves.

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DR. NOVOTNY: Okay, I understand that there's still some decisions to be made about the section on the NEPA accommodation that is necessary for approval of an application, so when does that happen? I mean, is that something that is going to be considered in terms of this application specifically, or is it not going to be part of this one specifically?

DR. BENSON: Okay, two points. One is we don't actually approve; we authorize our applications. But second, unlike everybody else that you've heard from, the epidemiologists and the behavioral scientists and the clinicians and toxicologists and chemists and all of that, who -- all of those reviews factor into one major decision about the authorization. The environmental assessment -- the decision on authorization is not contingent on the environmental assessment, so the environmental assessment kind of goes on its own tangential side pathway. It must be done in order for us to do -- to take an action, but it doesn't have to come to a decision, a finding of no significant impact in order for us to make a decision.

So what's going on right now is my scientists are working on the environmental assessment and writing that document and deciding then whether or not that leads to a finding of non-

significant impact, a FONSI as it's called, or whether that leads to the need to do an environmental impact statement. And, again, that's ongoing, and it will be ongoing through the timeline of the rest of the review.

DR. NOVOTNY: Okay. I'll be very interested in hearing about that, just because this morning Swedish Match did indicate how the product was intended to be disposed. But, you know, reflecting on how cigarette products have been disposed of in the past, I think it's at least worth exercising the sort of commitment that they have made towards product stewardship in the manufacturing as well as the cradle-to-grave aspect of the product, that this should be considered. Because there may actually be health effects, human health effects from even the disposal of these products.

Thank you.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: I just want to quickly go back to a comment Dr. Fagan mentioned, which she mentioned that they didn't -- the industry didn't study kids. This is a little bit of a tricky issue, and I just think a really quick -- and if it takes too long, we should do it, but industry is in a place where they've been criticized for studying kids and also

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they're a very vulnerable population.

On the one hand, you kind of really also want to hear, because it does affect future use and you do want to know issues related to youth. I wonder -- I ended up leaning toward I would almost rather then not study kids, but -- due to some of the past concerns I've had. But I wonder if other people think that that needs to be part of this broader package that comes before this committee. And if you feel this is out of line, we could discuss it at the very end --

DR. HUANG: Maybe -- yeah, that might be something that we can bring up at the end.

DR. CHOINIERE: Well, actually there's a question later --

DR. HUANG: Yeah, exactly.

DR. CHOINIERE: -- that you could discuss that, and that would be on Question 5b, other types of studies that could be useful to assess behavior.

DR. RIBISL: Yeah, okay. We'll do the kid issue there. Thanks. Sounds good.

DR. HUANG: Okay.

DR. CHOINIERE: Might I make a suggestion?

DR. HUANG: Sure.

DR. CHOINIERE: I have a feeling this Question 4 will be a

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little bit easier to tackle because it's really just general recommendations; there's no vote. And so, if possible, if we could tackle this question --

DR. HUANG: Sure.

DR. CHOINIERE: -- before breaking.

DR. HUANG: Sounds good. We'll proceed through 4 so at least we're over halfway then, by lunch. So Question 4 isn't -- yeah, really. It's just a question for the Committee:

Assuming that the behavior of the U.S. population does mimic those in Sweden with respect to the use of snus, 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 the Swedish products are comparable to the exposures to individual users of these snus products, or would knowledge about other characteristics of the tobacco product be needed to determine that the health outcomes would likely be comparable?

Okay, comments.

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Dr. Giovino.

DR. GIOVINO: So I thought the question I raised this morning, which was nicely answered, showed a lot of the same chemicals. What's the matter? Did I -- were you first?

DR. DJORDJEVIC: No, no, no.

DR. GIOVINO: Oh, I'm sorry. Okay.

I was wondering about biomarkers myself, and I would love to see some biomarker comparisons. And yesterday I raised the issue of do we know what the abuse liability of cigarettes are in Sweden compared to cigarettes in the United States, and quite frankly, my logic there was if cigarettes here, you know, provide a greater kick, to use the industry's own terms, than cigarettes in Sweden do, and theoretically, if snus in Sweden provides a bigger theoretical kick than snus in America, then you're not going to have the health effects in America because people aren't going to use snus as much. So I would like that sort of issue, which is kind of get down and deal with addiction issue. I think my advice to FDA would be to try to grapple with that or try to understand that.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: Well, there are several issues which precludes comparison between two countries and the use of the

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products. The first, a homogenous population in Sweden versus a very heterogeneous population here in the United States. Then homogenous product in Sweden -- I mean, smokeless tobacco products versus very heterogeneous products here in the United States. Then dual use in Sweden is minimal while it is very substantial in the United States. And then, because of that dual use, duration of use, which Dr. Giovino was talking yesterday, because the major risk factor for cancer is duration of use. So these are all the issues. And then marketing strategies, because in this country it is marketed, you know, when you cannot smoke or with different messages. So these are all major issues which would preclude comparison.

DR. HUANG: Thank you. Yes?

DR. CHOINIERE: I just want to focus us back on the product because Question 4 is about the product. Question 5 will be about the issues that you just raised.

DR. EISSENBERG: That's odd, because Question 4 is asking about the products, and then it talks about exposures and exposures interacts with use and use is user behavior.

MR. ZELLER: So, Mirjana, can I ask you a question in light of the factors that you put on the table with your comment? So in light of those considerations, would you like

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to address the question in 4, which is confidence that the health outcomes observed in Sweden would also be observed in the United States?

DR. HUANG: Is that a question?

MR. ZELLER: Yeah, it's in light of the consideration/differences/concerns that were expressed. How does that go to the question that we're looking for a discussion on, not a vote, and that is confidence that the health outcomes observed in Sweden would also be observed in the U.S.

Or any member of the Committee.

DR. HUANG: Dr. Eissenberg.

DR. EISSENBERG: Yeah, I certainly don't want to speak for Dr. Djordjevic, but I had listed the exact same issues that she had and thought that they interacted with potential health outcomes. So, for example, if people switch to Swedish snus and then for whatever reason determine in their heads that Swedish snus is no different than any other smokeless tobacco product and then switch to U.S. smokeless tobacco product, which there is no U.S. smokeless tobacco product, as I understand, available in Sweden, then you could expect to see differential health outcomes, something different than what you

would see in the Swedish experience.

The abuse liability of the product and its relative abuse liability to cigarettes could also have an impact on exposure. And then the different populations, I think, is critical because different populations might use the product differently, and then you would expect to see differential health outcomes, where you have a homogenous population in Sweden and so you only are going to see, I would guess, one set of health outcomes.

DR. HUANG: Yes, Dr. O'Connor.

DR. O'CONNOR: Yes. So I resonate to the point that you're raising. We're missing the first sentence of this whole thing is, assuming the behavior of the U.S. population does mimic those of Sweden with respect to the use of snus. So I think there are objections being raised to the premise of the question, which are -- but we're being asked to set those objections aside and say if you assume that people in the U.S. are going to behave like Swedes do, then would you, on the basis of what we've been given in terms of health effects, would you expect to see the same outcomes? I think we're arguing around the premise rather than actually answering the question that's posed.

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DR. HUANG: Dr. Bickel first, then Dr. Fagan.

DR. BICKEL: So to understand whether we're going to have the same health outcomes, we're going to have to know to what extent the price differential that historically occurred between snus and conventional cigarettes will be observed in the United States, because that may be an important factor in its uptake and use. Additionally, it strikes me that the more recent increases in price in snus effect on the population consumption of snus will indicate what happens when that changes. And you may think that price is irrelevant from considerations from the health effects of substances, but we know that addiction is a context-dependent phenomena, right?

It occurs in a certain context, and when certain products are highly available at a low price, the probability of addiction increases. So we cannot dissociate addictive processes from the context of its use, which includes price and relative price of tobacco products.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, this is a question for FDA. Why are we being asked to make this assumption about the behavior of the U.S. population mimicking those in Sweden? Because the discussion here is revolving around the fact that we can't make

the assumption, so I'm just wondering why are we being asked to make that assumption with regard to this question?

DR. CHOINIERE: The application contains data on health outcomes from the use of snus and that those outcomes were based on the behaviors observed in Sweden or in countries that use snus. And so we are asked by the Applicant, in some regards, to presume, well, if those behaviors are observed here in the U.S., then we should see a comparable change in the death and disease from the use of tobacco. The Applicant provided some information about the similarities between these products and those used in Sweden, and the question here -- and it's unfortunate the word "exposures" appears in here. It probably should have said harmful and potentially harmful constituents.

The question here is, is that enough information about these -- not that that's enough, but what information would you need to know, and perhaps it was addressed this morning in the presentation from Swedish Match. What information do you need to know about the products that would be sold here and the products that were traditionally sold in Sweden to be confident that they are likely to lead to the same health outcomes under the condition that people use them the same?

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DR. HUANG: Okay. Dr. Boffetta, Dr. Novotny, and then Dr. Ribisl.

So Dr. Boffetta first.

DR. BOFFETTA: Yeah. When I had similar concern, I mean, we know that the U.S. population does not use these -- well, we know that the U.S. population does not use smokeless tobacco products the same ways the Swedish population does. Whether they would use these particular products like the Swedes or like they use all the other products, obviously we don't know that.

It's a reasonable assumption to say that there is no such mimic effect that the first sentence, you know, refers to. I really think that, in a way, if the U.S. were exactly identical to the Swedes, one would expect the same effects perhaps, but we know that this is not the case. So, to me, it doesn't really make much sense, you know, to make this --

DR. HUANG: I think they're hearing a lot of discomfort with that assumption and that we're saying it really -- okay, Dr. Ashley.

DR. ASHLEY: Let me give it a try. You guys are trying to answer Question 5, which we will get to, and we really want answers to Question 5, but we knew you were going to go to

Question 5, so we tried to stop you from going to Question 5 and actually answer Question 4, which we're also interested in also. So to try to stop you from going to the differences between Sweden and the U.S., we said please assume that all those differences you're talking about now are the same and let's talk about the product a little bit and what we should be looking for in the product. So that's why we're trying to get you -- and that's why the first sentence is there, to try to get you to talk about the product and not talk about all these things, which is actually Question 5.

DR. HUANG: Okay, Dr. Novotny.

DR. NOVOTNY: Well, actually, the first line of number 4 is assuming that the behavior of the U.S. population mimics those in Sweden, but there's so many other factors. Sweden has a healthcare system, (a). The U.S. is a bit more piecemeal. And (b), it's a different population. There may be genetic differences that lead to changes in health effects. There may be, you know, besides behavioral differences, just issues of socioeconomic status that are significant confounders, I think, in terms of health outcome, so I don't think -- you know, you can limit the discussion to behavior. It's just these are two different places.

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DR. CHOINIERE: And that is fine. If the Committee is more comfortable discussing it in this manner, then we welcome that discussion.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: I think one of the key things that FDA needs to understand in the Applicant's data is sort of how the product travels from leaf to lip, okay? And so you've got to follow it through the whole supply chain. So you have the growers, the curing process, the manufacturing process. It sounds like, from what I heard this morning from Swedish Match, that that's identical; the products in Sweden are identical to the ones in the U.S. from up to that phase in the supply chain. Then it goes to a wholesaler, possible distributor, then to a retailer, and then to the end consumer, all right?

So you've got to understand what are the differences and similarities in all of these aspects of the supply chain. One of the issues that was raised in one of the public comments by Dr. Greg Connolly at Northeastern University was the issue of refrigeration. I raised it yesterday. There was data -- so Dr. Connolly had mentioned -- and I think I've got the expert sitting right next to me, so I'll try not to talk, just like I would never talk about foreign policy sitting next to Henry

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Kissinger. But the issue of, sort of, degradation and nitrosamine levels going up if there's not refrigeration. So Greg Connolly presented, said that there was an issue on this, and is there going to be refrigeration or not in U.S. stores. I've seen it in several U.S. stores because point of sale is my research area.

But Swedish Match presented data that you don't need to refrigerate the product but that they like to because of greater freshness, but it sounds like it's possibly maybe not a health issue. But I think you need to understand all of those differences across the supply chain from leaf to lip, as you think through this.

DR. HUANG: Other comments?

(No response.)

DR. HUANG: All right. So I think we're through with the discussion of No. 4. And probably many of the issues that come up in 5 will cross over with 4, and that's probably where we'll get the meat of that.

So we will -- it is now 12:05. We will take -- let's see.

UNIDENTIFIED SPEAKER: Are we going to vote?

UNIDENTIFIED SPEAKER: No, there's no vote.

DR. HUANG: No vote, yeah.

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So we will break for lunch. Actually, we're going to probably take a 45-minute break this time. And so we would meet back here at 12:50. So, Committee members, please remember there must be no discussion of the meeting topic during lunch either amongst yourselves or the press or with any members of the audience. And, again, we will reconvene in this room at 12:50. Please take any personal belongings you may want with you at this time.

Thank you.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)

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

(12:56 p.m.)

DR. HUANG: Okay, we'll go ahead and get started back again. And just for Committee members that have traveled, there's a taxi sort of thing going around to sign up, regarding your flights and travel to the airport. Okay.

Well, welcome back. We are now up to Question 5, right? So Question 5 is: 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 tobacco products:

The question: Discuss the evidence regarding the likely impact of these ten snus products on tobacco use behaviors among tobacco users and non-users.

5a is: Does the Committee believe that the epidemiologic data from Sweden concerning tobacco use behavior provide relevant information on:

- i. The likelihood that current tobacco users in the U.S. will switch to the use of these snus products?
- ii. The likelihood that non-users of tobacco in the

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U.S. will initiate the use of these snus products?

So those are going to be the votes. So let's open it for --

(Off microphone comment.)

DR. HUANG: Okay, Dr. Bickel.

DR. BICKEL: So this fundamentally goes to the question of abuse liability, and no data was presented that addresses abuse liability. The population data and their increase in the use of these products in Sweden may be suggestive of a very high abuse liability, because it seemed to go up. Now, there are other potential explanations, and there aren't sufficient data to distinguish between them. So I'm concerned that we don't know about the relative abuse liability of these products. And that is something that's necessary in order to try to answer these questions.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Agreed. And there are cultural issues. The product in Sweden was a gradual product that was in the fabric of the society. This is a product that is a variant of another product that is in the fabric of our society, and I don't know how that will be received.

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And the other issue is just marketing. For one thing, share of voice is an issue. You know, will the message get through with all the other messages being out there about various tobacco products?

And the third thing is the taste. If Americans have a taste for smokeless products that have existed for a long time, will they like the taste of the new products?

DR. HUANG: Mr. Henton.

MR. HENTON: I think it goes to the fact that if the label doesn't reflect something different, I don't know the likelihood that the U.S. consumer is going to read the data. I think that's the reason that the label change would be an inducement to switch.

DR. HUANG: Dr. Swauger.

DR. SWAUGER: I guess I have a similar view in some ways. I look at the Swedish story, and I think it sort of suggests what's possible here, what might be possible here. I share some of the concerns. I think I've heard, though, that unless somebody's actually going to speak to the issue in public, I'm not sure that anybody would notice. I don't think that it's a given that people will switch if they're not aware. If the government is not driving a migration strategy and Swedish

Match is going to remain silent, I think it's an issue.

DR. HUANG: Other comments?

Dr. Bickel.

DR. BICKEL: So one of the things that is also, I think, important is to look at relative abuse liability in the special subpopulations. So in the United States there's a greater prevalence of tobacco use among low SES individuals. It actually seems very proportional with -- you know, the lower the SES, the greater the prevalence of smoking. We also know that, as I mentioned yesterday, that low SES groups are more likely to initiate smoking, and they're more likely to find it hard to quit smoking.

And given the very small range of socioeconomic status in Sweden relative to us, I don't think we have a true understanding of the consequences that the addition of this product will have on participation and use of a variety of tobacco products.

Could it make total tobacco consumption greater in some subpopulations? Maybe. Could it reduce it? Maybe. But we don't have any data about the relative abuse liability that would inform such a decision. And given the differences in subpopulations, I think studies -- which is a little bit of the

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(b), right? Some studies on abuse liability and looking at some specific subpopulations would greatly inform all of these questions.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah. I wonder, Dr. Bickel, could you sort of clarify what you're looking for in ideal abuse liability? So if you have a product that is a lower-risk product -- and we've seen on the market several products come on. You have combustible dirty cigarettes that have a pretty high, extremely high, abuse liability, not, you know, gold standard. I don't know, whatever you want to call it. And then you take these other products that are poor substitutes, that have lower abuse liability and have weak adoption. So are you looking for an abuse liability that's somewhat similar to a dirty combusted cigarette, or are you wanting to see something much lower?

DR. BICKEL: So, first, I'm not sure that we can make any inference about what this particular product is in terms of relative to tobacco, because the large uptake in Sweden in the population is potentially consistent with -- it's a robust reinforcer potentially. Ideally, what would be useful is to have two comparators, right?

Conventional cigarettes, whatever the test product is, and

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perhaps something we have a great deal of understanding about that is actually used as a medicine -- Nicorette gum, for example -- as a spectrum of looking at a dirty substance that seems to function as a reinforcer. A therapeutic substance, we know, isn't that big a reinforcer. And then we could see where this product fits.

Is it more like gum? Well, that's one story. If it's more like cigarettes, that's another story. The substitutability is a very interesting and important question that, once again, I don't think with this product we have the data to be able to say whether it's a robust substitute, a weak substitute, and those are empirical observations that would inform the likelihood that one will switch from one to the other.

DR. RIBISL: Just to finish back. Yeah, as you think of the constellation of factors that are going to predict whether this product has uptake, I think three, arguably, of the top five strongest predictors are going to be, number one -- or not in any particular order of the three, but price. And another one is going to be the nicotine delivery, and then another is going to have to do with the marketing.

It sounds like they're not proposing to do much marketing.

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But when you look at -- those, I think, are three of the most -- you know, three of the strongest factors. There are probably a couple of others that I think would make the top, but I think those are things you need to know.

DR. BICKEL: Absolutely. And the price has already been on the table. One of the things that's important just when you think about abuse liability, it is really dependent upon the context, right? So we may think, for example, that methadone, which is used as a treatment for heroin dependence, has low abuse liability. But that doesn't mean that it's not an abusable substance, and understanding exactly where it fits helps us understand the likelihood, perhaps, of uptake by adolescents, which I think is another question that those studies could help inform, not necessarily conclusively identify.

DR. HUANG: And I'd just add on to what Dr. Giovino first said and Dr. Ribisl. I mean, just what strikes me is the marketing climate and the advertising climate for other products and tobacco and combustible tobacco, as well as just the cultural things. I mean, how this was in Sweden, this word of mouth was how this was largely promoted, which is totally different than anything that we have really here. And the

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social media is taking the place of that.

Dr. Tomar.

DR. TOMAR: Certainly, one of my concerns, and I think it was touched on earlier, is marketing specifically promoting these products as a bridge, as a situational substitute. And although one of the Swedish Match officials yesterday said that he found that type of advertising distasteful, there's actually very recent evidence that -- examples that were presented in some of the public comments that were submitted. And I don't know; maybe it's a question that FDA has to grapple with. And even if Swedish Match decided they would no longer be promoting situational substitution for cigarettes, they're currently a very small piece of the market for snus. Their major competitors are primarily in the cigarette business. And so you wonder, even if this company voluntarily says no, we're not going to promote it, how do you control the fact that the other ones are?

DR. HUANG: And, again, Sweden had no marketing. I mean, no advertising.

Other comments?

(No response.)

DR. HUANG: Are we ready to vote? And elaborate on

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people's viewpoints during their explanation of the vote?

Okay.

So let's try voting on Question 5(a)(i). The question: Does the Committee believe that the epidemiologic 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?

(Vote.)

DR. HUANG: Okay, everyone has now voted. The vote is now complete and locked in. And the vote is 6 noes, 1 yes, and 1 abstain. That was Dr. Ribisl is no; Dr. Eissenberg is abstain; Dr. Giovino, no; Dr. Huang, no; Dr. Fagan, no; Dr. O'Connor, yes; Dr. Bickel, no; Dr. Novotny, no.

So now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and any comments on their rationale.

DR. NOVOTNY: This is Tom Novotny. I voted no because I really think that the sociocultural environments between Sweden and here are so different and that what we at least know in large part here is the propensity for dual use, which would preclude the benefits of switching completely. The absence of evidence on the abuse liability and that evidence in particular

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subpopulations is not sufficient.

DR. BICKEL: Warren Bickel. I voted no.

DR. O'CONNOR: Richard O'Connor. I voted yes. I think the data from Sweden are at least informative to a potential pattern in the U.S. Any unknowns about the nature of how it will play out in the U.S., I think, are to be determined.

DR. FAGAN: Pebbles Fagan. I voted no because I'm very concerned about the sociocultural environmental context, and also the issue of dual use, which we've already seen in adolescents here in the U.S. are dual users of both snus and cigarette products.

DR. HUANG: Phil Huang. I voted no. Similarly, I'm very concerned about the differences in the social, the marketing environment, the demographics of the differences that are apparent. And so, again, I'm very concerned about that applying to the U.S.

DR. GIOVINO: This is Gary Giovino. I voted no because of the reasons that have been given. I think there are very -- there are differences in the societies and the cultures and the marketing and the taste and the abuse liability. Well, I'm not aware of what's about the abuse liability, but in those other things that make it hard to think that they will be relevant.

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DR. EISSENBERG: This is Tom Eissenberg. I abstained. I apologize. I was on my way to pressing no, and then I realized the ambiguity in the word "relevant." Of course, the information is relevant. It tells us something about a particular population in a particular place with particular restrictions upon it, and we can learn from that experience. Is it predictive of? Then I would say no. And I was also struck yesterday by something I just wanted to say very much informed my information about the predictive-ness of the Swedish experience, and that was that it was labeled as a food product in the early '70s. I think that's a huge difference between them and us. And it may, in fact, explain a great deal about the uptake of Swedish snus in the Swedish population.

DR. RIBISL: My name is Kurt Ribisl, and I voted no. This was one of the weaker parts of the application, and if you take a look at the wide array of factors that predict uptake of tobacco use, I think you could have a little bit more sophisticated approach to data provision that would help you understand the likelihood of this transition occurring.

DR. HUANG: Okay. Now, we have part (ii) of this question regarding the epi data from Sweden concerning tobacco use behavior providing relevant information on the likelihood that

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non-users of tobacco in the U.S. will initiate the use of these snus products. Do we need to have additional discussion, or are we ready to vote? Anyone like to discuss further?

DR. GIOVINO: I have a question. Can we assume the word "relevant" includes predictive, just to clarify the issue Dr. Eissenberg raised?

DR. CHOINIERE: It's up to you, or you can do like what Dr. Eissenberg did.

DR. GIOVINO: All right.

DR. HUANG: All right, ready to vote on 5(a)(ii), then, again. We'll now begin the voting process for Question 5(a)(ii). Please press the button on your microphone that corresponds to your vote.

(Vote.)

DR. HUANG: Okay, everyone has now voted. The vote is now complete and locked in. So now we have 5 votes no, 3 votes are abstaining. Dr. Ribisl voted abstain; Dr. Eissenberg abstained; Dr. Giovino, no; Dr. Huang, no; Dr. Fagan, no; Dr. O'Connor abstained; Dr. Bickel, no; Dr. Novotny, no. And so now we'll go around the table and have everyone who voted to state their name, vote, and any comments or rationale.

DR. NOVOTNY: This is Tom Novotny. I voted no for much

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the same reasons about the cultural, sociocultural differences and the evidence that we have so far about how U.S. new users have a propensity towards dual use.

DR. BICKEL: Warren Bickel. I voted no. I don't think there was adequate information about the potential uptake that would be real by, among other things, abuse liability studies and the different subpopulations.

DR. O'CONNOR: Richard O'Connor. I abstained on this because I felt there were more unknowns about the potential impacts on non-users. Not enough to push me to a no.

DR. FAGAN: Pebbles Fagan. I voted no for the same reasons I mentioned earlier.

DR. HUANG: Phil Huang. I voted no, similarly because of the significant cultural, social, and marketing climate differences.

DR. GIOVINO: And Gary Giovino. I voted no for a lot of the same reasons. And at least right now hookah is much more of an edgy kind of product, and I think young people will go toward things that are cool and stylish.

DR. EISSENBERG: This is Tom Eissenberg. I abstained again for my lack of appreciation of the full range of the word "relevant." I think that the data are not predictive, but they

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probably have some relevance to us. And I would be particularly worried about the pharmacokinetic profile of a product that could serve as a starter product for youth in this country.

DR. RIBISL: My name is Kurt Ribisl, and I abstained. I felt like I wanted -- I just didn't have enough information to really make a fully informed decision. There was a little bit of information in that consumer survey that was somewhat suggestive that -- suggested that non-users might not be that interested in the product, as interested as the other current users were. But, overall, I didn't feel like I had enough information to make a proper decision.

DR. HUANG: All right, moving on to Question 5b is 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, self-selection studies, or 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?

So maybe have some more discussion specifically on this. Comments?

Dr. O'Connor.

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DR. O'CONNOR: I guess I can toss this over to FDA by what you mean by actual use studies or self-selection studies?

DR. CHOINIERE: Well, a self-selection study could include -- you could have people view the product or the labeling of the product and determine if it's appropriate for them to use it. It's done often with over-the-counter drugs. There would probably be some sort of a modification to be done in terms of this product to determine if smokers are indeed the ones that would find that this product is appropriate for them to use.

An actual use study, I believe, would fall in line more with some of these abuse liability studies that you're discussing. We have people actually use the product, see how long they use it, the patterns of use that they have with the products themselves. Does that -- okay.

MR. ZELLER: Just one point to add.

Priscilla used to be with the Office of Nonprescription Drugs in CDER.

DR. CALLAHAN-LYON: Priscilla Callahan, FDA. Also with actual use, it's important whether or not that they actually follow the package directions, if there are directions. It's another component of the study.

DR. HUANG: Dr. Eissenberg.

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DR. EISSENBERG: Yeah, I guess obviously I have a bias because I run some of these types of studies myself. I was a little surprised that the application didn't demonstrate the variety of different study designs that could have been used, the information we could have gained from different study designs about the ability of the product to fully substitute in different populations, the possible ramifications of dual use. So I guess I'm coming down on the side of that there was not sufficient information and there certainly was the opportunity to provide more information.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, just one fine detail, which is some of the studies suggest that dual use behavior is higher among occasional users, and as occasional use or non-daily intermittent use is increasing here in the U.S., having that information is critically important because it might be suggestive that, as non-daily use increases, the dual use of cigarettes plus snus might also increase as well. So I think having that information would have been really helpful.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: I guess I would throw this back to Dr. Eissenberg. Would you consider the clinical trial evidence

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that they presented on smoking cessation outcomes to be akin to some of the data that we'd be looking for in terms of more behavioral-oriented outcomes, like withdrawal suppression?

DR. EISSENBERG: Yeah, absolutely. If I recall correctly, and I could be wrong, those were in people who were interested in quitting; is that right? So I mean, there's obviously going to be a different, a potential for a different response in different populations. I think that the studies you were referring to form a part of the package that I would certainly like to see, but not the entire package.

DR. HUANG: Other comments? Are we ready to vote on this? Okay.

Moving to 5b. So, again, 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, self-selection studies, or 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?

If you will please press the button on your microphone that corresponds to your vote.

(Vote.)

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DR. HUANG: Okay, everyone has now voted. The vote is now complete and locked in. The results are 7 voted no, and 1 abstained. Dr. Ribisl voted no; Dr. Eissenberg voted no; Dr. Giovino voted no; Dr Huang voted no; Dr. Fagan voted no; Dr. O'Connor abstained; Dr. Bickel voted no; Dr. Novotny voted no.

So now that the vote is complete, we'll go around the table, and everyone who voted state their name, vote, and any comments or rationale.

DR. NOVOTNY: This is Tom Novotny. I voted no because of the lack of appropriate behavioral studies. The cessation study was helpful but actually didn't really show good evidence of how it would actually benefit smokers in their cessation.

DR. BICKEL: Warren Bickel. I voted no for similar reasons, insufficient information about the broad array of behavioral effects.

DR. O'CONNOR: Richard O'Connor. I abstained because I felt that there was not the ideal amount of information. But the information that was provided, while limited and flawed, was informative.

DR. FAGAN: Pebbles Fagan. I voted no because there was just insufficient information.

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DR. HUANG: Phil Huang. I voted no. Again, I also felt there was insufficient information.

DR. GIOVINO: Gary Giovino. I voted no because I didn't think there was enough done.

DR. EISSENBERG: And Tom Eissenberg. I voted no because I felt like there was a missed opportunity to study the behavioral effects of these products in the population of most interest, which would have been, here, cigarette smokers and other tobacco users in the United States.

DR. RIBISL: Kurt Ribisl. I voted no. Like other Committee members, I felt like there just wasn't enough information.

Finally, I do want to come back. I think I missed my opportunity to talk about the youth issue and whether kids should be surveyed as part of the data package here. And perhaps we could start that discussion after -- as we transition before the next one.

DR. HUANG: Sure. Okay. Well, let's move on and have a little discussion regarding that youth survey issue.

Dr. Ribisl.

DR. RIBISL: Well, basically, I would love to hear what other Committee members know, because one Committee member said

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that they think you need to have -- you should have youth surveys, and if that's the feeling, I think it would be nice if that's signaled to prospective applicants. And as I had said, I think there are pros and cons of this. If you go back to some of the studies done by one of the companies that was doing a youth smoking prevention program, they did studies of thousands of youths, what factors predict their smoking, all kinds of stuff about their relationship to their parents, sort of all kinds of other issues about kids.

There was a fair amount of criticism from tobacco control researchers that the industry was, under the guise of setting up a youth smoking prevention program, doing a lot of really research on children and their attitudes. And I think there's some sensitivities there. So I see pros and cons. Youth are really, really important. And, again, they're not -- anyone under the age of 18, it's not a uniform group, and there are different protections for, say, someone who's 14 to 18 than someone who is 10 or 12 or so. But I just wanted to say that I have some reservations about a lot of data on youth, but I also feel like I'd love to see it, if it were there. So I'm really torn on it. I just wanted to say that. And I'd love to hear what others think.

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DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I understand your concerns; they're extremely valid. I want to make the point that the data from the U.S., the snus use among U.S. adults is 5.5% of reported, and among youth it's 4.1%. And so the difference is not that great in terms of reporting ever use among adults and youth. And then we have very similar dual-use rates among youth and adults as well. Not very different. And then the data also suggested that younger people, young adults, are more likely to use snus than other age groups.

The study that I mentioned earlier that just came out in 2014, it was specifically done among female athletes. One of the things that they also mentioned in that paper was that they were trying to understand the influences on the use of snus in these young women and found that it was not the coaches, but parents and peers. And so that data has also suggested to me that we do need to understand the context of youth using snus. You know, I'm not sure what to say about the other component because I do agree with you that it is still problematic. But we do need some data to really help us understand, because I am concerned that if these young people -- we don't know whether they're trying the snus first or the cigarettes first, you

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know, where the initiation process begins. But I'm concerned about whether or not these young people become chronic dual users, and is that a real phenomenon that we might observe in the future? I'm not really sure.

DR. HUANG: Sure, Dr. Ribisl.

DR. RIBISL: Yeah, my point would be some of those issues about the transitions are extraordinarily important. I'm hoping PATH, given all the money that's being spent on it and the sample size, I'm assuming there's going to be other studies that are going to give us that and they will cite those in there, rather than conduct them, themselves.

DR. HUANG: Right.

DR. RIBISL: So I definitely want to see tons of studies about youth in there. My question is more do you want the industry doing that?

DR. HUANG: And Dr. Giovino.

DR. GIOVINO: Yeah. Dr. Rutqvist yesterday alluded or gave me the impression that -- he brought up the issue that some kids in Sweden who start may be kids who otherwise would have gone to cigarettes. And when I think about this modeling issue, I think that's one of the groups we really have to get a handle on, and I don't know how to do that. But I think that

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would be a good issue to be worked out by grantees or something. You know, despite our best efforts to prevent youth initiation of smoking, some kids still start.

If some of the kids who would have started smoking combusted cigarettes instead use snus and, you know, despite our best efforts were to use snus instead of Marlboros, Camels, or Newport and stayed on them, that would be a gain in the long run. But, you know, obviously we still need to do everything we can to prevent youth initiation.

So I think that issue is important for several reasons. One is to understand psychosocial predictors; one is to model properly what's going on here, and so our models are based on less assumptions. I would think that -- and maybe you do have, FDA does have, mechanisms that you would -- and my guess is our colleagues from Swedish Match did not do the study because of sensitivities, and maybe there are ways to work with the FDA in ways that say, oh, we are going to work with this. Because I am aware of the Philip -- well, the survey, you might be referring to one.

But we spoke with a vice president for youth cessation from Philip Morris over a decade ago, and she said, yeah, we're surveying kids to inform our campaign, and I'm not sure how

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transparent that process was. So in a very transparent process, perhaps that type of work could be done for the betterment of public health.

DR. HUANG: Dr. Bickel.

DR. BICKEL: I just want to say that, you know, it strikes me that if companies would do it but did it in a very transparent way with an external scientific advisory board of people of note, and for very specific purposes that were, you know, clear from the onset, as opposed to market research for their own development of the product, I think it could potentially be worthwhile. But I'm very concerned about the ethical and human risk burden to the children and to future children if that were not to be transparent and if they were done for the reasons --

DR. HUANG: Yeah. I mean, I would echo the concern about having the industry actually performing the studies or sponsoring the studies and hope that there would be other independent entities that would do lots and lots of these sorts of assessments.

Dr. Eissenberg.

DR. EISSENBERG: Yeah, I think in support of a particular application, there's a lot of room for citing studies that are

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done independently from scientists from PATH. Just as you were saying, there are other studies that might be designed for a variety of different reasons that could be relevant to an application, but there's going to always be some studies, especially if we're talking about messaging in some way, that are unique to the application and are specific to the company who's making the application.

And there I think is a really strong role that CTP can play in making sure that the measures are selected that are appropriate, that no other measures are used, and that the study has the maximum effect in terms of information related to the application and no other effects.

DR. HUANG: Okay, good discussion.

All right, let's move on, then, to Question No. 6, which is: 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

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of the product.

So 6a: 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 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?

Actually to vote on that. How do we vote on that?

(Laughter.)

(Off microphone comment.)

DR. HUANG: Yeah. Comments?

DR. CHOINIERE: The question is, does the Committee believe it is appropriate to include the information in a warning label.

DR. HUANG: Okay.

DR. CHOINIERE: As an alternative, it could appear as a statement separate from, but in addition to, the warning label, such as you might see, say, a health claim on a food product.

DR. HUANG: Okay.

DR. GIOVINO: May I?

DR. HUANG: Yeah, Dr. Giovino.

DR. GIOVINO: So it's a little confusing because the intro

raises the concern about inclusion of benefits of -- I mean, information about the relative benefits. Oh, I see. No, you are consistent, I'm sorry. Within a warning label. When I saw that, I related an experience with my nephew, who was an inveterate cigarette smoker and he was on e-cigarettes, and all of his friends said to him those are just as bad for you as cigarettes, you know, whatever you were smoking before.

And obviously they didn't really know and I didn't really know, but accurate information -- and by the way, I always encouraged him to quit. So I would think that accurate information on the relative benefits of a product would be useful to people, if there indeed were scientific consensus on relative benefits. In terms of a warning label versus -- you know, there's a statement I use when I look at food, which is never believe anything on the front of the package. And you know, the FDA warning -- I'm sorry. Nutrition label, I will believe.

And I believe I recall from research that was done, that a lot of consumers don't believe product claims from the cigarette industry, but they do believe claims from the government. Now, if that's still the case, that's relevant. But it brings in the issues that are legal issues that were

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brought up the other day. But, you know, I think one of the issues that has to play in is believability on the part of the consumer.

DR. HUANG: And we have Dr. McAfee on the phone. Tim?

DR. McAFEE: Sorry, I'm just un-muting. Yeah, I actually had a previous comment about the youth survey, but I'll just go ahead and mention around this one that I do think this is the area that I think it would have been a lot cleaner and easier to think about if this had been put forward as a real modified risk claim with a marketing plan for how it was going to go about, because we know -- I mean the other thing we know, which I don't think really has been talked about very much, but in some ways some of this could ultimately be a tempest in a teapot in a sense that what we -- we know that the traditional United States text warnings on cigarettes and other products are contrary to Gary's approach, which is to always read the nutritional labels.

Actually, I think, in studies consumers are, in fact, influenced by packaging and implied claims that are included in both the visual display, the words that are chosen, and certainly I think our presumption has been that if Swedish Match were to get an okay on one of these labeling changes,

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that they would come back -- they would still be required to come back if they were going to make modified risk, if they conducted a marketing claim or social media or a marketing campaign, they would have to get that, come back, and get that approved by FDA.

So I think without the context of what that would look like, it's very hard to understand or think or even speculate on how really one complicated sentence in the context of what historically, in most products, is a warning, but this isn't a warning -- it's very confusing and hard to understand how it would be perceived by consumers. And you know, again, my bias would be a nice, clean modified risk packaging statement plus marketing that was reviewed, focusing on lung cancer, COPD, where it's clear with clear caveats required, however, because you couldn't have a standalone statement about that truth without also mentioning concerns about adolescents, pregnant women, and dual users. And if that was all packaged, then I think probably a lot of us could not only be, like, upset but even be a little bit positive about the potential impacts it has.

I'll stop there. Thank you.

DR. HUANG: Thanks.

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Dr. Bickel.

DR. BICKEL: I think it would be really remarkable if the company and its concern for product stewardship were to explore novel ways to convey this information that is heuristically easy for people to grab. Just off the top of my head, imagine a list of things and some of them have a green symbol next to them and some have a yellow symbol and some have a red symbol.

So somebody could scan and say addiction, red. That means if I use this product, I get addicted. Lung cancer, you know, I don't know if it would be yellow or green, whatever it would be, and I could say, oh, that would -- right? As opposed to burdensome sentences where we have to be concerned about the number of syllables, right? Make it heuristically easy. That would be a real boon, I think, to the whole issue of tobacco, and I would love to see this company explore that.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: I wonder if there is any, you know, consideration or concept that people have had, either at FDA or elsewhere, about a statement separate from the warning label. Are we talking about a package insert or something a little bit more abbreviated as opposed to what we see in pharmaceuticals or a mandatory placement on advertisements that goes into more

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detail, that can be done, you know, more easily than on a small, round package? What's the idea that we're sort of thinking in terms of?

DR. CHOINIERE: We aren't restricting -- we don't have any recommendations for how they should appear. We're only asking whether or not it's appropriate to appear in the warning label.

DR. NOVOTNY: If I could just follow up, because I think some of our previous discussions said that what we really want is much more detail, you know, in terms of what the real reduced risk is or the real risks are that are getting communicated and whether that could be done as a graphic display is a good question because we, of course, require now graphic displays on cigarette packages or we will at some point.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah, so there's a very, very sparse literature to inform this topic, and so this is a really hard kind of question. So on the one hand, you have the data from, to use Tom's word, the flawed consumer perception study that did seem to suggest that when you randomly assign people to get the suggested revised message that Swedish Match proposed, that they seem to be interested in trying the product. There are

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risk perceptions. The risk perceptions were lower for the product than people who saw the existing warning label messages, and they were a little more interested in trying it out.

There's the study by Michael Capella in *Journal of Consumer Affairs*; again, this is one study, and you need to see a body of evidence, but this one, where they suggested that it was encouraging people to -- that smokeless products are lower-risk products, and they kept the government warning label. They kind of cancel each other out in that study. So we need a lot more work. I don't want to be simplistic and say it seems like if you keep the existing label and have some other type of message, there's a possibility that they're going to cancel each other out. But if you replace it, you may be more likely to tilt people toward the product. So I just wanted to mention I think this is an area ripe for other studies.

DR. HUANG: Mr. Henton.

MR. HENTON: In the introduction there is a concern about information about relative benefit, and I don't know if the Applicant ever indicated there was a relative benefit. I think they indicated there was a relative reduced risk. Is that your all's word, the benefit?

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DR. CHOINIERE: That was the word that is -- we used, yes. I believe it is a statement of relative benefit or a statement of relative risk. It depends on how you invert it.

MR. HENTON: But if I might, but it would seem that you all are -- your labeling that they are claiming that there's a benefit. You're putting words in the Applicant's mouth, if you will.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Well, I just think the word "relevant" qualifies that enough. I didn't take it as a benefit, but that's just my perception.

DR. HUANG: So, again, this question is do we believe it's appropriate to include the modified risk information within the context of the required warning label, is really the question as opposed to a separate form. And in addition to the warning label, okay.

UNIDENTIFIED SPEAKER: So (a) and (b), maybe? (a) would be the first one and (b) the second?

DR. HUANG: Well, I think if we answer yes, that would mean we support (a). So are we ready to vote?

Dr. Boffetta.

DR. BOFFETTA: Just to clarify for the people who have to

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vote, yes means in the warning label, no means separate.

DR. HUANG: Yes, correct. So does the Committee believe it is appropriate to include it within the warning label would be yes. If you don't think it should be in the warning label in a separate thing, you should vote no. Okay?

DR. FAGAN: Just one more clarification --

DR. HUANG: Yes, um-hum.

DR. FAGAN: -- which is we're specifically referring to this particular case, right?

DR. HUANG: Yes.

DR. FAGAN: Because this is broadly stated.

DR. CHOINIERE: Yes.

DR. FAGAN: But I just want to make sure --

DR. CHOINIERE: This is for these --

DR. FAGAN: -- that we all understand we're --

DR. CHOINIERE: This question --

DR. FAGAN: -- talking about this case.

DR. CHOINIERE: Yes.

DR. FAGAN: Okay.

DR. CHOINIERE: It's about this --

DR. FAGAN: Yeah, this here --

DR. CHOINIERE: -- particular request.

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DR. FAGAN: Right.

DR. HUANG: It's the only thing we're talking about.

DR. FAGAN: Yeah. I just want to make sure everybody understands.

DR. HUANG: We're not saying in all cases or whatever.

Okay, are we ready to vote, then? We will begin voting on Question 6a, so 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 to include modified risk information within the context of the required warning label as opposed to a statement separate from, and in addition to, the warning label?

So please press your button.

(Vote.)

DR. HUANG: All right. So everyone has now voted. The vote is now complete and locked in. And we have 6 noes and 2 abstains.

Dr. Ribisl voted no; Dr. Eissenberg voted no; Dr. Giovino voted abstain; Dr. Huang voted no; Dr. Fagan, no; Dr. O'Connor, no; Dr. Bickel abstained; and Dr. Novotny voted no.

So now that the vote is complete, go around the table and have everyone who voted state their name, vote, and any comment

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or rationale.

DR. NOVOTNY: Tom Novotny. I voted no for the reasons I suggested earlier, is that a warning needs to be about risks and not about benefits, it's -- and that in the specific application, actually, is really inappropriate to include the reduced risk messaging that's in there, so I voted no, that it should not be in the context of the warning, as placed, but as something that should be added either separately in a statement or in the advertising or something else that would indicate the reduced risk of using this as an exclusive product rather than an additional product.

DR. BICKEL: Warren Bickel. I voted abstain because I don't think we have enough information of how we can effectively communicate this information to the consumer, and I would like to think that -- it would be incumbent upon the company to figure out and do studies to demonstrate methods by which they can effectively communicate the broad profile of risk associated with the use of their product.

DR. O'CONNOR: Richard O'Connor. I voted no because I thought a separate statement would be a more effective communication vehicle for the reduced risk message.

DR. FAGAN: I voted no, but I do agree that we need to

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better understand how to communicate risk, and if we have a separate warning statement from a modified risk statement, that that also needs to be tested as well.

(Off microphone comment.)

DR. FAGAN: Oh, Pebbles Fagan.

DR. HUANG: Phil Huang. I voted no for similar reasons. I feel it would be more effective to have a statement as a separate statement from the warning.

DR. GIOVINO: Gary Giovino. I abstained because I think we need more research and because the notion of a warning only stating a warning is not consistent. Our federal government warns people that there are benefits to quitting smoking, so I'm just in the gray zone on this one.

DR. EISSENBERG: This is Tom Eissenberg. I voted no. I have a great deal of empathy for what Gary just said, that we're inconsistent, it appears, across different labeling. I also have a great deal of empathy for the company that wants to make sure that the warning labels are accurate with regard to the risks of their product. What I just couldn't reconcile was the idea of putting relative risk information within the context of the warning. I would like to see it somewhere else.

DR. RIBISL: My name is Kurt Ribisl, and I voted no. I do

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feel like the product has some risks that need to be disclosed to consumers, so actually getting a buy or a pass on having any type of warning, I think, is -- or having a really watered-down warning is tough. On the other hand, while I don't want anyone to use a tobacco product, if they are using one, we need to find ways to nudge them toward the less-toxic products.

DR. HUANG: All right, we're now ready to move on to Question 7, which is -- well, it's actually more discussion and input, but -- so with respect to postmarket surveillance and studies to be conducted by Swedish Match, if FDA were to issue an order allowing the marketing of these snus products as modified risk tobacco products, what recommendations does the Committee have for postmarket surveillance and studies?

And we've had some discussion of this, but I will focus first on (a): 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, which may have a low prevalence of use?

Or do you want to do them all collectively or do them one at a time? Preference? One at a time.

(Off microphone response.)

DR. HUANG: Huh? Oh, collectively? Okay. Okay, then

we'll have one -- so let's move on.

So the other topics: 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 and behavior in a postmarket setting, particularly among youth?

What sources of data does the Committee recommend that Swedish Match North America use 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?

Okay. Comments?

Dr. Novotny.

DR. NOVOTNY: On (a), I really think that they need to really explore the use of big data, marketing data, social media data, and other kinds of data that have been demonstrated actually to be very useful in understanding what's going on with e-cigarettes, for instance. And I think this is somewhat more, sort of, responsive to current conditions than planning big surveys.

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On the other hand, I think that we -- you know, the government or the funders of large national surveys, especially of youth, need to be perhaps empowered to include appropriate questions to get at some of the surveillance information without necessarily depending on the company to do that.

DR. HUANG: Dr. Boffetta.

DR. BOFFETTA: Well, this is a very vast territory because I think during our discussion, we identified a number of major areas where better data or data more relevant to the U.S. market are missing, basically. So the way -- this should not rest on these different areas, which encompasses, encompass determinants of uptake, determinants of switch or quitting in terms of behavior, in particular, among adolescent and young people, but also prevalence of some of the health effects that we discussed today.

We can, in particular, I think, warn health effects in young people or current users, in particular, young people and the data with all the complex aspects of the market in the U.S., including women, including minority groups that have not been studied in Sweden, as we discussed before, and ideally also the long-term effects, which will require longitudinal studies of these different products. So obviously we can

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recommend, I don't know how much -- you know, the recommendation, I think, should address these different areas where clearly, we -- these are the areas where the major uncertainties, where we face the major uncertainties in our considerations.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Yeah, I think another thing to keep in mind, too, is that these marketing orders are issued for a defined period of time, and so the thing to keep in mind is that we would have to be recommending things that they do that they can reasonably accomplish within whatever window their order is given for. So I doubt you'd be able to see cancer outcomes and things like that, but -- so the issue would be what are the primary signals that you could pick up in the short to medium term that would be indicative of benefit or harm?

DR. HUANG: Yes, Dr. Eissenberg.

DR. EISSENBERG: Yeah, I think Dr. O'Connor makes a great point and that there's a limited timeframe in which to collect data before, I guess, the order might expire, and then they may want to sign up again. And in that respect, I would have thought that much more detailed, much more action-oriented

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plans would be provided initially so that the company can hit the ground running as soon as the order is given, that the modified risk tobacco product has been approved, the application has been approved. So I guess details, details and an action plan seem like an important thing to put in with an application, not sometime later when we get around to it.

DR. HUANG: Dr. Djordjevic.

DR. DJORDJEVIC: I think collecting biomarker data is also critical because it will address many questions including dual use and abuse liability and whatever we discussed during this meeting.

DR. HUANG: Yes, Mitch.

MR. ZELLER: Question for the Committee. Given the considerations that have been put on the table, any particular thoughts or recommendations given, time-limited nature of any authorization that would be given, the fact that certain longer-term effects couldn't possibly be known during whatever the timeframe for an authorization would be, but what I'm particularly asking about is -- and given the fact that we're talking about products with a low prevalence of use, are there any thoughts or recommendations especially given those other issues for products where there is a low prevalence of use?

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DR. HUANG: Dr. Novotny.

DR. NOVOTNY: You know, we collect information from clinical facilities on things like influenza, where there's a surveillance system with sentinel surveillance, and I'm just wondering whether or not consideration of sentinel surveillance with our oral health facilities might be set up in some way to report or at least have some trials that can be used to report on sentinel events, which I think would be much more, sort of, instantaneous and provide for things like case control studies or even other kinds of designs as well.

DR. HUANG: Another thing that may work towards -- I know locally we're working with our healthcare providers and electronic health records, you know, meaningful use as specific information regarding smoking behavior, but we're actually trying to make sure that electronic cigarettes and other products are included on that, so as the health information exchanges and things are being developed, that we can get more information on some of these other outcomes from that standpoint. The other thing, I do wonder from actual sales data if they can be required to report information that they have if it's not considered too trade secret, but require that reporting and changes in sales.

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Dr. Giovino.

DR. GIOVINO: There's a chapter in the 2001 IOM report, "Clearing the Smoke," on postmarket surveillance that you've probably already reviewed, but I recommend to you if you haven't. In the application, Swedish Match mentioned, you know, using the data from PATH, which are great, but there's not rapid response there, and as you suggested, Mitch, the need for a more rapid response system would be welcome. I have a sense that the Office on Smoking and Health is exploring that, such systems better, and maybe some synergies could be built.

In terms of surveys of youth, I would wonder if a message that this tobacco product is safe would have any effect on their susceptibility. And susceptibility, I think, is a construct that's measured in PATH and I think measured in all of the -- you know, NYTS and not YRBS, but at least NYTS. Oh, and it's measured in NYTS, I know it is.

But it would be interesting to me to see if youth susceptibility, you know, never smokers' susceptibility to smoke changes, if there's a message that, oh, tobacco isn't so bad; of course, it might even go down, which could be a positive thing because -- and they might decide to switch to -- if they're going to use other products instead. Just a general

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-- I don't think the government's been measuring this all along, but just a general measure of, you know, Monitoring the Future measures, things like this, about, oh, I don't believe all the -- I think they over-exaggerate about tobacco.

Monitoring the Future has a bunch of measures on attitudes about tobacco that may be illustrative, that if they go up or if they go down or if they stay the same, you know, might be beneficial. Of course, it would absolutely depend on the strength of the dose, of the message that gets out there.

But the message could be monitored, you know, via monitoring the airwaves and via monitoring social media, so it would be possible to get a sense of how much the message is getting out there. I'm not saying -- I have no idea what will -- I really don't know what will happen if a message of a reduced risk product gets out there, but these are just the kind of things I think it would be good to monitor. They're in place, we have them, and it would be good to monitor them to see if they fluctuate at all.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: Yeah, I want to return to my environmental concern, and one of the things that we do is cigarette butt cleanups on beaches and campuses and urban areas to really be

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more alert to the fact that this is a hazardous waste product. And I would like to see at least some attention paid to post-consumption waste monitoring of this product, as well, since it seems as though it's going to be another non-biodegradable waste product.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I just want to build off of what Dr. Giovino said with the social media component. You know, social media with regard to e-cigarettes has taken off. I mean, the product promotes itself through social media, and individual consumers are out there promoting the product already. And I think that postmarket surveillance could take advantage of the fact and make some assumptions that a product that would have a message of modified risk may also take off, okay, through social media, particularly among young people. And if it's a flavored product as well. Some of its other products, like Timberwolf, is flavored; it could also potentially further take off through social media. So I think the social media component and this whole peer-to-peer sales component, which is, you know, what they said was used in Sweden, it took off word of mouth. Our word of mouth, in the context of what's going on here, is the social media and peers

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promoting products through that medium.

DR. HUANG: I mean, that's where it is so important, also, to distinguish the new use versus the switching.

Dr. Bickel.

DR. BICKEL: So given the low prevalence of use, at least currently, it strikes me that there's going to have to be a systematic and distributed effort to collect panel data that's representative of the United States as a whole, that would provide information regarding uptake among youth or adults switching, concurrent use, as well as perhaps its use as a way to stop using all tobacco products. And I think a panel process would provide surveillance and give direct insight that perhaps would be -- you could estimate U.S. burden or U.S. participation on the base of.

DR. HUANG: Dr. Tomar.

DR. TOMAR: I don't disagree with that. I just think a product with very low prevalence of use, just feasibly, you would have to have a massive panel to be able to look at those patterns. I'm not saying it's not a good idea. I just don't know if it's feasible.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Which might suggest that you might have

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almost like a tiered approach to postmarket surveillance.

Let's say you see a rapid uptick in sales. That might suggest that you're getting uptake in the population. You might want to do some panel surveys, because at that point, you've probably got enough prevalence that you don't need a massive survey to track it.

But if you're not seeing much of a bump in sales, it's suggesting that whatever messaging there is, is not driving additional people to go out and buy it. So you might not need everything all at once, but you might, you know, sort of have a tiered approach of putting things in place as they're needed to build a story around, how you explain what's going on.

DR. HUANG: Dr. Novotny.

DR. NOVOTNY: I just wanted to see, from Scott, whether or not any sort of oral health provider sort of database might be of any use in monitoring this. You know, it's conceivable that youth may not admit to use of snuff, but there may be at least some clinical issues that may be able to be identified.

DR. TOMAR: No, actually, I thought that was a great idea when you mentioned it before, and in fact, there's a national dental practitioner research network, I don't know, a couple hundred dental offices scattered around the country. So

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there's potentially an infrastructure already in place for a pretty broad network. So it may be reasonably feasible to do that.

DR. HUANG: Yes, Dr. Boffetta.

DR. BOFFETTA: Yeah, obviously the low prevalence is a major issue, you know, but there are different ways to tackle this problem. For example, one can really focus on users and recruit them through points of sales of something like that and then creating just a comparable group among users.

You know, you don't need to have a full representative sample of the entire population; only a few percent are exposed. I mean, there are different ways to address these issues. I also think the idea of some surveillance system through the dental practitioners may also be relatively easy to set up, I mean, a web-based system out there which may or may not provide, you know, any -- but if there is something important going on, it may be captured at this point.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Just to follow up on that excellent point. And this might not fly with the survey people, but it seems to me that every year there's a lot of surveying being done, and with all the new samples coming in, if you requested permission

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to contact people, you know, before they did the survey or at the end of the survey and then you could selectively contact the people who say they use the product and every year you did that, after a while, you'll -- after 5 years or so, you'll get a fair bolus; it's not a huge bolus, but a fair bolus of users. Now, getting the people who run the surveys to agree to allow that question to be added to their survey by follow-up would be another issue, but we're just brainstorming.

DR. HUANG: Other thoughts?

Dr. Ribisl.

DR. RIBISL: Yeah, it seems like this is a good role for Internet surveys in terms of where you say you have a relatively small population. You're able to screen people pretty efficiently, often these omnibus surveys that are going on and getting questions and then honing in on the users, and I'm thinking just focus on the snus users or the general snus users. You'd also want to maybe look at smokers and additionally to track some of those transitions, as well as some nonusers. But you could start with a large number, a very large number of people, and then winnow and follow that group possibly.

I also want to maybe also endorse the idea of social media

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monitoring.

Having recently done a study on Twitter, looking at over 5,000 tweets related to tobacco use, and overwhelmingly, they're e-cigarette tweets; the ones that are promoting tobacco use are related to e-cigarettes, and they're really across the board. But even though it's typically "individuals," and I use air quotes there for the transcript, the majority of mentions, a large percent of the mentions have websites that they direct you to, to buy the product or to redeem a coupon. So there are sometimes -- people use the word "organic tweets," organic meaning that really, really truly bubbled up versus ones that are sort of fake or Astroturf tweets that are coming out -- that are meant to look grassroots but are really some other group causing buzz.

And so the idea that there needs to be some type of monitoring system to understand the dialogue that's occurring on Twitter and other social media channels, I think is something that's really important because that's the place where people are talking today. Now, you know, 3 years from now, 5 years from now, it will be a different website or a different social media platform, but I think that's really --

DR. HUANG: Dr. Moynihan.

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DR. MOYNIHAN: Yes. So although this Question 7 really is about what the Applicant is planning to do for postmarket surveillance, but I mentioned several times the complexities of tobacco companies gathering data from youth.

And in terms of 7b, for example, I mean, there's also questions that any actual use of these products by youth in most jurisdictions in the United States would actually be a crime, or the sale of the product would be a crime in those jurisdictions, and it raises some questions about what position does it put a company in if you're expecting them to make plans to gather information of criminal activity by their distribution chain, which is something the FDA is also involved in for other reasons for other inappropriate activity by -- in the chain. But it makes life quite difficult for a company to develop a plan that may lead them into a liability.

DR. HUANG: Dr. Bickel.

DR. BICKEL: You know, it's a little bit different, but I know that the makers of Suboxone, the treatment for opiate dependence, has a surveillance program, and it's looking for diversion, and they have systems in place to find that diversion. And it's certainly legal to use, but they're able to have some systems that are able to report that in. So I

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think there are some ways that challenge, which is a challenge, can be met.

DR. HUANG: Dr. Ribisl.

DR. RIBISL: Yeah. And these are pretty common in surveillance just to have a broad sense of the types of laws. There are four types of laws: sales, purchase, use, possession. And so in many -- in everywhere, in every state and federally, there's a law against the sale of the products. Purchase is not always illegal; nor is use, nor is possession. In my state, we don't have a possession -- in lots of places you're not collecting -- you know, you're not having data about legal activity in many cases. But I do think these are things that are regularly collected in all kinds of surveillance surveys, and I don't see a major concern about that.

DR. HUANG: Other comments? Anything from your perspective that you want specifically more feedback?

DR. CHOINIERE: No, I think on this issue and all the other issues before it, you have all provided some very useful feedback. If you are finished with this question, I do want to open it -- give you the option, as a Committee, to provide recommendations on other aspects of these applications that may not have already been addressed in the earlier questions today.

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DR. HUANG: Okay. All right, so we'll move on from this question unless anyone has any objection, and are there any other issues that the Committee members want to raise or provide back to FDA?

Dr. Tomar.

DR. TOMAR: Well, I think it's a point that Dr. Eissenberg brought up before, but perhaps one thing that the Center could help applicants with is to help establish a protocol for some of the -- particularly, some of the attitudinal and behavior issues so an applicant would know, sort of, the standard that they're expected to meet in terms of providing evidence on, you know, intention to use and interpretability of messages and things along those lines.

DR. HUANG: Any other comments?

DR. RIBISL: I'll just second what Dr. Tomar said. Kurt Ribisl.

I do think -- I think you want -- I think people need to have predictability as they're coming forward, because this is probably just the beginning of what will be many more applications going forward, and so I think the extent to which people can understand what the bar is going to be. And the bar's got to be at the right place, and it will deter some

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people by giving us greater predictability. Others, people who were maybe hesitant, can now come forward.

But it's a massive undertaking to present, what, 120,000 plus pages and a big risk for a firm to do this, and it is -- it's part of the law. It is, I think, a sensible part of the law. But I think we've got to -- the extent to which it can be clear what some of these expectations are. I know this is the first one, it's kind of messy on both sides of the process, but I think we have gotten clarity, and I think the Committee has begun, the TPSAC Committee has begun to say here's the broad shape of some of the things that we want to see. And we've agreed on, you know, many things, at least the criteria. We don't always agree on what the application was, and that's sort of understandable, but I think we have really moved this forward. I mean, it's been a pretty successful meeting in that regard.

DR. HUANG: Anything else?

Yes, Dr. Novotny.

DR. NOVOTNY: Just a comment on -- this is Tom Novotny -- the questions. Those are appreciated because at least it gets us down to focus on what it is you really want to know. And I appreciate the fact that we had the opportunity to sort of

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modify those or focus them a bit, but I don't know if that's something that could be done in advance or maybe it's good to have it as part of the discussion here, too, so it's just something to consider.

DR. HUANG: Sure. I know they had a lot of prior consideration of those questions, and I think things do come out in this format, it seems, but yeah, we appreciated that opportunity to still, at the last minute, provide some feedback and some flexibility with that. But definitely, I would agree, the questions were very helpful for identifying what your needs are and helping us focus our discussions.

MR. ZELLER: At an appropriate time CTP has some concluding statements.

DR. HUANG: I'm sorry?

MR. ZELLER: At an appropriate time before you gavel the meeting, CTP has some concluding statements to make.

DR. HUANG: Okay. Are we ready for that? I think we're ready. It's an appropriate time. It's 2:15, so great.

MR. ZELLER: Conrad.

DR. CHOINIERE: Yeah, I don't want to keep us much longer. I just really appreciate the time and effort that you all have put in to reviewing the materials before you and providing some

very useful recommendations for us to consider when making our final determinations.

Thank you.

DR. ASHLEY: I also want to put in my thanks to the Committee. This has been extremely helpful. This is a journey I guess we're all on together and -- but it's been -- the feedback we've gotten has been very helpful for us. I'm sure it's also been helpful for many people in the audience. But I also want to thank Swedish Match for being brave enough to be the first ones to try this and to go down this path. It took a lot to be willing to do that with not knowing exactly how this Committee was going to respond, and so I appreciate them being willing to do that and to kind of forge that trail for many that will follow.

MR. ZELLER: Let me add to the list of thanks, starting with Swedish Match. Thank you for all the reasons that David said. An unnamed competitor of yours, during lunch break, called you guys trailblazers, and you were the first ones to get a set of applications to the Agency for filing and review and to TPSAC, and we appreciate that.

I want to extend my thanks to all members of the Committee. I'd like to single out Phil for an outstanding job

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as Acting Chair for the first ever. This is not like a CDER advisory committee that's done a hundred of these for products. This is the first one ever for all of you and for whoever served as Chair. So, Phil, thank you.

I'd also like to thank the invited members who joined for this meeting. I'd like to thank the new members, the new voting members of the Committee, and a great deal of thanks to the Center's Office of Science for all of the work that they have done on these applications as part of the application review process and all of the work that they did more specifically to prepare for this meeting, their presentations, their responsiveness to the questions. We are enormously appreciative of that, and to everybody else who participated in what by FDA standards is a very unusual process when it comes to an application that comes before the Agency for the reasons that I stated yesterday morning. But this is different, we are different. It is a much more open and transparent process than the drug approval process or even when new tobacco product applications come in. And I just want to thank everybody for their participation.

DR. HUANG: Okay. Unless there's anything else, then I think we're all adjourned. Thank you all very much.

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(Whereupon, at 2:18 p.m., the meeting was concluded.)

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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 10, 2015

Silver Spring, Maryland

were held as herein appears, and that this is the original
transcription thereof for the files of the Food and Drug
Administration, Center for Tobacco Products.

TOM BOWMAN

Official Reporter

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