FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCTS SCIENTIFIC
ADVISORY COMMITTEE

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MEETING

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FRIDAY
FEBRUARY 14, 2020

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The Tobacco Products Scientific Advisory Committee met in the FDA White Oak Campus, Great Room, Salons B & C, 10903 New Hampshire Avenue, Silver Spring, Maryland, at 8:30 a.m., Robin J. Mermelstein, Chair, presiding.

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

PRESENT

ROBIN J. MERMELSTEIN, PhD, Chair
WILLIAM ANDY BAILEY, PhD, Industry Representative (Non-Voting)
ALBERTA BECENTI, MPH, Ex-Officio Participant (Non-Voting)
LAURA J. BIERUT, MD, Member
ERIC DONNY, PhD, Consultant (Non-Voting)
SONIA A. DUFFY, PhD, RN, FAAN, Member
SARAH E. EVANS, PhD, MS, Industry Representative (Non-Voting)
DOROTHY HATSUKAMI, PhD, Consultant (Non-Voting)
SARA P. HERNDON, MPH, Member
BRIAN KING, PhD, MPH, Ex-Officio Participant (Non-Voting)
MICHAEL OGDEN, PhD, Industry Representative (Non-Voting)
DEBORAH J. OSSIP, PhD, Member *
JAMES F. THRASHER, PhD, Member
KAY WANKE, PhD, MPH, Ex-Officio Participant (Non-Voting)
KENNETH E. WARNER, PhD, Member
MICHAEL WEITZMAN, MD, Member

ALSO PRESENT

SERINA A. HUNTER-THOMAS, MSA, RN, Designated Federal Officer
BEN APELBERG, PhD, Division of Population Health Science, Office of Science, CTP
JUSTIN BYRON, PhD, Assistant Professor, Family Medicine, School of Medicine; Adjunct Assistant Professor, Health Behavior, Gillings School of Global Public Health, University of North Carolina at Chapel Hill
ED CARMINES, PhD, Principal, Carmines Consulting, LLC
MOLLIE MILLER, PhD, Pharmacologist, Division of Individual Health Science, Office of Science, CTP
ALEXANDER PERSOSKIE, PhD, Social Scientist, Division of Population Health Science, Office of Science, CTP
JOHN PRITCHARD, BSc (Hons), MSc, CBiol, MRSB, Vice President of Regulatory Science, 22nd Century Group, Inc.
CHRISTI TROTTER, Director of Agile Solutions, M/A/R/C Research
CINDY TWOREK, PhD, MPH, Technical Project Lead, 22nd Century Group Inc. MRTPs; Branch Chief, Division of Population Health Science, Office of Science, CTP
MITCH ZELLER, JD, Director, CTP

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P-R-O-C-E-E-D-I-N-G-S

8:36 a.m.

CHAIR MERMELSTEIN: I'd like to thank everybody for coming this morning to hear our presentations and our committee discussion. And we also have people on the phone and joining us via webcast. So, occasionally, we will refer to other people who are not in the room.

I'm Robin Mermelstein; I'm the Chair of the Tobacco Products Scientific Advisory Committee, and I'm going to make a few statements before we begin this morning.

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

We look forward to a very productive meeting today. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee Members take care that their conversations about the topics at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until after its conclusion.

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

So we are going to start with introductions of the Committee members and consultants to introduce. Again, I'm Robin Mermelstein. I'm from the University of Illinois at Chicago.

Dr. Weitzman?

DR. WEITZMAN: And I'm Michael

Weitzman from New York University School of Medicine.

DR. DUFFY: Sonia Duffy from Ohio State University.

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

DR. DONNY: Eric Donny, I'm at Wake Forest School of Medicine.

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

DR. TWOREK: Cindy Tworek, I'm the Technical Project Lead for the application from FDA Center for Tobacco Products.

DR. APELBERG: Ben Apelberg, I'm the Director of the Division of Population Health Science at the FDA Center for Tobacco Products.

MR. ZELLER: Good morning, Mitch Zeller, CTP Center Director.

DR. EVANS: Good morning, I'm Sarah Evans. I represent Turning Point Brands in Louisville, Kentucky, and I represent small

business today.

DR. BAILEY: Good morning, Andy Bailey, University of Kentucky, grower representative on this committee.

DR. OGDEN: Good morning, Mike Ogden, Senior Vice President of Scientific and Regulatory Affairs for RAI Services Company in Winston-Salem, North Carolina. And I represent the tobacco manufacturing industry.

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

MS. BECENTI: Alberta Becenti, Indian Health Service.

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

DR. HATSUKAMI: Dorothy Hatsukami from University of Minnesota.

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

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

CHAIR MERMELSTEIN: Thank you.

Serina?

CAPT. HUNTER-THOMAS: Thank you. Good morning, everyone. My name is Serina Hunter-Thomas, and it is my pleasure to serve as the Designated Federal Officer for this Tobacco Products Scientific Advisory Committee meeting today.

Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the Federal Register Notice that was published on December 26, 2019.

The FDA press media representative for today's meeting is Ms. Stephanie Caccomo. Ms. Caccomo, if you could stand up, if you're here, so that everyone can identify you, along with the press here today.

The transcriptionist for the meeting today is Ms. Devin Shiple. Thank you, Devin.

And I would also like to thank my colleagues, Ms. Janice O'Connor and our supervisor, Dana van Bemmel, who's here today.

I would like to remind everyone to

please check your pagers and cell phones; please make sure that they are either turned off or in silent mode.

While making your comment, please state first your name and speak up so that your comments are accurately recorded for the transcription.

Please keep in mind that a Committee Member also is joining us remotely. Dr. Ossip, are you online? Dr. Ossip? She might be on mute. Okay, we'll circle back to her.

DR. OSSIP: I am, yes, I'm sorry. I had two things muted --

CAPT. HUNTER-THOMAS: Thank --

DR. OSSIP: -- so I just had to unmute those, yes. This is Deborah Ossip, I'm at the University of Rochester Medical Center.

CAPT. HUNTER-THOMAS: Thank you, Dr. Ossip. And there are also members of the public that are also listening via webcast.

I will now proceed to read the conflict of interest statement for this meeting.

The Center for Tobacco Products of the Food and Drug Administration is convening today, February 14, 2020, for a meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972 and the Family Smoking Prevention and Tobacco Control Act of 2009.

The Committee is composed of scientists, healthcare professionals, a representative of a state government, a representative of the general public, ex officio participants from other agencies, and three industry representatives.

The following information on the status of this Advisory Committee's compliance with applicable federal conflict of interest laws and regulations is being provided to participants in today's meeting, as well as to the public, and is available for viewing at the registration table.

The purpose of today's meeting, which is being held in open session in its entirety,

is to discuss the modified risk tobacco product application submitted by 22nd Century Group, Inc. for the following combusted filtered cigarette tobacco products, MR0000159, VLN King, MR0000160, VLN Menthol King.

Accordingly, this meeting is categorized as involving a particular matter involving specific parties or PMISP.

With the exception of the industry representatives, all Committee Members are either special government employees or regular government employees from other agencies and are subject to federal conflict of interest laws and regulations.

Based on the categorization of this meeting and the matters to be considered by the Committee, all meeting participants, with the exception of the three industry representatives, have been screened for potential conflicts of interest.

FDA has determined that the screened participants are in compliance with applicable

federal conflict of interest laws and regulations.

With respect to the Committee's industry representatives, we would like to disclose that Drs. William Andy Bailey, Sarah Evans, and Michael Ogden are participating in this meeting as nonvoting representatives.

Dr. Bailey is representing the tobacco growers, Dr. Evans is representing the small business tobacco industry, and Dr. Ogden is representing the tobacco manufacturing industry. Their role at this meeting is to represent these industries in general and not any particular company.

Dr. Bailey is employed by the University of Kentucky, Dr. Evans is employed by Turning Point Brands, and Dr. Ogden is employed by RAI Services Company.

This concludes my reading of the conflict of interest statement for the public record, and at this time I would like to turn the meeting back over to the Chair, Dr.

Mermelstein. Thank you.

CHAIR MERMELSTEIN: Thank you. We're going to start with our first presentation with Dr. Tworek.

DR. TWOREK: Good morning and welcome. My name is Dr. Cindy Tworek, and I'm a Branch Chief in the Division of Population Health Science in the Office of Science in the Center for Tobacco Products.

As the Technical Project Lead for these modified risk tobacco product applications, or MRTPs, under review, I'm going to present some general and application-specific information relevant to today's discussion.

I'd like to begin by showing a disclaimer for today's TPSAC meeting. My presentation will provide some brief information about the MRTP applications under review; highlight key information points related to 22nd Century's premarket tobacco product applications, or PMTAs, for these products without claims; summarize select requirements

from Section 911 of the Tobacco Control Act relevant to the applications; and finally present our questions for TPSAC discussion today.

In May 2019, 22nd Century submitted two modified risk tobacco product applications to market very low nicotine cigarettes, VLN King and VLN Menthol King, with reduced exposure claims.

Three reduced exposure modified risk claims were identified by 22nd Century in their MRTP submissions: one, 95 percent less nicotine; two, helps reduce your nicotine consumption; and three, greatly reduces your nicotine consumption.

Along with these claims, the company included the following voluntary warning in both product applications: nicotine is addictive, less nicotine does not mean safer, all cigarettes can cause death and disease.

On December 17, 2019, FDA granted orders to two 22nd Century products, allowing

them to market those products because FDA had determined that the marketing of those products with no modified risk claims was appropriate for the protection of public health.

The products under review here are identical to those products in their design and chemistry, and the company is seeking authorization to market them as modified risk products.

I wanted to note that 22nd Century is using the brand name Moonlight for the PMTA products marketed and using the brand name VLN for the products in these modified risk applications. However, we are not seeking specific feedback on the brand name, which will not be a focus of discussion at this TPSAC meeting.

I also wanted to mention that the MRTP applications state that studies were conducted using the lowest nicotine version of SPECTRUM cigarettes, SPECTRUM very low nicotine content, or VLNC, cigarettes, available for

research purposes.

The Applicant states that these results serve as the primary basis for supporting claims because aside from the name, SPECTRUM cigarettes are identical to the VLN King and VLN Menthol King products.

The Applicant also states that results from studies using the lowest nicotine version of Quest cigarettes, which were previously marketed as a very low content nicotine cigarette, serve as secondary supportive studies.

I would like to highlight a few findings from the premarket tobacco applications recently granted orders to provide context for today's discussion. FDA review found the following.

Overall toxicant-associated non-cancer hazards and cancer risks associated with VLN cigarettes are likely similar to the comparison normal nicotine content cigarettes if they are used in the same way.

However, it's likely that smokers who primarily use VLN cigarettes will smoke less, which means fewer cigarettes per day and increased quit attempts.

VLN cigarettes have a lower abuse liability than normal nicotine content cigarettes.

Use of VLNC cigarettes is not associated with compensatory smoking in general or vulnerable populations.

Smokers may not switch completely to VLN cigarettes because of low subjective appeal, increased craving and withdrawal.

FDA review also found that exclusive and dual-product users who primarily use very low nicotine content cigarettes would likely reduce their exposure to nicotine, reduce their cigarettes per day, and reduce their nicotine dependence.

Switching to very low nicotine content cigarettes can facilitate abstinence in smokers by increasing motivation to quit and

quit attempts, and use of both nicotine replacement therapy and behavioral intervention could improve these outcomes.

And finally, these PMT findings can apply to smokers who use menthol and non-menthol VLN cigarettes.

FDA issued an advanced notice of proposed rulemaking, or ANPRM, in March 2019 to obtain public comment early in the rulemaking process related to setting maximum nicotine levels in cigarettes. There is currently no additional information on this ANPRM or a potential time line, and we ask TPSAC Members to assume that such a rule has not gone into effect for today's discussion.

Next, I would like to highlight a few select standards from Section 911 of the Tobacco Control Act that we refer to in our TPSAC discussion questions.

Relevant standards from Section 911(g)(2) require that marketing these products with modified risk claims is reasonably likely

to result in a measurable and substantial reduction in morbidity or mortality among individual tobacco users in subsequent studies and that marketing these products with modified risk claims is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

There are also several standards in Section 911(g)(2) related to consumer understanding that I would like to highlight for today's discussion.

One requires that the testing of the actual consumer perception shows that as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products.

Another standard in Section 911(h)(1)

that relates to consumer understanding requires that the advertising or labeling enables the public to comprehend the information concerning modified risk and understand the relative significance of such information in the context of total health and in relation to tobacco-related diseases and health conditions.

I also wanted to quickly highlight a few other standards from Section 911(g)(2) that we won't focus on in today's discussion. One standard requires that the magnitude of reductions in exposure to a harmful substance or substances is substantial and that the product as actually used exposes consumers to the specified reduced level of the harmful substance or substances.

And the other standard requires that the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market.

FDA had no specific questions or

issues related to these requirements, and similar requirements were addressed in the premarket tobacco applications reviewed.

Next, I would like to present the questions we're asking TPSAC to consider for discussion in today's meeting. The first question is related to morbidity and mortality. Question 1, we would like TPSAC to discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.

The second question is related to the effect on nonsmokers. Question 2, we would like TPSAC to discuss the extent to which former and never smokers are likely to try and progress to regularly using the proposed modified risk tobacco products.

The third question is related to the effect on smokers. Question 3, we would like TPSAC to discuss the extent to which smokers who do want to quit and the extent to which smokers

who do not want to quit will dual use the proposed modified risk products with their usual brand of cigarettes or the extent to which these smokers will exclusively use the proposed modified risk products.

The fourth question is related to understanding. Question 4, we would like TPSAC to discuss whether the labeling enables consumers to accurately understand the addiction risk and disease risks of using these products.

I also wanted to note that we have switched the order of the discussion topics from our previous backgrounder document sent to the Applicant and the TPSAC Committee and also posted.

We have moved understanding to the last topic for presentation and discussion, and we will begin with presentation and discussion related to morbidity, mortality, and population health.

And finally, some Q&A about granting marketing orders. The first question, has FDA

restricted how products are marketed? Yes. There are already restrictions on how these products can be marketed under the premarket PMTA orders granted, including age restrictions for digital sales, websites, and social media accounts, such as age tracking, monitoring, and verification requirements.

The second question, how long would a modified risk order last once granted? The maximum duration is five years, and there is no minimum length of time. To continue to market a product, applicants would have to submit a new application, and the FDA would reevaluate it.

And question three, can FDA require that certain things be studied during post-marketing surveillance? Yes. FDA can require specific future studies. FDA required specific advertising information to be tracked, measured, and reported by channel, product, and audience demographics, including age range, under the premarket tobacco orders issued for these same products in December.

Thank you for your attention. I would now like to turn things over to 22nd Century, who will provide additional information on their modified risk tobacco product applications.

MR. PRITCHARD: Good morning, ladies and gentlemen. My name is John Pritchard, and I'm Vice President of Regulatory Science for 22nd Century Group.

And I'm here today to talk about our VLN King and VLN Menthol King products. And this is a very exciting meeting, it's an important meeting, and it represents a number of firsts.

This is the first ever meeting that will review a modified exposure claim. At the same time, it's the first and likely the only time that the Committee will consider a combustible tobacco product.

And perhaps most importantly of all, this is the first time ever that the Committee has considered a product that hasn't been

designed to create or sustain addiction. And this product, we believe, is aligned with FDA's policy intent.

So we need new batteries on this moment, so I'll just come to a brief overview of our presentation today.

So I'm going to begin by talking about the product in some detail, and then I'll move on to our claims in a little detail. I'll touch on the premarket tobacco product application, and I thank Dr. Tworek for doing such a succinct and eloquent job of that for us already. And then, again, I will touch on our modified exposure statutory requirements.

I'll then hand over to my colleague, Dr. Ed Carmines, a very experienced tobacco researcher and tobacco scientist, who will touch on aspects relevant to today's discussion, including morbidity and mortality and consumer perceptions and our own consumer perceptions study work and some of the findings relating the consumer interest and intentions to use.

And then I'll return to give a brief conclusion.

So how did we get here today? Well, back in 1994, as so many of you will be aware, there was the proposals coming forth from Benowitz and Henningfield on what the potential could be of reducing the nicotine in combustible cigarettes.

And soon after, our founder, using his own finances, sought to invest and participate in this. He wanted to know whether this could be achieved.

And he set about a series of collaborations with leading institutions around America to develop, ultimately, a tobacco variety with very low levels of nicotine.

And we arrived at this variety called Vector 21-41, and I'll touch on that a little bit more later. But this was the first of its kind that had been cleared through APHIS, or the Animal and Plant Health Inspection Service.

So as we heard earlier, the subject

of today's product discussion has a heritage in the SPECTRUM line of cigarettes.

And we were approached by different agencies with an interest in having such products coming from our very low tobacco to explore the effects and what would this mean, what would the research show from products with these very low levels of nicotine?

A number of organizations were involved in designing and developing those, including NIDA, NIH, the FDA, CDC. And we've been doing this for some time now. So for almost a decade, 28 million of such products have been produced.

And as so many of you will be aware, I feel very honored to have some of those leading authors present with us today for this key research, with over 60 studies having been done in this area.

And indeed, it's from the research that's been done with the SPECTRUM line of products that we find FDA developing its

thinking and its -- we see the ANPRM, where the potential of these products is really seen, built on this significant foundation of public health research already.

So, as was said, we are talking about products today which are the same as the low nicotine SPECTRUM products that have been used in so much research. And I will just go into a little more details on that product and then move into the claims.

So the product itself is made in the same manner, using the same processes, materials that are well-established in the tobacco industry.

And they're used like conventional cigarettes; there's no electronic component. The technology, where it is, is solely in the tobacco that's used, it's very low nicotine content tobacco. And indeed, there are no instructions for use, no special instructions.

The tobacco itself, we can see an example of the tobacco under cultivation here.

And again, this really shows, links back to what I was saying earlier about the feasibility of producing many millions of these such products for use in research. And it's something that we're very able to do, have been doing for a long time very consistently.

So as for the technology itself, you can see on the left here a typical plant, using the tobaccos that are used in conventional cigarettes.

So here, nicotine, which is a harmful substance as defined by FDA, a highly addictive substance, as we all know, is made in the roots. And then it's transferred through the plant up into the leaves.

And on the right-hand side, we can see the Vector 21-41 tobacco. So, here, a series of genetic changes and different technologies built on each other.

And the effect of this is to disrupt the nicotine by a synthetic pathway, such that, and you can see it with my hopefully to scale

small arrow here, but this is to drive home the point that 95 percent less nicotine is in the tobacco. It really is fantastic technology.

So to the claims themselves. Firstly, the claim of 95 percent less nicotine. So while we term this as a claim, it is and stands as a fact.

And it follows from this into Claim two, that by having 95 percent less nicotine, that it helps reduce your nicotine consumption.

And thirdly, that the product smells, burns, and tastes like a conventional cigarette, but greatly reduces your nicotine consumption.

And we can see also the voluntary warning, which we saw displayed earlier. So nicotine is addictive. Less nicotine does not mean safer. And all cigarettes can cause disease and death. And we'll be hearing some more from Dr. Carmines later how we arrived at that.

But this would be displayed prominently on the pack, on the front. And we

believe that we couldn't be any clearer on this, and our belief on the product and our reference to the facts as they stand.

I just want to be very clear that we are making no drug claims. So the references to cessations, dependence, abstinence, as they appear in the presentation, should not be interpreted to mean that the company intends to make any drug claims. We do not.

The company is requesting only exposure modification orders, as set out under the statutory requirements of the Tobacco Control Act Section 911(g)(2).

So let's look at the proposed labeling that we've submitted to FDA. Again, you can see the use of the claims that I've just mentioned here and the prominent display of the warning statement placed in the middle.

And this is an orthodox packet format. There are no gimmicks; it is plain. And all along, our intention has been, in developing this product, that we would maximize

the appeal to adult smokers with an interest in reducing their nicotine consumption. But at the same time, to minimize the appeal to former smokers and never smokers and youth.

And as well as our voluntary warning, clearly, we will also have all the statutory requirements. So our warning sits in addition to the Surgeon General's warning, which of course would also be on every single packet.

So to the proposed marketing. We've seen examples in some of the briefing material you've been provided with, and there's a further one here.

We submitted a wide range of different proposals to FDA on how we might present those claims that we've just seen to consumers. And we anticipate feedback from FDA, and we look forward to their guidance as we move forward with this.

So to the premarket tobacco products application. As we heard from Dr. Tworek, there were a number of findings under that that are

highly relevant to the discussion today and, indeed, bring focus to today's discussion, as those findings already stand. But I'll just touch on a few points here now.

So following its comprehensive and rigorous science-based review of the PMTA submission, FDA determined that these products are appropriate for the protection of public health and that they have the potential to reduce nicotine dependence in addicted adult smokers who may also benefit from decreasing nicotine exposure and cigarette consumption.

And that nonsmokers, including youth, are also unlikely to start using the product. And that those who experiment are less likely to become addicted than people who experiment with conventional cigarettes.

In announcing the authorization of these products, in FDA's press release, they stated the following, and these are comments from Director Zeller.

Conventional cigarettes are designed

to create and sustain addiction to nicotine. In announcing the FDA's comprehensive plan to regulate tobacco nicotine in July 2017, we noted our commitment to take actions that will allow more addicted smokers to reduce their dependence and decrease the likelihood that future generations will become addicted to cigarettes.

He went on, today's authorization represents the first product to successfully demonstrate the potential for these types of tobacco products to help reduce nicotine dependence among addicted smokers.

Now, just to touch on some of the science that sits behind those statements. So, firstly, that there is 95 percent less nicotine in the tobacco.

There was less than -- sorry, greater than 95 percent less nicotine in the tobacco. So there's a reduction of 95 percent in the tobacco smoke. And in the blood plasma of smokers who consumed the product, nicotine was also reduced by at least 95 percent.

At the same time, there were findings around the reduction in biomarkers of exposure. And that there was a lower abuse liability. And importantly, that the smoke chemistry was the same as other cigarettes.

We're very grateful and pleased to have received this authorization from FDA, but at the same time, under the PMTA process, as we all know, we're unable to communicate the difference, this profound reduction in nicotine to consumers.

And that's what really brings us forward to this discussion around the modified exposure claim. How do we let adult smokers know, how can they know that difference?

Imagine going into a store and every product all had the same labeling. There was no way to know which was high fat, low fat, diet, low-cal, caffeinated, decaffeinated, you just have to guess and see what you got.

And we believe that all adult smokers with interest in reducing their exposure to

nicotine have a right to know this information.

So on the modified exposure statutory requirements. We believe that from the evidence and the findings already by FDA, a number of those requirements have essentially been met.

And these relate to the labeling and how it's explicit to the representation of that substance, which will be reduced. And the reduction in the substance is of a substance that is harmful, and FDA has made very clear that nicotine is a harmful substance.

And the product as actually used will not expose them to higher levels of other harmful substances compared to similar tobacco products.

And that the scientific evidence is not available for obtaining an order under Section 911(g)(1) of the FD&C Act, recalling that this is the modified risk part. And we are not making or pursuing modified risk claims, we are at this time, in this meeting, considering modified exposure claims.

And that the exposure modification order would be appropriate to promote the public health.

So just to touch again on the preliminary conclusions of FDA, and we've seen those provided in the material today. As far as substantiation, that the three proposed claims are substantiated, the claims that I've just shown you this morning.

And from a consumer understanding, the consumers understand the addiction risk of using the products relative to normal nicotine content cigarettes, but it's unclear whether they understand other relative health risks of using the products.

And on morbidity and mortality, that the proposed modified risk products can reduce dependence among individual tobacco users. And at the same time, the magnitude of the reduction of the mortalities and morbidities from reduced dependence remains unclear.

And finally, from a population health

impact perspective, nonsmokers have low intentions to use the products and current smokers have moderate intentions to use the products.

And FDA goes on, all smoker groups have higher intentions to purchase VLN cigarettes compared to Marlboro Gold cigarettes. So this is the number one selling product in the U.S. today.

And this brings us to the topics of today's discussion, where the Committee will go into more detail, and I'll move through this slide as we've had this presented very well just a moment ago.

So for the remainder of our presentation, we're going to bring forward support for our modified exposure authorization and to bring perspectives on the data to the Committee.

We will cover the aspects of morbidity and mortality and that it is reasonably likely, this reduction in morbidity

and mortality is reasonably likely that this will occur in subsequent studies, and that the population level taking into account both users of tobacco products and persons who do not currently use tobacco products.

And finally, around consumer perception, the testing of this shows that consumers will not be misled.

So at this point, I'd like to hand over to my colleague, Dr. Ed Carmines, who will do a deep-dive into some of the science for us all now. Thank you very much, Ed.

DR. CARMINES: Thank you, Madam Chairman, and thank you, Committee, for allowing us to have the opportunity to come up and talk to you about this great product that I've had the pleasure of working on, and many of you have also worked on.

I see some great people here, Dr. Donny, Dr. Hatsukami, who have spent probably the last ten years working on this project, this concept.

As John mentioned, this started in 1994, that's approximately 25 years ago that Benowitz came up with this concept. And what we're seeing today is the fruition of really 25 years' worth of discussion, thought, and research.

From our estimation, over $125 million has been spent by the federal government on studies on this very concept of reducing the nicotine in cigarettes.

It's a daunting task for me to come here and talk to you about all of the work that all of you have done, but I'm going to try today to just talk about some of the items that are part of the discussion.

One of the requirements is that there's a likelihood that when people use this product that there will be a reduction in morbidity or mortality.

The requirement for a reduced exposure product is that you actually not have this data. If we had the data to prove that

morbidity and mortality would be reduced, we would do a reduced risk exposure application. We did a reduced -- excuse me, a reduced -- modified risk application, we did a reduced exposure application.

We do believe that there's sufficient evidence to lead one to conclude that it is likely that morbidity and mortality will be reduced.

The FDA has identified nicotine as a harmful substance. I just don't want to belabor that subject, but the key is that we reduced nicotine in our product.

One of the other requirements is that we don't have a chemistry in the smoke that's different from conventional or other products. On the left-hand side, we've tried to show the smoke chemistry of the six leading brands.

These include Newport Menthol Green, Marlboro Red, Marlboro Gold, Marlboro Special Blend, Marlboro Menthol, and Camel. So we compared the smoke chemistry of our product to

all of these products.

This is a log scale, so down at the bottom, the units are milligrams per cigarette. It goes from a carbon monoxide level, on the right-hand side at the bottom, of about ten milligrams down to about one nanogram.

And what we see is that VLN is very similar to a lot of the other products that are in the market. We do have some unique circumstances where VLN is actually less. Clearly, there's less nicotine, but there's also less tobacco-specific nitrosamines. We also observe a reduction in acrolein, formaldehyde, and BaP.

Our conclusions is that the, as the FDA concluded, is that the product is not really different than conventional products on the market. We believe that VLN is not safer and that VLN, if used just like a conventional cigarette, could cause disease and death.

We performed three studies ourselves on VLN, that complements about 60 other clinical

studies. One of the studies that we're presenting here is our pharmacokinetic study.

What we see is that at the blue line, the usual brand at the top, you can see the nicotine quickly rises and peaks in about two to three minutes, and then declines. The red is nicotine gum. And down at the bottom that you can hardly see is VLN.

When you look at the area under the curve, which represents the total exposure to the nicotine, you see that the usual brand for this king size product was 880, nicotine gum was about 280, and VLN was 28.

That's a 95 percent reduction in the nicotine levels, compared to the usual brand. And we are actually ten times less than nicotine gum itself. The FDA concluded, based off of this data, as well as our subjective test, that VLN has a lower abuse liability.

FDA noted that while there's limited evidence on very low nicotine content cigarettes, youth who experiment with such

products may find them less appealing and may be less likely to develop nicotine dependence. This is important, and we'll talk about this later. If youth choose to try our product, at least they won't become dependent on it.

The FDA, announcing the authorization of the PMTAs, stated the agency determined that nonsmokers, including youth, are also unlikely to start using the products and that those who experiment are less likely to become addicted than people who experiment with conventional products.

I can't say that any stronger; this is an important aspect of our product. If youth try, we believe that they won't become addicted and won't become lifetime smokers. That's a critical element of the product itself.

One of the other results of the studies -- and I'm sure Dr. Hatsukami has seen this slide, it's her slide, thank you, Dr. Hatsukami.

She performed a study in 1,250

subjects at ten sites, and Dr. Donny I believe was involved in this study also, where they gave SPECTRUM cigarettes, the low level nicotine SPECTRUM cigarette, which is the same cigarette as our VLN, to smokers and they switched them immediately, that's the tan area, or allowed them to gradually reduce their nicotine consumption by using other SPECTRUM cigarettes.

What we see here is approximately a 50 percent reduction in cigarettes per day after 20 weeks of use. This is comparing to the control group, who received a normal nicotine content cigarette, SPECTRUM cigarette.

So if you look at the numbers, you can see, well, there's about 50 percent reduction. If you say well, what happened compared to the beginning? It's about a 25 percent reduction.

In studies, it's very consistent, you give people free cigarettes, they tend to smoke more, and that's what was observed here. I believe Dr. Donny observed essentially the same

thing in his six-week study.

So what is the effect of reducing cigarettes per day? The literature reports that reducing the dose, that is the number of cigarettes per day, has an effect on risk.

It affects some of the risk, but not all of the risk. We know that the risk of lung cancer will go down. What we believe is that the cardiovascular risks probably are not going to decrease to the extent that lung cancer will go down.

The American Cancer Society performed a study and showed that approximately linear relation exists between lung cancer and number of cigarettes per day.

In Dr. Hatsukami's study, she also saw a reduction in the nicotine exposure. There was a reduction in biomarkers of the volatile organic compounds and also reduction in NNK. Clearly, these smokers who used the product reduced their exposure to nicotine and also reduced their exposure to some of the biomarkers

of toxic materials.

One of the questions that comes up continually in these studies is that of dual use. What happens when you use conventional cigarettes and our product?

The reality is that in all of these studies, some of the subjects cheated. I believe in Dr. Hatsukami's study, approximately 80 percent of the subjects cheated at some point or another.

This is clear in just about every clinical study that was done. The only study that I'm aware of where they didn't cheat was a study that Dr. Donny did, where he locked the subjects up in a hotel for a weekend and made them smoke this product and only this product.

Dr. Nardone reviewed a study, a 683-patient study, to try to find out why people cheat and when they cheat. And the number one answer of when they cheated was that first cigarette of the day. They're addicted to nicotine, they want their fix, they're in

withdrawal, they go to that.

The older the person is or the more addicted they are, they more they cheat during the study.

Even though there is cheating, or dual use of these products with conventional cigarettes, in every study, there's a reduction in nicotine exposure, there's reduction in biomarkers of nicotine exposure, proving that the nicotine was down, and cigarettes per day go down.

I'd like to focus on the six-week study that we performed. We had subjects smoke our product, VLN regular or VLN menthol, or their usual brand, and we asked them to smoke these products over six weeks.

The protocol said if they cheat, we're going to exclude them from the analysis of the population. And we assessed cheating by looking at their pre cotinine levels and post cotinine levels, this is a Benowitz correction to determine whether they had or were using non-

study cigarettes.

In addition, we collected all the butts. In addition, we had them record the number of cigarettes they smoked, both study cigarettes and non-study cigarettes.

So from this we were able to select individuals that we considered single users, this was the per protocol population, or dual users, those that didn't really follow the protocol.

On the left-hand side, we see the smoke constituents that are reduced in red in the smoke of VLN cigarettes. And then we see the biomarkers that we measured.

And what we see is that, generally, subjects who singly used our product had a larger reduction in the biomarkers of exposure than those that dual used. This is what you expect.

What we do see is that all of these were statistically significant. So irrespective of whether they were dual users or primary

single users of VLN, they benefitted from using the product.

I'd like to just summarize what the individual benefits of VLN are. This is one of the requirements.

Clearly, you'll see later, that never smokers and former smokers really are not interested in VLN. Current smokers are going to benefit from the lower abuse liability and reduced cigarettes per day.

Those people around the never smokers and former smokers, since they don't smoke or don't start smoking, won't be exposed to secondhand smoke. And those around current smokers who reduce their cigarettes per day, theoretically will experience a reduced secondhand smoke.

We developed a population model to try to understand what the impact of using VLN would be on the population as a whole. This is a flow diagram of the model.

And what we see is, just incoming

population can either decide to smoke or not. And the smokers decide to quit or not. And they become, at the end, they die.

In our model, we measured life years gained and avoidable cigarette-attributable deaths. You see, in orange, where VLN fits in. VLN has no impact on initiation. It has no impact on the never users.

So the only place that it plays a role is in conventional smokers that decide to switch and relapse back and forth. Either they become sustaining or they revert back to conventional cigarette smokers.

In our model, we made some assumptions based off of the perception studies. There was no initiation with VLN. There was no re-initiation of former smokers.

We estimate a 25 percent market penetration over the next 30 years and that 50 percent of the VLN smokers would sustain after a year and ten percent of the smokers would relapse back.

And driving the assessment of life years gained and mortality, we used reduction in cigarettes per day and we used a quit rate. The average quit rate in the United States, irrespective of what you use to quit, is about four and a half percent. So if you use NRT, if you use cold turkey, it's four and a half percent.

We used 5.3 percent. This was an 18 percent increase in quit rate, based off of Walker's study, six-month study. So while this doesn't seem very large, this is the strongest data to date about what happens with people that quit and sustain quitting.

We also looked at various cases. We talked about the base case, four and a half percent increase in quit rate to 5.3 percent. Our relapse rate, that is people who are using VLN but go back to conventional smoking, it was ten percent. This is based off of Hughes reference.

Our pessimistic case is that 20

percent relapse and none of them quit. And our optimistic case was that 150 percent increase in quit rate, that is from four and a half percent to 6.75 percent. And our optimistic case also was that no one relapses.

So this is what happens in the model with these assumptions. In red, we're showing the current state without VLN, and green with VLN.

VLN has no impact on initiation. VLN does impact and rotates back and forth with initial VLN users either using the product or quitting. And we modeled age groups, we modeled sex, we modeled whether the people were heavy users or light users.

In the end, the quit rate, the differences in the model of the base case were either four and a half percent or 5.3 percent. Quit rate is the major driver in the model. The other driver is the cigarette per day reduction.

So this is the bottom line of our model. Over the next 80 years, 340,000 avoided

cigarette-attributable deaths will be seen and over eight million life years will be gained. The optimistic case is almost a million avoided cigarette-attributable deaths and 18 million life years gained.

We developed this model, and Dr. Apelberg published his model. And he did a little bit different approach, but we took the assumptions of the proposed rule, that is that everyone smokes VLN cigarettes and they can't relapse, because there is no relapse cigarette, there's no conventional cigarette.

And we came up with approximately 8.4 million avoidable deaths, as compared to Dr. Apelberg's 8.5 million. Our life years gained was a little bit higher, but it's interesting that our model mirrors the conclusion of the FDA.

So in summary, for morbidity and mortality, we all know that nicotine is a harmful substance; FDA identifies it as that.

The VLN pharmacokinetics indicate

that there's a lower abuse liability, that subjects using low nicotine content products will reduce their cigarettes per day, the biomarkers of exposure are reduced, even when subjects dual use, and the modeling shows a clear benefit to the population as a whole.

The scientific evidence that is available demonstrates that it is likely there will be a measurable, substantial reduction in morbidity or mortality among individual users.

Next, I'd like to talk about consumer perceptions. I'm not going to talk about our perception study; I'm first going to talk about the consumer's preexisting misconceptions on nicotine.

There have been a number of publications that basically show that the consumer believes that either nicotine -- or, excuse me, that nicotine is responsible for cancer or most of the diseases of smoking.

I think we'll hear from Dr. Byron a little bit later about his work, his study here,

the public's misperception that low nicotine cigarettes are less carcinogenic. It's clear that people perceive that if you put less nicotine in a product, it's going to be less carcinogenic.

The FDA performed their own study. I believe Dr. O'Brien is here. Dr. O'Brien, somewhere? I don't see anybody raising their hand. I thought -- yes, there.

So most people believe that nicotine's the substance that causes people to smoke, that's clear. But about half of them incorrectly believe that nicotine is the main substance in cigarettes that causes cancer, and another 24 percent were unsure.

So what that means is almost 75 percent of the people believe or are unsure if nicotine is the cause of cancer. This was before VLN cigarettes came along. This is a misperception that the consumer has today. We didn't do this; this is what exists before we ever came to the table.

So now I'd like just to talk a little bit about our consumer perception studies, now that I've set the case that consumer already has a misperception about nicotine. And we've lowered nicotine, so what does this do to their perception of our product?

We performed five different qualitative studies, and these studies looked at both reduced risk and reduced exposure statements. We ultimately came to the statement, 95 percent less nicotine. But that wasn't where we started.

We started with statements like 95 percent less nicotine than the leading brands, 95 percent less nicotine than your usual brand, 95 percent less nicotine than all other brands. We tested statements like five percent of the nicotine of usual brands. We tested statements of 0.5 milligrams nicotine.

And what we concluded was the consumer lacked really the ability to understand anything other than 95 percent less. When we

said usual brand, if they're not a Marlboro smoker, they don't know what that means. Most people don't know what the leading brands are. They might have an opinion, but they don't have the data.

So we concluded that 95 percent was a better statement. And while it's not shown here, we actually tested the product against the top 100 brands chemically to demonstrate that it was less.

So we performed these qualitative studies, and then we performed a quantitative study on the final statement that we put on the label.

When we developed the labeling, the terminology, we assessed the consumer's intent, what did they know about the product and what did they believe? And as we added statements like 95 percent less nicotine, we asked them what their health perception was about this.

In doing this, we could see, as we provided terminology about the product, our

description, that their perceptions of the health impact changed.

Our goal was to create a pack and wording that was informative to the subject, the smoker, but did not attract nonsmokers, but also was truthful. We wanted the consumer to understand that reducing nicotine did not mean that this was a safer product.

And clearly, when we ran the studies, as we talked to the people about their perceptions and used different terminology, their perceptions of where the product fell on the risk continuum moved.

So we would continually change our warning statement or our claims about the product to move them back to believing that our product was just like a conventional cigarette. And John spoke of the wording that we ended up with as a result of this.

So we ran 42 focus groups and 104 in-depth one-on-one interviews. And these were done around the United States. We selected

people who were smokers, former smokers, never smokers, we tried to cover age, gender, and race in doing this, so we could talk to as many consumers as we could to make sure that we were getting a representation of what could be the clear impression of the product.

The findings were that consumers didn't interpret the VLN labeling or the exposure modification claim to mean that the products were safer.

We still detected a problem that there was a concern that some people, even though we told them nicotine was addictive and the product wasn't safer, they still misinterpreted the health effects of the product.

That led us to this warning statement. We wanted to be sure that the consumer clearly understood that we reduced nicotine, nicotine is addictive, and that all cigarettes, even this one, can cause disease and death.

We did not want to mislead the consumer into thinking that this product was safer in any way. We put the warning label on every pack. As I'll talk about in a minute, we tested the packaging in 28,000 consumers.

You could say well, what is the impact of this messaging? Dr. Villanti published a paper just recently that says, you know, if you do a brief nicotine message on the product, similar to what is done with the warnings, that you can correct some of the misperceptions of nicotine.

That's really what we're trying to do. We can't change the world, but we're trying to make sure that people who see our pack will understand that it's not safer.

So I mentioned our quantitative study. There were 28,000 participants. This was done across the United States. It included all census groups. We looked at age, sex, race. We looked at menthol use, non-menthol use. We looked at their earnings, so low earnings, high

earnings.

We cut the data, we talked to adult smokers, we talked to never smokers and former smokers. We were able to ask questions about their intention to quit or no intention to quit. We also cut the data by how long ago they quit.

And for the adult never smokers, we over-sampled in the legal age to 25 to make sure we had a good measure of these individuals' impressions about the product. We're trying to understand or make sure that youth are not attracted to the product, so we over-sampled those individuals.

The study, and you'll see, I think later on there's a much better slide about the study design than we have here, we showed, initially, the subjects conventional cigarettes, moist snuff packs, e-cigarette packs, pictures, and nicotine replacement therapy. And we asked them about their health or addiction risk perceptions.

We then showed them either our

product or Marlboro Gold and we asked them the same questions.

We then went back and showed them the conventional products again, to see whether their health and risk perceptions changed.

Finally, we asked them about their intent to purchase and intent to use our product. After they saw our pack, we asked them direct questions about the pack to make sure that they could comprehend the label.

We also addressed their familiarity of the different products. So, you can see, for example, that never smokers don't really have a lot of familiarity with NRT or with oral tobacco. But current smokers do, they're aware of these. So, we were able to tease this out in our data.

The four major diseases or health risks that people think about, I believe that we looked at 16 different measures of health risk.

What we see here today is that, for our product and Marlboro Gold, that, in the case

of lung cancer, 94 percent of the Marlboro subjects said there was a very high risk, high risk, or moderate risk of lung cancer. For our product, it was 87 percent.

You see this pattern throughout. There is a slight reduction in our product versus Marlboro Gold.

This is clear in the next slide. So, here, we see the ranking, almost the continuum of risk. You see conventional cigarettes on the left and you see nicotine replacement therapy on the right.

So, in the case of lung cancer, conventional cigarettes was 95, lung cancer is 94, and our product's 87.

We believe that the reduction is a misunderstanding of the risk of nicotine. That's why these people are reporting this material this way.

It's interesting to note, if you look at mouth and throat cancer, that snuff moves up. These people understood that snuff causes oral

cancer and they rated that higher. So, they had some understanding of the disease risk.

I stated that there were 28,000 people in this study. We asked people to tell us about the product. Our goal in this design and in the product was to make sure that they didn't misinterpret that less nicotine was safer.

If we look just at the first verbatim, it says, if I was serious about quitting smoking and was trying to get off nicotine, then I might consider it, but I certainly wouldn't think it's safer in any way.

The second one, the Chattanooga female, a recent quitter. I'm going to put it up there with regular cigarettes, because it's just less nicotine. You're still getting all the smoke in your lungs. I'd say it's the same. I don't care what kind of smoke it is, it's not good for you.

Our goal, again, was to not have the consumer believe that this is less risky or

safer.

The study clearly showed, from the verbatims, that the subjects understood the health risks. When asked how to describe VLN to a friend or a family member, 66 percent of the people stated that it was low nicotine. They understood that this was a lower nicotine product.

Sixteen percent, off the top of their mind, mentioned the health effect. When asked about the health risk of the product, 31 percent associated VLN as having the same health risk as regular cigarettes.

Fifty-five percent responded appropriately with diseases such as cancer, lung and respiratory disease, heart problems, and general mentions of the product being harmful.

When asked about the health or addiction risks associated with VLN, only seven percent said there were no health risks. That means 93 percent concluded that there were indeed health risks with the product.

I'd like to move on to addiction. So, the product is labeled 95 percent less nicotine, helps reduce your nicotine consumption. We see here that the consumers perceived that VLN had a lower nicotine addiction potential.

The questions that we asked them were, does this product make you feel addicted? Feeling unable to quit? Better to use or make you feel better? Can't stop using?

You can see, in every case, the VLN is less than conventional cigarettes. This is what we would expect. They clearly understood that the product had less nicotine and potentially had a less addictive potential.

I mentioned earlier that 50 percent of the population, the studies show, basically are misled or have the misperception of nicotine causing cancer or being responsible for the diseases.

We just look at the rating for NRT. So, NRT, as we all know, is nicotine in a patch,

nicotine in gum, nicotine in a lozenge. Universally, about 50 percent of the people concluded that NRT had a very high risk of lung cancer, of mouth and throat cancer, of emphysema and heart disease.

This is the background that we're working with. We didn't do this to them. We didn't mislead them. They concluded before we ever came to the table or we launched this product that nicotine is the cause for most of the diseases related with smoking.

Next, I'd like to talk a little bit about the consumer interest and intent to use. I'm going to talk about never smokers and former smokers, as well as current smokers.

When we looked at the intent to use the product, the average intent to use, this is across all respondents, we see for total never smokers that it's a very small amount. The respondents were asked to rate the product, ranging from definitely would not to definitely would.

So, the rating, the difference between the one and two, is really them saying they definitely would not use the product or it's very unlikely that they would use the product. So, I think the difference between VLN and Marlboro Gold there was probably 1.2 and 1.3.

In all of the cases that you'll see, there's a higher intent to use our product than Marlboro Gold. It doesn't matter whether it's never smokers, former smokers, or current smokers.

When we look at the individual ratings that the respondents gave us, for current smokers, about 60 percent indicated an interest in the product, nine percent said they definitely would use it, 16 percent very likely and 34 percent somewhat likely.

When we look at former smokers and never smokers, 95 percent of both of them said they were somewhat unlikely, very unlikely, or definitely would not use the product. There

really was not much interest in the product at all by former smokers and never smokers.

I mentioned that we over-sampled the legal age to 25, as a proxy for youth. In this case, we see that never smokers are really not interested.

There was a little bit of an interest by the youth, they went from definitely would not to very unlikely, somewhere in that range. They never reached very unlikely, they're still very close to definitely would not. There was a higher interest in VLN than Marlboro Gold.

When we look at smokers, we see those smokers with an intent to quit, it's very likely that they'll use VLN, more so than Marlboro. And even in the smokers that have no intent to quit, they were interested in the product also. This is markedly different than the very unlikely or definitely would not response of the never smokers and former smokers.

So, in summary, the consumer perception, I'd just like to remind the

Committee, we made no health risk or addiction risk statements on the product. We just said, 95 percent less nicotine.

The perceptions that they gave us are really based off of their understanding and misunderstanding of the role of nicotine in smoking-related diseases.

As was demonstrated, there are many misconceptions about the role of nicotine. It's clear from the literature, and Dr. Byron I think will talk a little bit about his work, that there's a misperception. Our perception studies show that 50 percent of the people believe that NRT causes cancer and the diseases of smoking.

The perceived health risks of VLN are similar to Marlboro Gold. We're at the same range on the continuum of risk. We're over there with conventional cigarettes. We're not down where nicotine replacement therapy is.

We believe that the slight reductions in the risk, as measured by differences between us and Marlboro Gold, are really a misperception

of the risk of nicotine.

It's clear the subjects understood that VLN cigarettes had less nicotine, that they may be potentially less addicting, and that never smokers and former smokers and the legal age to 25 youth proxy really are not interested in the product.

We believe that our label did not mislead the consumers into believing that the product was safer. We put a label, a warning label on the product to make sure they clearly understood that our product is not safer.

At this point, I'd like to turn it over to my colleague, John Pritchard, to summarize where we are. I thank the Committee for their time.

MR. PRITCHARD: Thank you, Ed, for taking us through in detail there. Madam Chair, Committee Members.

So, as we move to our concluding slides now. So, by way of providing a quick recap of some of the science that is out there

for these product, it's well evidenced over research that spans almost a decade, of which the majority has been conducted by leading public health institutions and research institutions around the U.S.

And it goes along these lines. There's at least 95 percent less nicotine in the tobacco. And we see in the smoke, at least 95 percent less nicotine in the smoke. And there's at least 95 percent less nicotine in the blood plasma of subjects in the various studies that have used these products.

We've seen the reductions in cigarettes per day that flow from this very low level of nicotine in these particular products.

And we've seen the reduced biomarkers of exposure. Critically, we see the lower abuse liability that's associated with reducing nicotine by such amounts in these products.

And importantly, that the smoke chemistry is the same as other cigarettes. And we believe it's very clear, both from our own

research and our intent, that all cigarettes can cause diseases and death.

So, we're looking forward very much to the Committee's discussion that will follow in the coming hours, where the committee will explore different aspects around the perceptions of addiction risk and disease risk, and the mortality and morbidity and how the dependence translates into substantial reductions in this, and the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products.

And we'll explore and hear from the Committee their views on never smokers and former smokers.

And lastly, on dual use and the extent to which we'll find that difference between cigarette smokers who want to quit smoking and cigarette smokers who do not want to quit smoking.

Finally, our conclusions on the VLN product that we've brought forward to the FDA

under our modified exposure application.

We believe from the labeling that addiction and health risks are understood and we've seen examples of people in their own words, not just data but actual people's comments, as they've tried to balance their understanding of addiction and disease risk. And we've seen how they get it.

We've seen very clearly how never and former smokers have little interest in the product. As I said, in making this application and conducting our studies and designing the product, we had in mind, how do we maximize the interest among smokers with an interest in reducing their nicotine exposure, while at the same time minimizing the interest in former and never smokers? And we believe we've achieved that.

We've seen how, at the same time, dual users still reduce nicotine exposure. So, even with the cheating and the dynamics and those effects that are well understood by

researchers in that area, they still have a reduction in nicotine exposure.

And we've seen from different aspects of science showing we believe very clearly the effect of the reduction in cigarettes per day and how this translates to effects on morbidities and mortalities and how this is likely also in future studies.

And as I said at the beginning, this product is very much aligned with the policy intent of FDA. And from that, 22nd Century believes it is appropriate for FDA to issue an exposure modification order for VLN.

We thank you all very much for your attention to our presentation and we look forward to the discussion that will follow. Many thanks to you all. Madam Chair?

CHAIR MERMELSTEIN: Thank you, Mr. Pritchard, and thank you as well for all the presentations. We're going to hold a general discussion later, after we have several other presentations and time for more questions.

But just to see if there are any very specific clarifying questions about a particular slide, but not a general question. So, are there any specific clarifying questions about any of the slides?

DR. OGDEN: I have one question for clarification. On Slide 37, you mentioned your assumptions included 27 percent market penetration. Could you define that term, please?

MR. PRITCHARD: Certainly. We use the rate to establish at what -- how would we find the effects in this? I mean, we have to assume that someone is using it and 30 years is a long time to do that.

I mean, perhaps, at this point, I could turn over to one of my colleagues that was involved in the development of the model?

DR. CARMINES: So, Mike, what that means, we projected that over the next 30 years, that we would have 25 percent of the market share. That 25 percent of the cigarettes sold

in the United States, irrespective of whether there's a proposed rule or not, would contain this tobacco.

DR. OGDEN: Thank you.

CHAIR MERMELSTEIN: Dr. Hatsukami?

DR. HATSUKAMI: On the slide that you showed of our study, that showed a reduction in cigarettes per day, which I believe you extracted from the JAMA article, we incentivized people to only use very low nicotine content cigarettes.

And so, I was wondering whether in your study, the six-week study, where you were looking at dual use, what the instructions were, in terms of the use of these cigarettes, and whether there was -- well, I was just wondering what the instructions were.

DR. CARMINES: The subjects were instructed to use our product and encouraged to use our product.

But we also collected all of their butts, we counted the butts, and we could tell,

basically, from the design of the cigarette, whether they were using our cigarette or another cigarette.

We also asked them to keep a diary, which they indicated whether they smoked a study cigarette or a non-study cigarette. And the ones who were significantly different, we excluded from the patient population.

DR. HATSUKAMI: I see. So --

DR. CARMINES: So, we tried to encourage them, as strongly as we could, as you do, as many people have done in their studies, we can't prevent them. And we wanted a truthful response.

DR. HATSUKAMI: So, they were told to just use the cigarettes or were they informed to completely switch over to --

DR. CARMINES: They were not forced to switch, they were encouraged to switch, they were told --

DR. HATSUKAMI: But not --

DR. CARMINES: -- that was the goal of

the study.

DR. HATSUKAMI: Okay.

DR. CARMINES: But we also wanted them to record whether they did use non-study cigarettes.

DR. HATSUKAMI: Okay. Thank you.

CHAIR MERMELSTEIN: Dr. Thrasher?

DR. THRASHER: Thanks. In summarizing the qualitative studies that you all went through in landing on the messaging that we're evaluating today, on Slide 47, you talk about a series of qualitative studies.

And my interpretation of what you presented is that the only message that was really tested through that series of qualitative studies was the message on 95 percent less nicotine.

And that the other messages on helps reduce your nicotine consumption, greatly reduces your nicotine consumption, and then, the kind of voluntary labeling that you put on there around nicotine is less addictive, et cetera,

that those messages were not evaluated in the qualitative studies. Is that fair to assume?

DR. CARMINES: The -- those messages were evaluated in parts and pieces throughout the process. And there were other messages that were tested. We tested reduced risk messaging, as well as reduced exposure. I only gave --

DR. THRASHER: So, were the --

DR. CARMINES: -- you examples --

DR. THRASHER: -- was the specific wording that we're considering here, outside of the 95 percent less nicotine message, was that specific wording tested in the qualitative interviews and seen as being comprehensible and understood by people who participated in those initial qualitative studies?

DR. CARMINES: We tested parts and pieces of it, that led us to, at the end, to the final quantitative. So, yes, we refined the labeling throughout this process to try to convey the message.

But we did not run a qualitative

study at the end on what we were running our quantitative study on, if that makes sense. It was an evolution of wording that got us to the end.

DR. THRASHER: But the message number one, 95 percent less nicotine, was specifically evaluated in those groups and kind of came out as being --

DR. CARMINES: Yes, it was in essentially all of the qualitative studies. Initially, we didn't -- we included 95 percent less, but we also tested the concept of five percent of the nicotine or a statement of the pure nicotine content.

DR. THRASHER: Yes.

DR. CARMINES: And then, there were comparative statements, like usual brand, leading brands, things of that sort. But 95 percent was a consistent message throughout all of the claims related research. We also tested various warning statements about whether nicotine causes cancer, nicotine causes disease,

or smoking --

DR. THRASHER: Okay. Thanks.

CHAIR MERMELSTEIN: We want just really specific clarifying questions right now, because we will have a general discussion about perceptions later today. Okay.

DR. CARMINES: So, we have another response.

MS. TROTTER: Hi.

CHAIR MERMELSTEIN: Okay.

MS. TROTTER: I'm Christi Trotter with M/A/R/C Research, the contract research organization for this project. And I just wanted to note that those claims were tested in the fourth round of qualitative interviews, to clarify, to make sure you were understanding that that was the case.

CHAIR MERMELSTEIN: Okay. Dr. Weitzman?

DR. WEITZMAN: Could you clarify for us how these messages were actually presented to the participants? Did they see them with any

kind of images tested as well or just the wording? And was the wording on a package, on a sheet, how did they actually see them?

MS. TROTTER: So, for the first round of qualitative interviews, it was essentially a piece of paper that had images of the pack, the front of the pack and the back of the pack.

For the subsequent rounds of qualitative testing, we actually did have packs available for them. They looked just like a standard cigarette pack and it had the claims printed on them.

CHAIR MERMELSTEIN: Dr. Donny?

DR. DONNY: Okay. So, this is a question about something, I think I understood it correctly, so for the nicotine replacement, for the other products in which you first, I think, believe, looked at risk perception, and then, exposed participants to the products, and then, reassessed risk perception, is that correct, in the quantitative study?

MS. TROTTER: That is correct.

DR. DONNY: Can you speak to whether you've analyzed the data or whether you have any information about the change in risk perception for those other products as a function of exposure to those?

MS. TROTTER: We do have the data, I think that we would probably want to take a look at it. So, maybe in the next break, we can just review it before I provide a summary.

CHAIR MERMELSTEIN: Sally?

MS. HERNDON: Just a followup question on the method of the qualitative analysis. So, these messages were tested first on paper and then on packs, but not with advertising or marketing mockups, is that correct?

MS. TROTTER: That's correct.

DR. WARNER: That was my question.

CHAIR MERMELSTEIN: Okay. Dr. Warner, did you have a followup?

DR. WARNER: That was exactly my followup question, is whether they ever were shown the ads themselves? And --

DR. WEITZMAN: That's really the question I was asking as well.

CHAIR MERMELSTEIN: Okay, great. We have one question from Dr. Ossip on the phone, and then, Dr. King. Never mind, actually, her question got asked.

DR. OSSIP: Actually, my question, yes, my question was just asked, yes. Thank you.

CHAIR MERMELSTEIN: Thanks. Okay. Dr. King?

DR. KING: Yes, thank you. So, I'm trying to better understand the projection model, just so I can get a grasp around a broader population impact. So, you can just confirm that, in terms of the 340,000 avoided deaths, that's over an 80-year period, correct? So, over 80 years, there would be 340,000?

DR. CARMINES: That's correct.

DR. KING: And in terms of the model, the assumptions for initiation among never and former smokers was both zero percent in that?

DR. CARMINES: That's correct.

DR. KING: And do you happen to have any estimates of what would happen if you accounted for the five percent or so never and former smokers in your likely initiation? If you put that into the projection model, do you have any numbers of what that number would do, then?

DR. CARMINES: I don't have that, but we can get that.

DR. KING: Okay. Thank you.

CHAIR MERMELSTEIN: Dr. Warner?

DR. WARNER: Yes, I wanted a followup question on the model as well. You said you get penetration of, I think it's either 25 or 30 percent, which, congratulations if you could do it, that would be pretty impressive.

Let's say that that happened. You made the observation that your results are very similar to Dr. Apelberg's model and Dr. Apelberg's model, it's 100 percent very low nicotine.

DR. CARMINES: No, I'm sorry if I misstated, what we took was our model and we assumed that 100 percent of the users, the people who are smoking, would be forced to use our product and that they could not regress back to a conventional cigarette because there would be no conventional cigarette available.

So, we took basically the assumptions of enactment of the proposed rule and ran it through our model. And we came up with substantially similar results.

CHAIR MERMELSTEIN: Dr. Weitzman?

DR. WEITZMAN: Could you just clarify for me the VA 25 again? How did you sort out youth response to what they saw?

DR. CARMINES: Yes. I don't -- sorry, which slide is it?

We did not test perceptions in youth. What we did is, we sampled youth, we sampled all age groups, but we over-sampled subjects in the range of legal age to smoke, which was 21 to 25, so we could make sure of the perceptions of

those individuals. So, there were more than the census would have suggested you should have sampled.

DR. WEITZMAN: But we don't have any information about how those under the legal age would perceive this --

DR. CARMINES: We did not --

DR. WEITZMAN: -- is that correct?

DR. CARMINES: -- perform perception studies in those under the legal age.

CHAIR MERMELSTEIN: Okay. Thank you. We will have more discussions this afternoon and a chance to circle back as well. So, thank you, again, for a very clear presentation and for the followup questions and your responses, appreciate that.

So, we're going to take a brief 15-minute break and we will get back at 10:25 and have our public comments.

(Whereupon, the above-entitled matter went off the record at 10:13 a.m. and resumed at 10:25 a.m.)

CHAIR MERMELSTEIN: Okay. We're going to reconvene again and we are going to the open public hearing session.

Please note that both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, or if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in

connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

Okay. We are going to start with our first speaker is Nina Zeldes, from the National Center for Health Research.

DR. ZELDES: Good morning. Thank you for the opportunity to speak here today. My name is Dr. Nina Zeldes and I'm here as a Senior Fellow speaking on behalf of the National Center for Health Research.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from drug and medical device companies

or tobacco companies, so I have no conflict of interest.

We strongly oppose the approval of this modified risk application by the 22nd Century Group for their low nicotine combusted filtered cigarette tobacco products.

According to the FDA, a modified risk tobacco product needs to demonstrate that it significantly reduces harm to smokers and promotes public health.

Unfortunately, evidence is lacking to support the claim that this product significantly reduces harm for smokers. At the same time, it is likely to entice people who have never smoked, especially adolescents, to start smoking.

As the Applicant has pointed out, this low nicotine cigarette poses similar risks to tobacco-related disease as conventional cigarettes. Its only advantage is that it contains much less nicotine and could, therefore, be less addictive.

However, their claims of reduced harm seem to be based entirely on the assumption that people would smoke less often, an assumption that was not adequately supported by the Applicant's data.

For example, this product was rated as less satisfying than smokers' usual brand of cigarettes and less likely to be used again compared to nicotine gum, raising questions about whether smokers would switch completely to this product and ultimately quit smoking.

The FDA briefing document points out that nicotine is often perceived as causing smoking-related health risks. That means that a claim of a product having 95 percent less nicotine will be misunderstood as being less likely to cause cancer, when in fact, it just means potentially less addictive.

Although the Applicant provided a voluntary warning that less nicotine does not mean safer, study participants who were shown this warning still perceived this product as

safer than conventional cigarettes.

Additionally, the Applicant only tested their claims on packaging and not how they would be used in ads and social media. We've all learned that the context and imagery in these ads can vastly alter how these claims are interpreted. Tobacco companies have learned how to make very persuasive ads that go beyond the specific claims that they make.

As we all know, smoking is a habit that is very difficult to break. An addiction to nicotine is only one of the reasons that quitting is so difficult.

Most smokers start smoking as children and adolescents and, yet, adolescents were not included in any of the studies provided by the Applicant.

Previous studies have demonstrated that this group is likely to perceive products with a risk medication claim as less harmful, but that is not proven in this case.

In conclusion, while the claim that

this product contains 95 percent less nicotine may be factually correct, the company's claim of health benefits are based on the implied assumption that this product would help smokers quit.

If that is supposed to be the benefit, their product should have sought to market this product as a cessation aid. Moreover, the packaging does not explain how to achieve this health benefit.

Because of such claims, smokers interested in reducing smoking-related health risks might start using this product instead of quitting or using available FDA-approved cessation products.

Meanwhile, non-smokers, particularly adolescents, might start using this product thinking it is a safe alternative to other tobacco products.

If we have learned anything from the vaping epidemic, it is that adolescents are easy to influence and once they start a habit, like

smoking or vaping, they are unlikely to stop.

We encourage you to let the FDA know that you do not believe that this will be an acceptable outcome. Thank you.

CHAIR MERMELSTEIN: Thank you. Our next speaker is Michael Borgerding from RAI Services Company. Thank you.

DR. BORGERDING: Good morning. My name is Mike Borgerding. I'm the Vice President of Scientific and Regulatory Affairs at RAI Services Company.

RAI Services Company is a wholly-owned subsidiary of Reynolds American and bears primary responsibility for regulatory compliance for RAI's operating companies, including R.J. Reynolds Tobacco Company, American Snuff Company, Santa Fe Natural Tobacco Company, and R.J. Reynolds Vapor Company.

With the recent FDA clearance order that authorizes the marketing of VLN cigarettes as new tobacco products, Reynolds American looks forward to seeing how these products will be

used by consumers in real-world conditions.

While VLN cigarettes can now be legally marketed in the U.S., the question before FDA and this Committee is whether an order should be issued to advertise the cigarettes as modified risk tobacco products under the Act, based on the scientific evidence and the proposed reduced exposure claims set forth in 22nd Century's application.

The possibility of marketing VLN cigarettes as modified risk tobacco products presents a unique consideration.

As Dr. Apelberg from the Office of Science has made clear in public comments, FDA must evaluate any proposed modified risk tobacco product as it will actually be used by consumers, to determine whether it will significantly reduce the risk of tobacco-related disease to individuals.

Unlike the smokeless tobacco and heated tobacco products that have previously come before FDA and this Committee for

evaluation as modified risk tobacco products, some of which have been under review for far longer than this application, VLN cigarettes do not reduce the risks of smoking-related disease as actually used by consumers.

Rather, VLN cigarettes present the same risk of disease as other traditional cigarettes when smoked.

In recognition of this fact, 22nd Century has requested a clearance order for a reduced exposure message. However, the proposed advertising does not satisfy the legal requirements set forth for reduced exposure advertising under Section 911(g)(2) of the Act.

As we've heard this morning, to make a reduced exposure claim, the Act requires that available data must demonstrate that a measurable and substantial reduction in morbidity and mortality among individual users is reasonably likely to be found in subsequent studies.

However, 22nd Century acknowledges,

that FDA found in its PMTA review, that no such evidence was presented in the application for continued smoking of VLN cigarettes.

Indeed, as the Applicant makes clear, any potential reduction in tobacco-related disease will only be realized if a smoker quits smoking their usual cigarette brand, switches to VLN cigarettes, and then also quits smoking those cigarettes.

It's important to understand that VLN cigarettes have not been demonstrated to be safe and effective for smoking reduction or smoking cessation.

Clearly, if the underlying premise for VLN cigarettes is to reduce cigarette consumption and increase smoking cessation, then the product, together with its proposed labeling and advertising, can be fully evaluated for safety and efficacy by CDER under an FDA product clearance pathway appropriate for smoking cessation products.

Another key statutory requirement for

making reduced exposure claims that is not met by the proposed advertising relates to consumer perception.

Specifically, consumer perception testing must show that proposed advertising will not mislead consumers into believing that VLN cigarettes present less disease risk or are less harmful than other commercially marketed tobacco products.

Quantitative testing sponsored by 22nd Century shows just the opposite. After viewing the proposed advertising, current, former, and never smokers believed that VLN cigarettes are less harmful than traditional cigarettes and other tobacco products.

Such misperceptions are not surprising, since its well-established in the literature that many consumers, especially smokers, erroneously believe that low nicotine cigarettes are less harmful than other cigarettes.

Finally, TPSAC should note that while

the proposed advertising clearly communicates the benefit, it fails to provide any balancing information that would inform consumers about the potential for unique product risks, including the concerns noted by FDA in the PMTA review process.

Three examples of concerns found in FDA's TPL report include, first, VLN cigarettes contain genetically engineered transgenic tobacco.

Chronic and subchronic tox studies are not available for the tobacco in VLN cigarettes. And only short-term clinical studies have been conducted with the product. Therefore, the future consequences of inhaling transgenic tobacco from transgenic plants are unknown.

Second, there is the possibility of increased platelet activation and increased risk of thrombosis when smoking VLN cigarettes compared to smoking other cigarettes.

Third, adverse events related to

nicotine withdrawal and weight gain are possible when smoking VLN cigarettes.

Beyond FDA's stated concerns, 22nd Century has not taken the opportunity to emphasize that minors and pregnant women should never smoke any cigarette, including reduced nicotine cigarettes.

In summary, VLN cigarettes are not reduced cigarettes under the Act and the advertising before you does not meet the statutory requirements for reduced exposure advertising.

In addition, any modified risk advertising that is authorized by the agency should inform consumers not only about the possibility of reduced nicotine exposure, but also about any unique aspects of the product that may affect their health.

Thank you for the opportunity to make these remarks.

CHAIR MERMELSTEIN: Thank you. Our next speaker is Mr. Matt Myers, from the

Campaign for Tobacco-Free Kids.

MR. MYERS: Thank you for the opportunity. My name is Matthew Myers, I'm the President for the Campaign for Tobacco-Free Kids. I have no conflicts of interests.

There's a couple points that we want to make. One is, it's important to distinguish between this single application and the proposed rule that FDA had for a nicotine standard.

We are, and many other public health organizations are, completely in support of the proposed rule for nicotine.

The research that's been done, much of which was cited here today, was done with the contemplation that you would have a marketplace where all products would have reduced nicotine levels, so that not only dual use would be addressed, but another host of other issues there.

It is very important for us to look at this application in the context of not having a nicotine reduction standard as we go through

here.

Second, this is not a hearing today about whether this product should or should not be available. We may have different views about that.

But it is pure and simple a hearing about what claims they should be allowed to make in the current marketplace, where we're not doing this as an experimental level, where people aren't instructed how to use it or where to use it, as has been done in the other studies.

We have serious concerns and they fall into several categories. And let me just tick them off quickly for you with regard to it.

Risk perception. Risk perception is very important. 22nd Century made the point, repeatedly, that they walk into a marketplace which already has misperceptions.

That can't be used as an excuse. It means that you still have to evaluate how this product and its claims will be perceived in the

existing marketplace.

And that puts a greater burden on them to ensure that if they walk into a marketplace with misperceptions, for whatever reason, they don't take advantage of them or they don't continue those.

But if they want to make claims, the statute is very, very clear. Those claims have to ensure that consumers are not misled into false understandings about relative risk and relative harm.

It's not an option to say the marketplace is already confused and we will just move forward with it, the statute is very clear, you have an obligation, if you want to make a claim, to ensure that consumers are not misled and to ensure that consumers do not perceive, particularly with a reduced exposure claim, that that reduced exposure has been shown or is likely to lead to reduced risk in the absence of concrete evidence. And if you have concrete evidence, you should be making a modified risk

claim.

Very important point here, because you're setting a precedent today, it isn't whether you like the idea of this product or not, you're setting a precedent for how reduced exposure will be held.

And if you allow a reduced exposure claim to take place where their own studies show consumers falsely believe about reduced risk, even -- and their own studies take place with regard to the disclaimer. So, that the disclaimer obviously isn't changing that. A very important point for your analysis.

Second, the specific claims. The 95 percent reduction claim works perfectly in the utopian world, but doesn't work with actual use, according to their own studies.

That's very, very important, because nowhere on their label, nowhere on their advertising do they say, if you want to get the 95 percent, you have to switch completely. Their own studies show that whether or not there

is a reduction or not, with regard to dual use, it is far less than 95 percent.

And yet, as Jim Thrasher pointed out, when they were looking at the qualitative studies, that was the primary one that was looked at.

Ninety-five percent is true only if a consumer uses these products uniquely and with no other product. And yet, under a best case scenario, as Dorothy Hatsukami's studies show, you have 80 percent dual use, and that's even where people are being instructed to use it.

So, if there's any single claim that is factually not accurate as the product will be, quote, actually used in the marketplace, that's it.

And therefore, while it may be the clearest one, while it may be the most motivating claim, the statute requires you to analyze this under a circumstance of actual use, and that claim, under terms of actual use, can't pass the statutory standard.

It's intriguing that nowhere in the label and nowhere in the advertising does 22nd Century go out of their way to say, you only gain these benefits with completely switching to the products, if you want to get that.

It becomes even more important because the data on their second and third claims, greatly reduces, is far less persuasive with regard to those issues.

So, if you allow the 95 percent claim, you're walking down a very tricky slope, because it violates clearly the statutory standard with regard to actual use.

Third, as has been pointed out repeatedly, the perception studies looked at the label and packaging, but did not look at the marketing.

There was a very attractive slide that 22nd Century put up, but if you take a look at some of the other ads that are in their application, they're nowhere near as focused on what we would think of as adults looking to

smoke. They have some of the very same attractive images that we have seen used elsewhere to reach a very different audience.

If you're going to have perception studies and this Committee is going to rule on those, it is very important that those studies look at not just the labeling, but how the product is being marketed and that that be a component of that. It's another area where this application falls short.

Fourth, it is unfortunate that FDA continues to allow applications to come to this point without requiring youth perception studies. It is a fatal flaw that will crush FDA's consideration of MRTP going forward if it doesn't change.

This may be a low abuse product because of low levels of nicotine. But if this Committee and FDA continues to allow claims to move forward without requiring actual understanding of youth perceptions, it will undermine the purposes of this Act. I can't say

that too strongly, as we move forward, with regard to it.

Fifth, as FDA considered the PMTA application process and after all the data was in, the brand name was changed from VLN to Moonlight.

Brand names make a difference. I don't know at what stage of the modified risk application process 22nd Century may try to do the same thing.

But I think one has to, when we're talking about risk perception, when we're talking about how consumers will see this product, be very, very concrete that those kinds of name changes late in the process, where studies haven't been done on their application, has to have a direct impact on the consideration.

Particularly when you have a name like Moonlight. We have all lived through the nightmare of, quote, the light deception. Whether Moonlight does that or does not do that

shouldn't be for all of us to guess. There ought to be very concrete data on that issue as you move forward with regard to it.

So, in short, where we come out is whether somebody thinks low nicotine cigarettes are a good idea or a bad idea. This is not the place where we're doing the product standard, which frankly, we support completely.

What is critical to understand is how these claims will compare to the statutory requirements. And when you look at them, they don't meet the actual use test.

They did not look at how these products would be marketed. The 95 percent claim is not accurate in the real world in which we are now working. They didn't deal with addressing the actual risk perception misunderstandings. And they failed to look at the issue with regard to youth.

And whether or not these are low abuse products, that doesn't give them an excuse. Thank you.

CHAIR MERMELSTEIN: Thank you. Thank you. Okay. That brings us to the end of the open public hearing period.

So, we're going to move ahead with our next presentation, which is Dr. Mollie Miller from the FDA.

DR. MILLER: Good morning. My name is Dr. Mollie Miller and I'm a pharmacologist at the FDA Center for Tobacco Products.

Today, I'll be discussing the evaluation of VLN cigarettes as modified risk tobacco products, considerations of morbidity, mortality, and population health.

I'm going to start with a reminder of the statutory requirements for MRTPs related to morbidity, mortality, and population health impact.

I'll then provide a high-level overview of the data used to evaluate the effects of using VLN cigarettes as MRTPs on morbidity and mortality.

Next, I'll present the data used to

evaluate the effect of marketing VLN cigarettes as MRTPs on population health. Specifically, these data were used to evaluate the likelihood of both nonsmokers and current smokers using VLN cigarettes.

And finally, I'll summarize overall conclusions.

As mentioned earlier, 22nd Century requested an exposure modification order for VLN King and VLN Menthol King cigarettes under Section 911(g)(2) of the Tobacco Control Act.

Related to morbidity, mortality and population health, Section 911(g)(2) permits the FDA to issue an exposure modification order if FDA determines that an applicant has demonstrated that the scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies and that issuance of a modified risk order is

expected to benefit the health of the population as a whole, taking into account both users and non-users of tobacco products.

In evaluating the products with the proposed reduced exposure claims, FDA is particularly interested in TPSAC's insights with respect to the following three questions.

Related to morbidity and mortality, we're asking TPSAC to discuss the likelihood that reductions in nicotine dependence associated with VLN cigarette use translate into substantial reductions in other morbidities and mortality among individual tobacco users.

Related to the effects in nonsmokers, we're asking TPSAC to discuss the likelihood that never smokers and former smokers are likely to experiment and progress with regular use of VLN cigarettes.

And related to the effects in smokers, we're asking TPSAC to discuss the likelihood that cigarette smokers who want to quit smoking and cigarette smokers who do not

want to quit smoking will dual use VLN cigarettes with their usual brand of cigarettes or exclusively use the products.

The evidence used to evaluate these three questions included the Applicant's two abuse liability studies evaluating nicotine pharmacokinetics and subjective appeal of the products, the Applicant's six-week actual use study, which evaluated changes in cigarettes per day and biomarkers of exposure after switching to VLN cigarettes, and a consumer perception study evaluating intentions to use VLN cigarettes.

In addition, the Applicant submitted a literature review of clinical studies investigating the behavioral and pharmacological effects of other very low nicotine content cigarettes.

In their application, the Applicant states that studies using SPECTRUM VLNC research cigarettes serve as the primary basis for supporting claims on VLN King and VLN Menthol

King cigarettes, because aside from the name, these SPECTRUM cigarettes are identical to VLN King and VLN Menthol King cigarettes.

Results from studies on VLNC cigarettes aside from SPECTRUM, so for example, Quest cigarettes, served as secondary supportive studies.

And finally, the Applicant also submitted a literature review of epidemiological studies on the effects of reducing cigarettes per day.

The following slides will inform the discussion on the likelihood that reductions in nicotine dependence with VLN cigarette use will translate into substantial reductions in other morbidities and mortality among individual tobacco users.

Abuse liability refers to the potential of a substance to result in dependence or addiction.

The evidence reviewed showed that the abuse liability of VLN cigarettes is

significantly reduced compared to normal nicotine content cigarettes and similar to nicotine replacement therapy gum.

This conclusion is supported by the published literature on VLNC cigarettes and the Applicant's abuse liability studies, which shows that the plasma nicotine levels after smoking VLN cigarettes were 97 percent lower than plasma nicotine levels after smoking usual brand or normal nicotine content cigarettes.

In these studies, participants rated VLN and VLNC cigarettes as having lower positive subjective effects ratings, and these are ratings such as liking, satisfaction, and taste, compared to usual brand or normal nicotine content cigarettes.

In addition, there is consistent published evidence indicating that use of VLNC cigarettes for an extended duration of time is associated with significant reductions in cigarettes per day among both smokers interested and not interested in quitting.

Specifically, clinical studies that evaluated changes in cigarettes per day across various populations after six weeks of smoking VLNC cigarettes reported reductions ranging from 11 to 46 percent, and this range included populations with mental health or substance use comorbidities.

So, I'd like to highlight one published clinical study by Dr. Hatsukami and colleagues that examined the effects of VLNC cigarette use on changes in cigarettes per day over 20 weeks.

We're highlighting this study because it's the longest clinical study examining these VLNC cigarettes to date.

In this study, smokers who did not want to quit were assigned to a control condition in which they smoked a research cigarette with normal nicotine content comparable to their usual brand of cigarettes or a VLNC cigarette condition in which they were told to immediately switch to SPECTRUM VLNC

cigarettes.

A third condition received gradually reduced nicotine content cigarettes over the course of the study. However, this condition is of less relevance to the current application, because VLN cigarettes would not be introduced to the market in this manner.

The figure on the right shows changes in cigarettes per day throughout the 20-week study, where time is on the X-axis and cigarettes per day are on the Y-axis.

The orange bars and line represent participants who immediately switched to VLNC cigarettes and the light blue bars and line represent participants who were provided with normal nicotine content cigarettes.

Data can be compared between conditions, as noted in Bracket A, and within condition, as noted in Bracket B.

As noted by Bracket A, at the end of the 20-week study, average cigarettes per day were approximately 50 percent lower in the VLNC

cigarette condition compared to the control condition.

As noted by Bracket B, average cigarettes per day decreased by approximately 25 percent from baseline to Week 20 within the VLNC cigarette condition.

For the within condition comparison, it's important to note that participants received study cigarettes free of charge, which may have contributed to greater patterns of VLNC cigarette consumption than would be anticipated if participants had to purchase their own VLNC cigarettes.

For this reason, we feel that the between condition comparison noted in Bracket A is more appropriate.

While there were high levels of noncompliance with strict adherence to VLNC cigarette use in this study, cigarette per day decreases were observed even among smokers who dual used VLNC cigarettes with their usual brands of cigarettes.

It's also important to note some additional context to consider in the clinical studies evaluating changes in cigarettes per day.

First, in most studies, participants were not interested in quitting. Participants interested in quitting may have increased adherence to VLN cigarettes.

Second, participants were instructed to switch to VLNC cigarettes. The proposed labeling and advertising do not explicitly state that smokers should switch to VLN cigarettes.

Third, study cigarettes were provided at no cost. The influence of cost on use and adherence to VLN cigarettes is unknown.

In addition, in most studies, participants are blind to the nicotine content of the research cigarettes and they were not exposed to any claims.

And finally, there are no studies that assessed smoking outcomes with greater than 20 weeks of using these type of VLNC cigarettes.

As previously discussed, the available data show that smoking VLN cigarettes is associated with an approximate 97 percent reduction in plasma nicotine uptake and substantial reduction in cigarettes per day over time.

Reducing nicotine exposure and cigarettes per day can result in reductions in nicotine dependence. The published literature shows that switching to VLNC cigarettes for between six to 20 weeks is associated with decreased self-reported nicotine dependence scores among smokers interested and not interested in quitting smoking.

These reductions in nicotine dependence with VLNC cigarette use may promote quitting. In clinical studies, among smokers not interested in quitting, using VLNC cigarettes did not affect motivation to quit. However, it did increase quit attempts.

Among smokers interested in quitting, using VLNC cigarettes along with nicotine

replacement therapy and behavioral therapy was shown to facilitate smoking abstinence.

Taken together, smoking VLN cigarettes can contribute to a measurable and substantial reduction in nicotine dependence, resulting from reduced nicotine exposure among individual tobacco users following extended VLN cigarette use.

While using the product can substantially reduce nicotine dependence, the magnitude of reduction in other morbidities and mortality remains unclear.

In general, epidemiological data showed that compared to smokers who do not reduce their cigarettes per day, smokers who reduce their cigarettes per day by at least 50 percent decrease some, but not all disease risks.

For example, one study found a reduction of at least 50 percent from heavy smoking was associated with a 27 percent reduction in lung cancer risk.

In addition, while some studies found that a cigarette per day decrease of at least 50 percent was associated with a decrease in some cardiovascular risk factors, such as cholesterol levels, others saw no change in risk of myocardial infarction.

And similarly, some studies found that a 50 percent reduction in cigarettes per day was associated with a decrease in pulmonary symptoms, while others found no robust improvements in lung function.

Overall, these studies suggest that a cigarette per day reduction of at least 50 percent could lead to a substantial reduction in some tobacco-related morbidities, but not others.

However, it's unclear from the available literature what proportion of smokers who use VLNC cigarettes will reduce their cigarettes per day by at least 50 percent. Thus, the magnitude of the reductions in other morbidities remains unclear.

As previously discussed, clinical studies show that at six weeks, smokers assigned to VLNC cigarettes had cigarette consumption that was 11 to 46 percent lower compared to baseline.

In the 2018 Hatsukami study, comparing cigarettes per day at 20 weeks showed that cigarettes per day in the VLNC cigarette condition were about 50 percent lower than the control condition.

However, examining within group changes revealed that cigarette per day decreases were about a quarter in the VLNC cigarette condition.

In all, these studies provide evidence of the variable levels of smoking reduction that could be observed with VLNC cigarette use.

With regard to mortality, in general, studies of different populations have not consistently demonstrated that a reduction in cigarettes per day reduces all-cause mortality.

For example, while one study found that a reduction in cigarettes per day is associated with a reduction in all-cause mortality, two other studies found no such association.

However, aside from decreases in cigarettes per day, the increase in quit attempts and potential increase in quit success associated with using VLNC cigarettes could lead to a decrease in morbidity and mortality.

So, now, we'll move on to discuss the information related to Questions 2 and 3. These questions deal with the likelihood of VLN cigarette use among various populations.

Related to the effects in nonsmokers, Question 2 is for TPSAC to discuss the likelihood that former smokers and never smokers will experiment with and progress to regular use of VLN cigarettes.

Related to the effects in smokers, Question 3 is to discuss the likelihood that cigarette smokers who do and do not want to quit

smoking will dual use VLN cigarettes with their usual brand of cigarettes or exclusively use the products.

In the Applicant's consumer perception study, which was used to evaluate the likelihood that adult nonsmokers will initiate use of VLN cigarettes and progress to regularly using them, participants were randomized to see VLN cigarette packs or Marlboro Gold cigarette packs.

The figure on the right depicts intentions to purchase on the top panel and intentions to regularly use on the bottom panel. Results for Marlboro Gold cigarettes are presented by the blue bars and VLN cigarettes are presented by the yellow bars.

The data show that former and never smokers intentions to purchase and use VLN cigarettes were low, with means between one and two on a five-point scale for purchase and a six-point scale for use.

Compared to Marlboro Gold cigarettes,

never and former smokers reported higher intentions to purchase VLN cigarettes by about 0.08 on a five-point scale.

And compared to Marlboro Gold cigarettes, never smokers, but not former smokers, also had higher intentions to use VLN cigarettes on a regular ongoing basis by about 0.1 on a six-point scale.

In this study, findings were similar among a subset of never smokers of legal age to age 25, with higher intentions to purchase and use VLN compared to Marlboro Gold cigarettes by about 0.2 on each scale.

Overall, findings suggest that it's unlikely that nonsmokers will initiate smoking VLN cigarettes and progress to regularly using them.

With regard to youth initiation, there is no direct evidence to determine whether the products with the proposed claims would affect youth nonusers in the same way as young adult nonusers.

One published study found that other modified risk claims similarly decreased risk perception among youth and adults, but affected susceptibility to product use only among adults.

Lower risk perceptions have been shown to increase product use. Therefore, exposing youth tobacco nonusers to the products with the proposed claims could increase the risk of initiating VLN cigarette use.

However, should youth initiate use of the products, the lower abuse liability of VLN cigarettes reduces the potential for youth to become regular smokers due to nicotine dependence.

It may also be relevant to consider that youth and young adults were not particularly interested in a cigarette brand that was marketed with similar claims from 2002 to 2010.

During the period when Quest cigarettes were on the U.S. market and advertised as low nicotine, extra low nicotine,

and nicotine-free, youth smoking rates declined, indicating a lack of substantial youth uptake of the products.

Although smoking rates are affected by numerous factors, this indicates a lack of substantial increases in youth smoking rates when a similar product with similar claims was marketed.

In addition, a study of college students showed that Quest cigarettes were rated as having lower positive expectancies than Marlboro Lights on a scale that predicted willingness to try the products.

However, the generalizability of this information is limited, because the Applicant proposes to market VLN cigarettes using different labeling and advertising.

Moving on to the effect of the proposed claims on the likelihood of use by smokers.

As noted earlier, in the Applicant's consumer perception study, participants were

randomized to see VLN cigarette packs or Marlboro Gold cigarette packs.

Overall, smokers reported moderate to high intentions to purchase and use VLN cigarettes. Compared to Marlboro Gold cigarettes, smokers' intentions to use VLN cigarettes were significantly higher. And compared to smokers not intended to quit, smokers intending to quit had similar intentions to use Marlboro Gold cigarettes, but higher intentions to use VLN cigarettes.

In addition, the previously discussed clinical studies in the general population have found that most smokers who are randomized to VLNC cigarettes will decrease their cigarettes per day and may increase quit attempts.

However, up to 80 percent of smokers in these studies were noncompliance with strict adherence to VLNC cigarettes and smoked an average of between one to four usual brand cigarettes per day.

Despite the high rate of

noncompliance, participants still experienced a decrease in nicotine exposure and cigarettes per day.

In the real world, where smokers haven't been told to completely switch, noncompliance may be higher.

It's unlikely that current tobacco users who are not interested in quitting will switch to VLN cigarettes. However, among smokers interested in quitting, switching to VLNC cigarettes may facilitate smoking abstinence as a result of reduced nicotine exposure, particularly when used in combination with nicotine replacement therapy and behavioral intervention.

There have also been several clinical studies assessing the effects of VLNC cigarettes in vulnerable populations. There is little to no evidence that VLNC cigarettes increase the risk of adverse effects among smokers with mental illness or substance use disorders.

In smokers with mental health

symptoms, using VLNC cigarettes was not associated with increased markers of compensatory smoking compared to the general population.

Although infrequent, there have been reports of adverse events related to nicotine withdrawal in a general population sample among individuals with a history of poor mental health.

For example, in the 2018 Hatsukami study, two subjects were discontinued due to suicidal ideation assessed as possibly related to VLNC cigarettes and nicotine withdrawal.

And in addition, published studies found no evidence that alcohol or marijuana use moderates the effects of VLNC cigarettes.

So, in summary, we're asking TPSAC to discuss the likelihood that reductions in nicotine dependence with VLN cigarette use will translate to substantial reductions in morbidities and mortality.

Data show that the proposed modified

risk products can reduce nicotine exposure, cigarettes per day, and dependence among individual tobacco users.

However, because it's unclear what proportion of the smokers will reduce their cigarettes per day by at least 50 percent, the magnitude of reduction in other morbidities and mortality remains unclear.

We're also asking TPSAC to discuss the extent to which never smokers and former smokers are likely to use VLN cigarettes.

Data from the Applicant's consumer perception study show that nonsmokers had low intentions to use the proposed modified risk products. However, intentions to purchase the proposed modified risk products were higher than intentions to purchase Marlboro Gold.

While there is no direct evidence related to youth initiation, FDA did not identify concerns based on the indirect evidence evaluated.

And finally, we're asking TPSAC to

discuss the extent to which smokers interested and uninterested in quitting will dual use VLN cigarettes or use them exclusively.

Data from the Applicant's consumer perception study showed that smokers have moderate to high intentions to use the proposed modified risk products. Intentions to purchase and use the proposed modified risk products were higher than those for Marlboro Gold.

And studies did not identify significant concerns related to VLNC cigarette use among people with mental illness or substance use disorders.

This is just another reminder of the next three questions for discussion. I'm going to leave these on the screen and would like to thank you all for your attention.

CHAIR MERMELSTEIN: All right. Thank you very much.

I think we're going to move into starting to discuss these questions a little bit before lunch, since we are somewhat ahead of

schedule. And I want to take them really one at a time, so that we can stay focused on what the topic of discussion is.

And the first question is for us to discuss the likelihood that reductions in dependence translate into substantial reductions in morbidities and mortality among individual tobacco users.

And here again, the assumption is that with very low nicotine cigarettes, dependence gets reduced, individual smokers may reduce the number of cigarettes that they smoke. And then, the inference is, as a result of reducing the number of cigarettes, what's the potential for reductions in morbidity and mortality?

So, I open that up for the Committee discussion to focus at least first on that question. Okay. We're going to get the right questions up.

So, the first question that we should be answering is -- these are, they are the right

ones. Discuss the likelihood --

DR. TWOREK: These are the correct questions, yes. As I had mentioned in my presentation this morning, the question order has changed, and it corresponds with the order of these presentations and it is correct.

CHAIR MERMELSTEIN: So, we'll start with the very first one, which is, again, the assumptions here, the sort of sequence is the very low nicotine cigarettes lead to a reduction in dependence, which tends to lead to a reduction in the number of cigarettes per day.

And do reductions in cigarettes per day then have a subsequent reduction in morbidity and mortality? Again, this is at the individual, not the population level.

So, overall, do we have sufficient evidence that as you reduce cigarettes per day, dependence gets reduced, cigarettes per day gets reduced? Dr. Donny?

DR. DONNY: So, this is a bit of a

clarifying question for you. You're phrasing it in terms of cigarette per day reductions, but --

CHAIR MERMELSTEIN: This is --

DR. DONNY: -- the question --

CHAIR MERMELSTEIN: Right. I just made that inference.

DR. DONNY: Got it, okay.

CHAIR MERMELSTEIN: But the question is that, it's reductions in dependence. And I said, usually, that might drive. But you're right, I made that inferential leap, but the question is specific. But there's some mechanism here that we have to assume.

DR. DONNY: Right, but it would include increases in quit attempts --

CHAIR MERMELSTEIN: Correct.

DR. DONNY: -- and quitting, abstinence --

CHAIR MERMELSTEIN: Correct.

DR. DONNY: -- not just reductions in number --

CHAIR MERMELSTEIN: Exactly.

DR. DONNY: -- of cigarettes per day.

CHAIR MERMELSTEIN: So, those are the different ways that it could happen, correct. Thoughts from the Committee? Dr. Weitzman?

DR. WEITZMAN: In the absence of long-term data, we saw some presentations on biomarkers, but with the absence of puff topography and how people actually use these cigarettes, is it really justified that we make the leap that there's going to be a reduction in morbidity and mortality?

CHAIR MERMELSTEIN: So, fortunately, we have Dr. Hatsukami and Dr. Donny here, who do have data on the reductions in biomarkers from how they are used.

DR. DONNY: Sure, I can comment on the topography question broadly, and then, if Dr. Hatsukami wants to comment on her biomarkers even more, that would probably be handy.

So, on the compensation side, from a topography perspective, there's different ways in which you can measure that. And we've

measured it in a variety of different approaches.

So, one is a mechanism by which you look at the degree to which smoke is inhaled through a device that measures kind of the flow of smoke across a sensor. We've looked at it in terms of cigarette butts. And all cases -- and certainly, we've looked at it in terms of biomarkers.

And in all cases, we see no evidence of compensatory smoking. And this is very consistent across the literature, with the exception maybe of the first cigarette or two that someone smokes, there may be an initial attempt to draw more deeply, but that quickly dissipates under every study that we've basically looked at.

DR. HATSUKAMI: And so, your question is the extent to which there's a reduction in biomarkers of exposure, is that correct?

DR. WEITZMAN: That was a part, but the other was, how well do these biomarkers

track with long-term effects? Did that make sense?

DR. HATSUKAMI: Right. So, there's a lot of literature in terms of biomarkers of tobacco-specific nitrosamines.

And what you do see is that people that have higher levels of total NNAL, which is a biomarker for NNK, actually are at higher risk for lung cancer. Similarly, if they have higher levels of NNN, which is a, well, it's a biomarker for NNN, they are at higher risk for esophageal cancer.

And my understanding is, typically, you do see a dose response curve with the other biomarkers of exposure as well.

CHAIR MERMELSTEIN: Okay. I'm going to go to the phone first, to Dr. Ossip. And then, Dr. Bierut. Dr. Ossip?

DR. OSSIP: Yes, thank you. I actually have two questions, would it be appropriate to ask two questions?

CHAIR MERMELSTEIN: Go ahead, Debbie.

DR. OSSIP: Okay. I have two questions. Is it appropriate to ask two questions?

CHAIR MERMELSTEIN: Yes, please go ahead.

DR. OSSIP: Okay, thank you. The first is -- I think I'm getting a bit of the echo here, let me -- okay.

The issue was raised, maybe during the public comment, and I'm interested in a follow-up on this, on whether we have any evidence on whether or how the genetic modifications that were done to the tobacco to produce the low nicotine tobacco could have an impact on health or health risks?

The second is, in terms of the reduction in cigarette, potential reduction in cigarettes per day, which would be one of the potential drivers of reduced morbidity and mortality, the Hatsukami paper has been cited a number of times, including the very helpful figure that shows the results for people who are

in the immediate quit to gradual quit or the essentially same-use condition.

And we've been told a couple of times that the gradual uptake is not relevant to the current consideration.

But I wanted to get a little bit of clarification on that, because if we look at actual use in the population, particularly in the absence of instructions or clear understanding or evidence that people in fact with instructions would do the immediate and complete switch over, I wonder if the gradual uptake would be an outcome that we would see in real world, so that those data would become relevant?

CHAIR MERMELSTEIN: Okay. There are two questions and I'll just first go to the company for whether or not you know any, have any data about the tobacco product itself?

DR. CARMINES: Yes. Yes, the tobacco itself was reviewed by APHIS and was released for unconditional use with no concerns. It was

actually the first plant product, genetically modified product, that I believe was reviewed and released by APHIS.

CHAIR MERMELSTEIN: Thank you. Okay. Dorothy, your response?

DR. HATSUKAMI: So, the gradual reduction group was a not necessarily a gradual reduction in cigarettes, but a reduction in the nicotine content of the cigarettes. So, I don't think it's --

CHAIR MERMELSTEIN: It's not relevant.

DR. HATSUKAMI: -- really relevant here.

CHAIR MERMELSTEIN: Right.

DR. HATSUKAMI: Yes.

CHAIR MERMELSTEIN: Right. Dr. Bierut?

DR. BIERUT: So, I'm going to be focusing on this question of reductions in dependence translating to reductions in morbidity and mortality.

As a physician, looking at

individuals who have dependence, when they have fewer symptoms of dependence, it is associated with fewer comorbidities and lower mortality. And this is seen generally across the board.

So, it does seem likely that reductions in dependence will translate into reductions in morbidity and mortality.

CHAIR MERMELSTEIN: Thank you. So -- oh.

DR. DONNY: So, I just wanted to add and reiterate that I think it's important that we recognize both pathways to reduced morbidity and mortality.

That is, a reduction in cigarettes per day could have effects, which I think we're mostly focused on here.

But also, that a reduction in dependence is likely to lead to an increase in cessation. And there are data that speak to this that were not presented.

But Dr. Hatsukami's paper in JAMA actually does demonstrate an increase in

abstinence, point prevalence abstinence rates in those that were in the immediate reduction group. And I think that's important to get on the record.

CHAIR MERMELSTEIN: Great, thank you. I think with all these questions, a lot of times, we have to make a little bit of some inferential judgments and leaps and synthesizing the evidence that we have for what we know.

But it seems like there are some compelling pieces here of reductions that as dependence gets reduced from the very low nicotine cigarettes, other things follow, which are very likely to lead to some reductions in morbidities and mortalities at the individual level.

So, yes, it's not that everything is perfectly tied together, but I think that there is a accumulation of evidence along each step of the way that we could link them and pull that thread through to come up with a reasonable suggestion.

Other comments about the first question? Okay.

DR. WANKE: So, in consideration of the reduction in cigarettes per day aspect that you mentioned, and also Dr. Hatsukami's comment that observation that reduction in tobacco-specific nitrosamines may lead to a dose response decrease, I think we should keep in mind that it may be different for -- that that is specific to cancer outcomes.

And for cardiovascular outcomes, it's not likely to be a dose response. So, any decreases in exposure are not likely to, in a dose-dependent manner, reduce adverse cardiovascular outcomes. But we're still --

CHAIR MERMELSTEIN: Yes.

DR. WANKE: -- likely to see higher out --

CHAIR MERMELSTEIN: Right.

DR. WANKE: -- higher levels of outcomes might be --

CHAIR MERMELSTEIN: And I think the

presentations were also clear that not everything is reduced, that there are some things that reduced and it's not all equal across all disease and conditions. But there's some data still that some benefits can occur.

DR. WANKE: Right. So, just a caveat.

CHAIR MERMELSTEIN: Right. Dr. Thrasher?

DR. THRASHER: I guess what I'm struggling with is the extent to which these clinical studies that are asking people or telling people to switch map on to actual use, in the context where the product is available but people aren't being told or even communicated about the need to switch.

Dr. Donny and Dr. Hatsukami, I wonder what you think about how your clinical trials translate to actual use under the conditions where this product would be released as we're told to evaluate it today?

DR. HATSUKAMI: I think with both Dr. Donny and my research, we were conducting it in

the context of a product standard.

And so, it was really important for us to make sure that the cigarette smokers were going to be completely switching to very low nicotine content cigarettes and we incentivized those individuals to make the complete switch.

And so, it isn't really reflective of what might happen if you have both very low nicotine content cigarettes on the market and conventional cigarettes with normal nicotine content.

So, and that's why I asked the question of 22nd Century, what were your instructions to the cigarette smokers when they did the six-week trial? Because, certainly, I don't think you can really generalize the research that we conducted into what might happen if you have both types of cigarettes on the market.

CHAIR MERMELSTEIN: So, just to be clear, I think your question is a good one and it's very relevant to the third question, which

is to discuss --

DR. THRASHER: Is it not -- I mean, for me, if we're talking about using the clinical trial data to make assumptions about what happens in the real world and then, how that relates to morbidity and mortality amongst individual tobacco users through the mechanism of reduced CPD or quitting, to me that seems entirely relevant to Number 1.

CHAIR MERMELSTEIN: I think it's relevant. I think you're right in that, but we also have epidemiological data about what happens as people reduce and not just the clinical trial data as well.

DR. DONNY: So, I think this is an important point that I'm glad is coming up, because to me, I read that first question and it isn't about this product or the claims being made, it is about the reduction in dependence and the relationship between that and morbidity and mortality, specifically.

And I think it's important that we

distinguish that from the application itself, if that's what we're responding to.

CHAIR MERMELSTEIN: Good clarification. Dr. Ossip, you have a question again?

DR. OSSIP: Yes. I just want to get back to that gradual condition, in listening to this discussion.

And I am -- I think what we're looking at is actual use. And though, in the absence of clear instructions or understanding or data that in fact people will do an immediate switch to exclusive use of the very low nicotine cigarettes.

And what in fact people may do in the real world would be to try, to gradually ramp up, to try a few, they can titrate their nicotine dose differently, even in the context of a very low nicotine cigarette.

Without the experimental conditions manipulating how much nicotine is in the cigarettes, they can titrate their own dose by

what combination they use of their own cigarettes or the very low nicotine cigarettes.

So, in that sense, they may be doing a gradual transition or in a stage of potential gradual transition to very low nicotine cigarettes.

And I keep coming back to that, because the data were very different in terms of cigarettes per day for that condition compared to the immediate switch, under those very carefully controlled experimental conditions.

DR. HATSUKAMI: So, just going back to what you had said, Dr. Ossip, it is true that there was more noncompliance earlier on, where people were using more of their usual brand cigarettes, probably to adapt to the very low nicotine content cigarettes.

And so, I'm not quite sure if that's what you're asking, if they would tend to titrate the levels of nicotine by using their own cigarettes, but that's one of the things that we did observe.

DR. OSSIP: Right. So, I guess I'm saying, you observed that even in the condition where you instructed them to do the immediate switch.

And I'm wondering if in the absence of that, in fact it might look more like, in actual use, that gradual kind of a condition, where there is even more of that sort of going back and forth between the very low and their own cigarettes, so that they're not -- in fact, their combination of their own cigarettes relative to very low nicotine is a higher ratio of own cigarettes, so that the reduction in nicotine intake would be attenuated in real world, actual use.

And that could have an effect on reduction and dependence and could have an effect on their change of number of cigarettes per day.

I'm struggling with the question of what could we expect would happen in real world use, in terms of cigarettes per day, and I'm

wondering if there still is something informative about that condition because of how people may use or may transition to very low nicotine cigarettes in the absence of a clear experimental condition that's trying to get them there very quickly.

DR. HATSUKAMI: So, now I'm getting a better understanding what you're saying. Yes.

So, if he had -- if it weren't for the type of experimental design that we had, where we were incentivizing people to completely switch, in a world where you do have normal nicotine content cigarettes and very low nicotine content, you might see the same kind of lack of reduction in cigarettes, or actually reduction in dependence that we saw in the gradual reduction group.

I think that's where you're trying to get at, right?

DR. OSSIP: Right, that's what I --

DR. HATSUKAMI: Yes.

DR. OSSIP: -- was asking about.

DR. HATSUKAMI: Yes. And it's not clear, because I don't think we've done that type of study.

DR. BIERUT: So, I'm kind of a concrete person here and I want to get back to, are we really looking at Question 1, which is does a reduction in dependence translate to reductions in morbidities and mortality with individual tobacco users?

And I understand this question of how we use it and I see that as Question Number 3. But are we comfortable with this idea, do we think that there's the scientific data that a reduction in dependence translates to a reduction in morbidity and mortality?

And thinking of that as a harm reduction approach and moving in that way. And I would just say, I think the evidence says yes.

CHAIR MERMELSTEIN: Great. Dr. Apelberg?

DR. APELBERG: Yes. Can I -- this question has come up a few times, so I just

wanted to clarify. Question 1 isn't just asking kind of in theory, does reduced dependence lead to reduced risk.

It really is a question about the reduction in dependence that you would expect to see with this product on the market, whatever that may be, would that translate into substantial reductions in morbidity and mortality?

CHAIR MERMELSTEIN: Can you tell us now what the question is?

DR. APELBERG: Yes. So, the question is, basically it requires you to think about, given the data that you've seen, the reduction in dependence that you would expect to see with these products being marketed, would that translate into reduction in risk to individual tobacco users? So, it is relevant --

CHAIR MERMELSTEIN: It is -- okay.

DR. APELBERG: -- the question about, how will people us this product?

CHAIR MERMELSTEIN: Right.

DR. APELBERG: Can you translate the clinical studies into real world?

CHAIR MERMELSTEIN: So, I think what you're saying is, how much dependence might result, a reduction in dependence might result in the world today if individuals used that, and is that level of dependence that you see reduced sufficient to drive health outcomes changes?

So, your concern is, are we going to see enough reduction in dependence that it would make a difference?

Dr. Warner?

DR. APELBERG: Correct.

DR. WARNER: Yes, I was going to keep my mouth shut, because I figured I had no expertise in this particular area. And particularly after what Dr. Beirut said, which was my interpretation of the question as well.

If you have reduction in dependence, does that therefore lead to a reduction in morbidity and mortality? And from what I hear from my colleagues who know something about

this, I'd say yes.

But now that you add the complicating factor, which is in fact more relevant here to this particular issue, I do want to express an uncertainty. And with the uncertainty goes the concern.

One thing we've learned over the years is that smokers most want an alternative to quitting. We've certainly seen that with low tar nicotine cigarettes. Before that, we saw it with filtered cigarettes.

I mean, it's at least arguable that if we never had either of them, smoking rates would be a small fraction of what they are today, because we gave smokers an alternative that they perceived, it turns out incorrectly, to be lower risk.

In this instance, I think the alternative, probably used by itself, does have some of these benefits.

But what most concerns me here, and we haven't had any evidence with regard to this

today, because we haven't had any evidence about how people will respond to the advertising that should be anticipated here. Which, actually, I think is a major flaw in the consumer perception data that we've been given.

But my biggest worry here is that you are giving smokers an alternative to quitting, especially those who perceive nicotine to be the problem. Because if they can switch over here, partially, and this goes to the dual use issue, how many of those people would have quit smoking if they didn't have this alternative?

And the alternative, maybe they go 50/50 smoking these and smoking regular cigarettes. They believe that they've improved their health, because they think nicotine is the problem and they've been told that this is reducing their nicotine exposure substantially.

So, I don't know the answer to the question with that kind of complicating factor, but I think it's a serious concern.

CHAIR MERMELSTEIN: Okay. Thank you.

So, I think that in the absolutely case, perhaps we're more comfortable with reductions and dependence translating. In the real-world case, that gets us into 3. So, let's move on. I think we've probably done a good job of just understanding what might be ideally possible with 1.

Let's see if we can, before lunch, cover Number 2, which is to discuss the extent to which the following groups are likely to try and progress to regularly using the proposed modified risk tobacco products.

So, are never smokers or former smokers going to, not just try, but progress? The question here is both just try and progress and the question is, even if they are tempted to try and curious, people can try lots of things because they are curious about what it is, what's the probability that they might progress? Sally?

MS. HERNDON: My concern about this, as a public health practitioner, is young

people. And we still know that most tobacco use begins at a very young age, about 12 to 14, I think, on average. Dr. King can correct me if I'm wrong.

And experimentation happens in peer crowds, with tobacco products coming sometimes from purchase sources, but also from social sources.

And so, it does very much concern me that there's no evidence that this application thought about testing this with young people, at the age of initiation, and including perceptions of risk.

Nicotine naivete is a concept that's been discussed in the paperwork that we read and I can tell you from my experience that that's pretty rampant at that age. Kids really don't understand nicotine, they don't understand addiction, and oftentimes become dependent before they know it.

CHAIR MERMELSTEIN: Dr. Ossip, question?

DR. OSSIP: Yes. My two real concerns here are, one, what was just said, that this wasn't tested in adolescents. And I think that really is a flaw.

And it's not been tested as it will be promoted. And that also, as we know, can have a large effect on actual use.

And so, in looking at some of the images that we've seen, maybe in the FDA briefing there was an image that creates that very positive image, as has been done in other advertising, of using these products.

One can imagine a scenario, for example, where adolescents might want the image of being smokers in social situations, but perhaps they have concerns about nicotine addiction and see this as safer or less addicting and use it.

And so, I think those are two major flaws and those are my concerns with this particular question.

I do have one question for others.

And that is, is there any reason, is there any evidence that the small amount of nicotine in these very low nicotine cigarettes would be sufficient to have an impact on the developing brain in adolescents, among adolescents who have not used nicotine in any other form in the past?

CHAIR MERMELSTEIN: Dr. Donny?

DR. DONNY: So, I can comment on the second part in a second. I just, again, I'm stuck with the question, which focuses on the likelihood and extent to which progression to regular use would occur with this product.

And I think we need to keep in mind that risk -- I think we need to discuss the degree to which changes in risk perception is likely to maintain regular use, as opposed to experimentation, and particularly in the context of which you believe it's a reduced abuse liability product.

So, I just want to comment on that. And then, in terms of neural development effects of low doses of nicotine, we of course don't

have clinical data relevant to that.

We have preclinical data and we've conducted a number of studies in rodent models, trying to look at this question. And in those situations, we don't see that low doses in an adolescent model result in a higher abuse liability product.

CHAIR MERMELSTEIN: I think that that's a very relevant point, is that there is a difference between trial and experimentation and curiosity.

And then, is there the abuse liability, the dependence development, so that the kids will stick with it? Which is really quite low, and the appeal and the satisfaction.

So, it doesn't mean that they're not driven by the initial curiosity for it, but will they progress, data seemed to be there.

Wow, that one got a lot of people going. Okay. Actually, I think, Brian, you were first, and then, we'll go to Mitch, and then Dorothy, and then Ken.

DR. KING: Yes, sure. So, my comment doesn't relate to that, so if you want to go first, if you want to follow on that, I'm happy to succeed.

CHAIR MERMELSTEIN: Let me first go to Mitch and let's get that.

MR. ZELLER: So, it's a question for the Committee on the issue of youth experimentation and progression. And to the degree that any members of the Committee have any thoughts about the Quest experience that was shared, we would be interested in hearing.

Recall, it was an eight-year period of time where a very similar product was on the market, real-world experience, actual use, absolutely no FDA regulation, except for maybe the last year, when the Center finally opened its doors.

So, any comments that the Committee has on the Quest experience, the relevance of the Quest experience, would be appreciated.

CHAIR MERMELSTEIN: Okay. First,

Brian?

DR. KING: So, I have comments on that, yes. I think that it's basically tantamount to comparing a rotary phone to an iPhone 11. I think that it's particularly important to consider the context of the promotion environment.

And when Quest was around, you did not have the machine of both mode of delivery of messages, particularly through social media, but also the types of advertisements.

And if you look at a Quest ad, it's nothing like these, what I would call borderline saucy, salacious images that are being used to promote some of these products, including some of the ones in this packet.

So, I think it's important to consider also the broader environmental context. And to that end, I'm not convinced that the Quest comparison is entirely relevant and apples-to-apples here, in terms of what could happen among youth.

CHAIR MERMELSTEIN: Okay. Now, I lost track. We were going down this line. Dorothy, Ken, and I'll go back to Dr. Ossip, too.

DR. HATSUKAMI: Yes, I think I just want to make clear that, in the context of only having very low nicotine content cigarettes on the market, there probably is not going to be a progression of never smokers or even adolescents to continue to use these cigarettes.

But in the context of having both very low nicotine content cigarettes and normal nicotine content cigarettes, I'm not really sure whether kids who experiment with very low nicotine content cigarettes might graduate to the normal nicotine content cigarettes.

But I don't think we have real clear data to either support or refute that.

DR. WARNER: Yes, actually, I want to follow up on each of the last two comments.

I agree with Dr. King that the Quest ads were an order of magnitude different from what we are looking at here.

And again, I think a major failing of the consumer perception data is that we don't have any consumer perception data regarding how consumers respond to the ads that we have seen, along with the name Moonlight.

And actually, I thought the comment that's been made today and also in some of the public comments submitted to us about Moonlight being a problem because it says light, I think it's a bigger problem because, frankly, it's got a kind of seductive quality to the word Moonlight.

And if you combine that, along with these ads that are themselves reasonably seductive, I think we really would need to know how people, including kids, would respond to them.

And I believe, if I may offer a modification to the wording of the question here, I think at the very end, after it says progress to regularly using the proposed modified risk tobacco products, we should add

and/or conventional cigarettes.

Because my specific concern here is what you were saying, Robin, basically, I don't care about kids experimenting and I don't think they're going to get addicted to this product. I doubt that there would be long-term, substantial long-term use of this product.

But I could easily see kids saying, oh, I'm going to try that, it doesn't have any nicotine, and getting the experience of smoking and then, deciding they might want to try something that gives them a little more of a kick, that their friends who see them smoking saying, you can get more of a kick out of these other cigarettes. That's where this becomes a problem.

And for the context, let's keep in mind that both with adults and kids, but specifically kids, we have made incredible progress. I mean, we are down to minuscule numbers of kids who are smoking cigarettes.

So, I think there is actually an

importance here to saying, are we going to be reversing a trend that has been unbelievably favorable for 25 years and it's been more favorable for the last half dozen years? So, I do think that's an issue.

I think as well, with former smokers, I go back to the point I made earlier, that smokers want nothing more than an alternative to quitting.

And particularly for those smokers who believe, former smokers who believe that nicotine is the dangerous toxic agent in smoke, if they're told that they can smoke without nicotine, with 95 percent less nicotine, I think there's a real risk that they will, some of them, a subset, will try this product, particularly given the imagery of the ads.

And that having done so, because they're not quite as satisfying as cigarettes, regular cigarettes, they'll go back to the conventional product.

And again, I'm not saying this is

going to happen, I just don't think we've been given any evidence to address what are, to me, a couple of serious concerns.

CHAIR MERMELSTEIN: Dr. Ossip on the phone, and then, we'll go to the Committee.

DR. OSSIP: Yes. I agree with Dr. Hatsukami and Dr. Warner, and these are the points that I wanted to make as well.

I do think that we don't have evidence on whether this will be viewed as essentially a starter product or a gateway product for adolescents.

And I think the point is well-taken about potentially former smokers who may go back and then, use that as an opportunity to relapse.

I might suggest a modification to the change in wording at the end that Dr. Warner suggested, not just cigarettes, but perhaps other higher nicotine yield tobacco products, in that there could be other combustible tobacco products, and even with adolescents, in terms of e-cigarettes or other.

So, I think maybe a more generic -- that's certainly part of my consideration in looking at this issue, what will happen, since we don't have evidence on how adolescents might be enticed to try this and where is that, where will it lead them?

CHAIR MERMELSTEIN: Dr. Ogden?

DR. OGDEN: I recall from previous TPSAC discussions, and even some of the marketing authorizations that have been granted so far, FDA is at liberty to allow or remove or tweak language, if you will. I'm not sure whether that extends to the product name itself.

So, perhaps FDA could remind or clarify what the position would be on exact imagery, exact wording, and how that would play out going forward.

MR. ZELLER: I think the safest thing to say in a public setting like this is, if there are members of the Committee that have questions or concerns about the product name, that this would be the time to put those

concerns on the table for our consideration, and just leave it at that.

Let me also say, we're not going to change the wording of the questions, for the record.

But if you have additional concerns that have already been expressed, because the question only went so far, and you want to state for the record, as at least two members of the Committee have, additional concerns that you have in this space about progression to other products, this is the time and the place to make that point, as a couple of members already have.

CHAIR MERMELSTEIN: Thank you. Dr. Tworek?

DR. TWOREK: Yes. For context, I just wanted to remind the Committee that, as I mentioned, in the premarket tobacco product application, there were specific restrictions placed on digital media and digital marketing, including age restrictions for digital sales, websites, and social media, and requirements for

tracking and age-gating.

I just wanted to mention that, in the context of our discussion about youth and social media.

CHAIR MERMELSTEIN: Great, thank you.

DR. TWOREK: Thank you.

CHAIR MERMELSTEIN: Dr. Warner?

DR. WARNER: Just a very quick follow-up to that. I noted that when I read it. And the age restrictions and the imagery restrictions only go so far, and we need to be aware of that.

I'm very rarely concerned about ads that are going to show 16-year-olds using the product, but if you show someone who's a 25-year-old or even late 20s, these are the kinds of people that kids aspire to be. And I think a lot of that imagery, such as appears to be the case in the ads that we were shown, can be quite attractive to youth.

So, that's hard to get around. You can have a rule that be complied with, but it

doesn't necessarily achieve the intended effect.

CHAIR MERMELSTEIN: First Dr. Thrasher, then Dr. Bierut.

DR. THRASHER: I guess this just makes me think about some of the prior meetings where we've gotten hung up on this issue about not having data for youth.

And how -- I think one of the things that needs to come out of this, and we've said it before, but I'll say it again, is some kind of strategy for collecting data from youth around these kinds of products and the claims and the marketing.

I don't know exactly what that looks like, whether things get contracted out by FDA to some independent agency, but we're going to continue to stumble over this issue until we have data from youth. And we haven't seen it for most of the review processes we've gone through.

CHAIR MERMELSTEIN: Dr. Bierut?

DR. BIERUT: So, I just have to riff

on that for a second, because I just see this as such an ethical issue of doing any of this testing in youth, so, with the concern that it may promote the use.

DR. THRASHER: But independent researchers do work on messaging and consumer perceptions all the times with youth around these kinds of characteristics. So, I wouldn't be so concerned about that.

Use of the product would be a different thing. Giving them free low nicotine cigarettes is entirely different, I think.

DR. BIERUT: So, but let me look at this question in two ways. So, I'm on Question Number 2 and being very concrete here.

Former smokers, I believe that smokers smoke for the nicotine and die from the tar. So, knowing that it's a low nicotine product, I don't see a lot of the former smokers really thinking, wow, this is a product that I want to use, or if they do use it, I don't think that they're going to get the type of hit that

they're used to.

So, I am not particularly concerned about former smokers relapsing with this product. And the product still has all the combustible issues that drove them to quit already.

Now, the never smokers, I do see that there will likely be experimentation, because youth are built to experiment and that's what their job is in the world. And so, I do see them experimenting.

The -- I, again, believe that the transition to regular smoking and addiction is driven by the nicotine. And much of that is that biological underpinning, I understand that there are also environmental aspects to that. And so, transitioning to other tobacco products I see as low with this.

I want to also put it in the context of, we have a rapidly changing environment about tobacco products and smoking products, with e-cigs, a variety of different things. And in

this environment, we continue to see decreases in combustible tobacco product use amongst youth. So, which is, I think, a great success.

So, given -- I'm very concerned about the e-cig usage, but that slope of decreasing combustible tobacco product use continues to go down. And so, I don't see the evidence of why this would change that slope.

DR. WEITZMAN: So, I'd like to respectfully disagree. We don't have evidence. This is a public forum, so I'll try to -- this is not aimed at you.

But I question the ethics of bringing products forward that don't provide data about the most susceptible group for uptake. I don't understand why we continue to come to these meetings, unless somebody knows something that I don't know, which is my fear.

I also think that there are many, many other things that go into people smoking than their addiction to nicotine. There are, we've talked about environmental influences, but

there are personal pleasures that come with smoking.

So, if I identify or I think that somebody who looks like the people in the ads will identify with me, that may very well be something that contributes to my using this.

And we know that part of being an adolescent is not just experimenting, but keeping the species going. And so, salacious advertising to me, without providing any evidence of whether or not kids are going to see this that way, to me seems very, very unethical.

But there are pleasures to inhaling, there are pleasure to exhaling, there are countless things that go on besides nicotine. But I remain concerned that we review products where people have done tests, but there's no data about the group that's most likely to uptake the product.

CHAIR MERMELSTEIN: Dr. Donny?

DR. DONNY: So, I just, I want to come back to what Director Zeller pointed out about

not changing the question, but getting on the record how you feel about two different versions.

And to me, I think as we've discussed earlier, it's important to recognize that the question as worded is about the regular progression to regularly using the proposed modified risk tobacco product. I think the odds of that are low.

But I think if you add the unaddable extension to that, in terms of the probability or potential for progression to using any other tobacco or nicotine-containing product, I don't think we have much data for that.

CHAIR MERMELSTEIN: Dr. King?

DR. KING: Yes. So, I'd like to reiterate the point around lack of youth data. That's been my soapbox for it seems like years now, which I still can sleep quite well at night continuing to reinforce the need for those data.

But I think it's also important to note in this context, around never smokers and

former smokers, that lower likely doesn't equate to it not happening. And so, lest we forget that there's still 275 million never and former smokers in this country.

And so, even a few percentage of that is going to ultimately negate that potential benefit. And our ultimate aim here is to see what the benefit is to the population.

And so, if you're trying to sell a couple hundred thousand deaths averted over 80 years, what's happening to the initiation of the, even if it's a couple percentage points, of 275 million, you're talking about millions of people that are now using a combustible product, half of whom, in the long-term smokers, die from smoking-attributable disease.

So, I'm questioning in the long-term what the benefit is here. And just because it's lower likelihood doesn't mean it's going to happen and we have to look at the full scope of the population.

And without data on the youth, and

particular these data among never and former smokers, with even five percent showing they're inclined to try it, that's lower likelihood, but it doesn't mean it's not going to happen.

And that's concerning to me, in terms of looking what the benefit of this is going to be to the populace.

CHAIR MERMELSTEIN: Okay. Oh, Sally?

MS. HERNDON: Yes. And back to, following up on Dr. King, back to Mitch's question, I think that's particularly concerning in the social media market that we have today and with some of the images.

And, yes, to Dr. Warner's point earlier, the name change is very concerning, especially along with these seductive images.

Young people will not read those words, they will look at the image and hear the term Moonlight and that has risk from both those perspectives. The light, we have dealt with that before, and then, the Moonlight makes it sound like something very, very appealing.

CHAIR MERMELSTEIN: Okay. Yes?

MS. BECENTI: As a public health person, I'm definitely concerned about not being tested in the youth, because no matter what, youth will experiment with products.

We say age, but we know that they get access to tobacco products from their parents or even brothers and sisters. And so, I'm definitely concerned about that.

And then, also, the imagery that is used, they're using, they're glamorizing it, they're using young people to be able to sell their product.

And then, also a concern about the new name, the Moonlight. I mean, just light, also concerning.

And then, plus, in some population, the age of uptake of tobacco products is actually younger, in some minority populations than others. So, just wanted to share that concern.

CHAIR MERMELSTEIN: Okay. Dr. Tworek?

DR. TWOREK: I just wanted to remind people, for the purposes of this meeting and these applications that we're reviewing, we are reviewing and evaluating them with VLN as the name. So, I just wanted to remind people of that, that's what we have to do in our review process.

CHAIR MERMELSTEIN: Right. Thank you.

DR. TWOREK: Thank you.

CHAIR MERMELSTEIN: Thank you, that's a good distinction. So, probably the sentiment is the name VLN is a clearer name than Moonlight, and didn't seem to have the concerns of the Committee. So, that's a helpful reminder.

And just to sort of close up the second question discussion, with the clarifications of what this -- I think the Committee, very disparate sentiments about it.

But if we take the question exactly as it's worded, which is looking at what's the progression that people would experiment and try

this particular product and progress more of this product, it's probably a low probability for that and less of a concern that this would be a product that people would progress through and escalate with.

The question is, is that opening the door to potentially wanting to then try a greater hit of nicotine, is unknown. And this is where the concern is perhaps on what the accompanying imagery might be, which may make it more appealing to youth.

So, the product itself is probably of less a concern than what might accompany that product and how that's phrased. Yes?

DR. THRASHER: Can I just -- I know it's going to be really hard to anticipate this, but the other thing that I wonder about is cost.

Is there an expectation that this product is going to be marketed at about the same price for consumers as premium brands, discount brands? Like, where is it going to fall? Because that could also influence the

extent to which people may start using it as opposed to other products.

CHAIR MERMELSTEIN: Right, of course. I don't know if there's an answer to that at this point or whether that matters.

MR. PRITCHARD: I mean, the Chair is correct, in so much as we don't have a dollar-cent price for the Committee today.

We appreciate this is built on decades of investment and research and is a unique technology of itself. So, to the extent that would guide the Committee, that's what I would say at this stage.

But, clearly, we will respond to FDA's guidances and requirements they put on us. And I think I just want to make that abundantly clear.

Some of the comments that have come forward, I recall a point from Dr. Tworek earlier that of all the proposals that have been submitted across the board, all of those are examples, proposals, and are subject to FDA

scrutiny and review.

As I said at the time, we look forward to feedback and guidance from FDA.

CHAIR MERMELSTEIN: Thank you. Okay. I think we will take our lunch break now and come back and discuss the third question.

So, we're going to have an accelerated lunch, if that's all right with people. We're going to try to shoot for a 30-minute lunch, if that works, and target getting back here at 12:30.

So, for the Committee Members, we have to pick up our lunches out front -- no? Oh, they were at the back. Okay. Committee Members, our lunches are already in a room in the back, so we can just adjourn to there.

(Whereupon, the above-entitled matter went off the record at 12:00 p.m. and resumed at 12:34 p.m.)

CHAIR MERMELSTEIN: So, thank you all for coming back promptly.

So we're going to pick up with the

third question. So, if we could get that back on the screen.

So, the third question, when we get there, is the one about discussing the extent to which groups will dual use the proposed. Modified risk products are with their usual brand of cigarettes are exclusively used, and cigarette smokers who -- among cigarette smokers who want to quit and cigarette smokers who do not want to quit.

So, again, this is a lot of what we've been alluding to in our discussion which is in the current world where individuals who still have their usual brand available, how much will do dual use?

Dr. Wanke?

DR. WANKE: So, I have a clarifying question about this question. And that is, are we asked to consider this in the context of the product itself or the product with the marketing statement?

DR. TWOREK: So, the modified risk

tobacco product applications are all considered with the claims. So, this would be in the context of the product with the claim.

CHAIR MERMELSTEIN: Dr. Duffy?

DR. DUFFY: And I just had to go back to my -- to the original document, and I just need clarification. And the claims are 95 percent less nicotine, helps reduce nicotine, consumption, and greatly reduces your nicotine consumption. Those are the three claims?

CHAIR MERMELSTEIN: They're the three claims. Correct.

DR. DUFFY: But there is no claim saying they're reducing mortality and morbidity?

CHAIR MERMELSTEIN: No.

DR. DUFFY: Okay. Just, I just needed to clarify that in my head.

CHAIR MERMELSTEIN: Right. Those are, those three claims.

And then there is the voluntary statement that is accompanying those materials as well.

So, we know certainly, just to quickly recap from the data and the studies that have presented that it's hard for smokers when they switch to the very low nicotine cigarettes to completely switch. And so that some dual use definitely seems to be more the norm than exclusive use. And that that happens under a variety of different instruction conditions and scenarios.

So, it does seem that dual use is likely common in those scenarios, and obviously while they're available, and that it may happen for both smokers who want to quit and smokers who don't want to quit, but that extent of the dual use may vary.

Is that --

DR. DONNY: Yeah. So, I think certainly for the second bullet, for cigarette smokers who do not want to quit, I think it's highly likely that dual use is going to be a common pattern.

I think the first bullet on cigarette

smokers who do want to quit, I'm wondering whether Dr. Hatsukami, she ran a study in smokers who were interested in quitting, I believe using the Quest cigarettes early on.

And I don't know, and I can't remember, Dorothy, if we've looked at or whether you looked at whether compliance was improved in that subset of the population.

DR. HATSUKAMI: We didn't look at compliance with that particular study where people are interested in quitting. So, I really don't know. And at that time we were a little less sophisticated than we were when we conducted our study, so we didn't even know what the cutoff point would be, the threshold for showing compliance, so.

CHAIR MERMELSTEIN: I mean, I think the general point is that smokers, like many other people, have a hard time changing their behavior. Switching from something that they've been used to doing can be a struggle. So, it's not unexpected that they would dual use, but it

doesn't mean that they can't change and that they can't switch over. And that can vary.

DR. DUFFY: So, in regards to the second bullet, if somebody doesn't want to quit why would they bother with it? Wouldn't you just keep smoking your brand?

CHAIR MERMELSTEIN: Well, I think, you know, sometimes people may indeed, you know, I think if somebody doesn't want to quit in the moment, I mean most, most smokers eventually want to quit at any given point in time if a given smoker may not want to quit right then.

I think the majority of smokers are interested in, aspire to quit at some point. So, they may, it may be a trial.

We also know that sometimes reduction trials and practice quit attempts may have benefits to smokers on the road to quitting. So, you know, it sometimes may be a safe experiment in the sense of, you know, if they're not yet ready to commit to quit but could be. So, it's not --

DR. DUFFY: People are ambivalent at different times, I totally agree with you. They go back and forth. And the period of when they're wanting to quit smoking would be the first bullet point, and the period when they're not wanting to quit smoking would be in another period of the same person's, you know life.

So, I guess I would just think that when they're in the period of not wanting to quit they're going to quit -- they're going to use what they like to smoke. And when they're trying to quit they may dual use. That's my opinion.

CHAIR MERMELSTEIN: Dr. Warner?

DR. WARNER: Yeah. I just want to remind all of us that we're talking about the quote, unquote rational smoker here. And as we've heard before, and as we all know, a lot of smokers believe that nicotine is the toxic substance in cigarettes. So, it's entirely plausible that somebody not wanting to quit would switch over at least in part, dual use

this product, believing it's going to lower their nicotine and thereby lower their risk.

CHAIR MERMELSTEIN: Yes, Sally.

MS. HERNDON: This is not necessarily relevant to the question on the page, but in response to Dr. Duffy's question, the UNC tobacco treatment system was trying to build evidence related to an opt-out system of tobacco treatment with their hospital patients. And they pulled out people who said they definitely want to quit, they definitely don't want to quit, and levels in between.

They gave all of them FDA-approved tobacco treatment medications, including combination nicotine therapy and an adequate dose of counseling.

And those who said they did not want to quit after given evidence-based tobacco treatment quit at a higher rate successfully after six months than those who even did want to quit.

CHAIR MERMELSTEIN: And I've done

similar studies with smokers who are currently unmotivated or not willing to quit but who are willing to try reductions or do other things. And there's benefits for them as well.

So, it's certainly if you ask someone, it may be of benefit, and if it's another option, even among people who are not willing to quit.

Dr. Ossip, on the phone, has a question.

DR. OSSIP: Yes. Actually I guess more of a comment.

So, I agree with the statement that based on evidence that we've seen so far the likelihood is that if people use these products, this product it would be -- or these products it would be they'd be dual using them, up to 80 percent for dual use.

So, that leaves the question of why would people use them at all? Why would they switch to them or dual use them?

And I agree with Dr. Warner that if

people perceive that they're harm reducing, that could be an incentive to switch or dual use instead of quitting or just because they want to -- they think they'll be a little bit better off. And that gets probably to Question 4, but that could be misleading if they're doing it as a harm reduction strategy for health outcomes and not changing anything else other than dual usage.

The second is, if they want to quit and they see this as a way to help them quit but what we're looking at with this review process I think would be serendipitous quitting because there are not specific instructions on how to use this for quitting. It would just be people who would kind of figure it out: well, if I want to quit and I use less nicotine it might be easier for me to quit. Unless there's some marketing like that, that that I think would do through that separate review process in CDER.

And, in fact, if it were presented in that way, complete switching, immediately

switching to the very low nicotine cigarettes, using it in a context of nicotine replacement and behavioral therapy, that you can perhaps enhance your quit rate, that could potentially be a benefit of this project.

But this isn't that review.

So I, you know, I think the short answer to this seems to be very likely that they would dual use if they use it, and what might drive them to use it. And it seems like that would be either the perceived harm reduction or the wanting to quit. And this is, you know, maybe a more, a kind of a watered-down version of using this as a pathway of quitting.

CHAIR MERMELSTEIN: Dr. Hatsukami?

DR. HATSUKAMI: Yeah. I have to agree with Dr. Ossip. I think what's missing here, and it was raised before, is the instruction of completely switching. You know, completely switching, then you'll get the significant reduction in nicotine.

And I think for one of the modified

risk claims that was approved they did talk about complete switching with some of the general snus products. And at that, you know, with the complete switching then you get a reduction in some of the tobacco, you know, cigarette-related disease.

So, I think that that really is an important component that's missing out of this claim.

CHAIR MERMELSTEIN: Dr. Thrasher?

DR. THRASHER: Just a comment. I guess in reviewing some of the intentions to use data that were presented comparing the VLNC with Marlboro Gold, as I understand it, Marlboro Gold users were excluded from the study.

And to me a more meaningful comparison would be intentions to use the VNLC -- or VLNC versus their own product that they're already using because that would help me understand how they would respond to this other alternative, relative to what their current product is, which is obviously the one they

prefer.

DR. DONNY: So, I just want to comment on the assumption of the 80 percent use which is pulling largely from studies that we conducted in which participants do not know, they are blind to the condition which they're in and there is no explicit information about that.

And I think a question that I wish we had answers to, and I don't think it's in the application, is the extent to which having that information changes the likelihood of dual use. That is, does someone who is -- does the information have a benefit potentially to driving down dual use because the purpose and understanding of it is clearer?

I don't think that was tested. But I think that's the kind of information that would be useful.

CHAIR MERMELSTEIN: That's a good question.

First, Dr. Ossip on the phone, then Dr. King. Dr. Ossip?

DR. OSSIP: Yes. I agree with -- I forget who said this a comment or two before -- that, maybe it was Dr. Hatsukami, that perhaps with clearer messaging and marketing around the issue of you need to completely switch to these products to get the reduction independence, you might see an increase -- or a decrease in the number who would dual use, or the percent who would dual use.

And then the question becomes is that a good thing or a bad thing? And which gets back to our morbidity and mortality question.

And, also, the need for long-term studies to see what happens. Would they sustain that level of use to the point that if there are benefits that accrued, they would accrue them. And the comparison to persons quitting versus just complete switching.

So, I think there's still a lot of questions remaining here.

CHAIR MERMELSTEIN: Dr. King.

DR. KING: Yeah. So, I would agree

with all that's been said and then just underscore again that, you know, in this environment when you have a regular combustible product with the standard nicotine strength, the likelihood of exclusive use is going to be low. And a good case study of that is what happened with e-cigarettes.

If you look at e-cigarettes in the market, the people who are quitting using those products are using them more frequently or using products that deliver the nicotine more efficiently. So, you have enough to replace what you otherwise would have gotten from a combustible cigarette. And in this case you're not going to get that.

And so, the likelihood of transitioning exclusively, it's going to be very difficult in an environment where you have other products available. And so, just looking at what's already happened in the society when you have this, you know, broad breadth of different products, I just question what would actually

happen in the population.

I mean, we've seen that with NRT. We've seen that with e-cigarettes. And I doubt that we'd see anything different here with these products.

CHAIR MERMELSTEIN: Okay. So, other thoughts about the probability of dual use?

I think we are all in agreement the probability of dual use is rather high in the current environment. It might be stronger if we had a message about completely switching to enhance the likely benefits of accruing the use of this product which may then make the other potential benefits more likely. And, of course, we would all hope that people who would use this product would just decide any combustible use is not worth it and get off. That would be a nice side effect.

Other last comments before we move to our afternoon presentations?

(No response.)

CHAIR MERMELSTEIN: Okay. We're

going to transition to some of the discussion now and we're going to have a couple of other presentations.

The first one is by Dr. Justin Byron. And that will be followed by another presentation from the FDA. And we're going to focus now on looking at perceptions of risk.

DR. BYRON: Thank you. So, again, my name is Justin Byron. I'm with the University of North Carolina School of Medicine and School of Public Health. And I was asked to talk today about two things: what we know about perceived risk of nicotine and VLNC cigarettes; and the current state of the science in correcting misperceptions.

These are my disclosures. I have no conflicts of interest to disclose.

So, first, the perceived risks about nicotine and VLNC. And just to be clear, today when I say VLNC I'm referring to very low nicotine content cigarettes generally speaking, not the VLN brand in this application.

So, there is a well-established, well-documented, widespread, false belief that nicotine is the main carcinogen. This we've talked about already today. This was recently looked at in the HINT Survey with an item "the nicotine in cigarettes is the substance that causes most of the cancer caused by smoking."

And people were asked to indicate their level of agreement or disagreement with this statement. Among smokers, 64 percent incorrectly either agreed with this statement or they were unsure.

Among nonsmokers it was 76 percent.

And then in a similar item on the PATH survey, 80 percent of people said that they agreed with the belief that the nicotine in cigarettes is the chemical that causes most of the cancer caused by smoking.

This also is very much in line with actually a few decades now of research showing that many people believe nicotine causes cancer and other health problems.

So, again to reiterate, as we have also talked about earlier today, there is a well-established, widespread misbelief that nicotine is the main harmful chemical in cigarettes.

So, now on to perceptions about VLNC cigarettes. I'll show that the evidence indicates that there is a misperception that VLNC cigarettes are less risky to smoke.

About in 2015 and 2016, which was before the FDA made an announcement about the new plan for nicotine regulation, we did a nationally representative survey and we found that among smokers 47 percent incorrectly said that smoking VLNC instead of current cigarettes for 30 years would lead to less risk of cancer.

This is our response distribution.

And also importantly, we found that this VLNC misperception was associated with a lower intent to quit. This suggests that people may be thinking if the cigarette has less of the harmful nicotine, now I have less of a reason

that I need to quit. So, this is an important finding that these people who tend to say that these cigarettes are less harmful said that they would be less likely to quit under a VLNC scenario.

When we looked at the results among non-smokers we found a similar percentage with a similar distribution, 44 percent.

I'd like to just show our survey item here because I think it's very important how our perceived risk item is asked.

We said, imagine the government required tobacco companies to remove most of the nicotine from cigarettes. Compared to smoking current smokers, smoking cigarettes with much less nicotine for 30 years would cause: and then we had a 5-point response scale from a lot less to a lot greater risk of lung cancer.

So, first of all, they could point out that this item is asked in a way that we can measure the percent of people who are misled. I think this is a helpful, one of the helpful ways

to ask a perceived risk question.

I know, in a lot of other studies and the application that have been talked about people ask mean levels of harm about different products. But that won't give you a percentage of people who are misled. That's one of the reasons that I think this is a helpful question.

I'd also like to point out that we followed a number of the recommendations for perceived risk questions as outlined by Brewer, et al., in 2004. This includes talking about a specific health outcome - the risk of lung cancer, a specific behavior - smoking use of current cigarettes, and a specific time frame - 30 years.

We worded this question in a way to convey to people that we're talking about continued smoking of these cigarettes, not just whether this is a generally good idea for health.

Whoops. Okay. In a related study we found that how nicotine content is described

affects perceptions.

Here we looked at different wordings of introducing the VLNC idea to the public and we looked at how that affected perceptions. Because currently among the public, most people obviously are not familiar with this product, and so the way it's introduced is probably very important.

We looked at seven different wordings. I'll talk about four of them today. And these were all based on established principles and risk communication.

So, for example, on the left here one of the principles to follow is just using concise plain language. So we said, imagine tobacco companies were required to reduce nicotine in cigarettes.

Then we used minimally or non-addictive, which is some of the wording that the FDA has used in press releases as a control. We used nearly nicotine free as an interpretation of the nicotine content. And, we used, removed

95 percent, because in this communication providing a percentage gives people a more accurate understanding about what you're talking about.

And these were our results:

With nicotine content, the more specific you get in conveying the nicotine content in these cigarette, the more accurate people are in understanding that. So, this is good news.

Similarly, the more specific you are, the more people understand that these products are going to be less addictive.

However, unfortunately, the more specific you are in conveying the nicotine content in smokers, the more people are misled. So, you can see here when we used the more general, vague wording of "reduced", 80 percent of people are accurate.

Whereas, when you use "95 percent" wording, that gets down to 60 percent.

And so, of course, this is important

because 20 percent of all smokers in this country is about 7 million people. So, there's an important question to be figured out in the big picture here about what is the most important thing to communicate to the public about a low nicotine cigarette? Is it that they most accurately convey -- is it to most accurately understand the nicotine content, or is it most important to not mislead people.

And, again, I will refer to this a little bit more later. So, on the left side here we have the vague wording which has -- which is less misleading but less accurate in nicotine content. And on the right we have the more precise wording, which is more misleading but more accurate in other ways.

So, it's also helpful to look at other research on this when a number of other recent studies that have looked at VLNC perceptions.

VLNC cigarettes were rated as a significantly lower risk of lung cancer, heart

disease, stroke, emphysema, chronic bronchitis, and other cancers. These were asked as individual items. And, importantly, people were specifically told to assume the same current rate of smoking.

In the VLNC trial there was a positive correlation between perceived nicotine content and perceived risk.

And the Quest cigarette brand and this -- so, they had VLNC cigarettes and low nicotine cigarettes, they were perceived as being healthier, safer to smoke, and less likely to cause cancer than other cigarettes.

It's also helpful to look at the research about low nicotine.

In the light cigarette marketing era, the reduction in nicotine cigarettes was perceived to make cigarettes less dangerous. The HINT Survey found that cigarettes advertised as low nicotine were rated as less harmful by 30 percent of U.S. adults. This actually fits congruently with the previous research because

this would follow as -- this would be categorized maybe as one of those sort of vague terms, just saying advertised as low nicotine.

It's important to think about the difference rate, as the chart clearly shows, the difference between communicating 95 percent less, which is very clear, to saying lower in nicotine, which is a little more vague. It may still mean a lot of nicotine to being low in nicotine. Each of these words I think is very important in meaning.

And so, 30 percent would make sense, that if you have the more vague wording you're misleading fewer people.

And focus groups have also looked at perceptions around low nicotine cigarettes and found mixed opinions. And just that a lot of people are confused about the harm.

It's also helpful to just look at the bigger picture about chemical communications for cigarettes.

At the University of North Carolina

we've done a number of studies looking at how people understand communications about the levels of harmful chemicals in cigarettes. We found that people associate the quantity of a harmful chemical in cigarettes with harm. And there's a certain intuitiveness to this, that, you know, and typically you would imagine that somebody is told a product has half as much arsenic as another product that you're being told that information because you think that it means that this product's less harmful, and that's likely to be your conclusion.

This goes back to Gricean norms of communication, that people assume that the information they're given is given to them for a reason, that there's a relevance to the information they're given.

One of our important findings and conclusions was that harmful chemical disclosure requirements can be misleading. So, if they were referring to the parts of the FSPTCA that require a public posting of the levels of

harmful chemicals in cigarettes, that information can be misleading because people may think, and our research has certainly shown, that people believe that a cigarette with less of the harmful chemicals would be less harmful in itself.

Also in the bigger picture -- and we submitted a comment on this -- we have substantial concerns with the MRTP exposure modification pathway. May fundamentally -- may not be viable. It's possible there may be some exceptions to that. But just at a very intuitive level you can imagine that any communications that a product is lower in a harmful chemical may well be interpreted to mean that this product is less harmful.

So, just to recap, there's a number -- so, we have specifically found that VLNC cigarettes are perceived as less harmful. And that's also congruent with a lot of the other research from decades of different angles of this, which I think makes a stronger case.

So, now on to what we know about correcting misperceptions. I'll just talk about three approaches: communications campaigns, inoculation, and disclaimers.

So, a communication campaign we know now that a broad reach, well-designed, well-funded campaign can be effective in reducing tobacco use. A campaign is recommended to advance -- I'm sorry, in advance of a VLNC policy. A numbers of papers looking at perceived risk have suggested that a campaign -- so that if there was to be a nicotine reduction policy at the federal level that a campaign come out in advance to explain to people what this means and what this doesn't mean about harm.

A pilot study of messages on nicotine shows some promise. I'd just like to be clear here, this is the study by Villanti et al. And I think it's an important study but it also has some limitations, that 81 percent of the people were not smokers, so only a 19 percent smoking rate in the Canadian sample. And the cigarettes

in this study were advertised -- I'm sorry, were described as being lower in nicotine. So, again, that would be the more vague kind of wording.

And so, that study finding that it was possible to change perceptions was under those conditions. So, I think it's a promising study but it's really just the beginning of what a communications campaign might be able to accomplish.

Also, I'm currently leading an R21 grant from FDA and NCI using established cognitive science techniques to correct VLNC misperceptions. There's been some nice work collating different approaches to correcting myths. Some of this comes from research on global warming, for example, and looking at different ways of correcting the public's misunderstanding in ways that are evidence-based and likely to be effective.

I'll just give a few examples here of what we're looking at.

One of them is to state the truth without repeating the myth. And I think this is a really important, very simple one. A communication that says vaccines do not cause autism is still reinforcing in people's memory vaccines and autism. That is problematic in the way that people actually process information. They are going to keep associating nicotine -- sorry, they'll keep associating autism and vaccines.

So, a more appropriate response may be to say vaccines have been well studied and they are safe. That way you're not referring to the myth.

It's also helpful to provide an alternative account. So, if you're explaining what, for example, does not cause autism it's helpful to explain what does cause autism. And this way you are fixing the gap in people's mental models of how a process happens. Because if you're invalidating part of their mental model, it's helpful to explain what's supposed

to go there instead.

And third is value affirmation, which is framing statements in a way that affirms people's natural sense to have correct and truthful information about their own health.

So, just to recap, on the communications campaign this seems to be a promising direction. It may be difficult to change misperceptions about low nicotine cigarettes, but based on the cognitive science techniques we're hopeful that there will be a way that will be effective.

I'd also like to talk about the approach of inoculation. So, this is based on the biological principle of inoculation. In this case it's about communication messages.

The idea here is to neutralize misinformation before it is cognitively encoded. There's two elements to this: an explicit warning of the impending threat; and the refutation of the anticipated argument exposing the fallacy.

So, for example, when referring to VLNC cigarettes the campaign or something could say, you may be told that these low nicotine cigarettes are safer, but don't believe them because the truth of the matter is all cigarettes are equally deadly, and the harm comes from the 70 other carcinogens in cigarettes.

Essentially this is prebunking rather than debunking. And I think this is an important point here. Because most people are not yet familiar with VLNC, there is a unique opportunity to prepare them before they develop misperceptions. So, again, if most of the public is not familiar with this policy, then the way it's initially presented to them can be very meaningful in allowing them to have a correct understanding and not form misperceptions.

And now on to disclaimers. So, these are often used to reduce seller's liability or as a remedy in legal settlements. They are not

grounded in communication persuasion science. This has been studied for decades now, and the science does not support the use of these disclaimers. They typically come from a legal setting, not necessarily from communications experts.

A review of 18 studies concluded that there was no evidence that consumers benefit from mandatory disclaimers. I'll point out here that this refers specifically to mandatory disclaimers, but I would posit that the presented claim from the VLN brand, which has been variously portrayed as a disclaimer, or a voluntary warning, or a statement, would be interpreted by the public the same way these other mandatory disclaimers are interpreted.

I'd like to also just point out that another study which was a little bit more focused on dietary supplements, but it was also a systematic review about disclaimers, summarized its findings by saying a few small studies reported a modest impact of disclaimers

on consumers' attitudes about dietary supplements. But the larger and more rigorous studies generally revealed that many consumers were unaware of the disclaimer or reported that it did not affect their perceptions of the product.

So, again, in these two reviews there is a strong evidence that disclaimers are not effective.

This also fits with what we know about how people process ads generally speaking. On average, people see an ad for about 2.2 seconds of print ad. And they glance at an ad, they make an impression, and that's when they form their attitude and intentions to buy. It's important to think about realistic conditions and the way people really see ads in the real world.

As an important cautionary example about the ineffectiveness of disclaimers we can look at the brand Natural American Spirit. So, as a result of settlements -- or, sorry, just to

go back for a minute.

The Natural American Spirit brand as advertised for decades now has used words such as "natural," "organic," and "additive free." These claims have helped propel the brand to be one of the top ten brands in the U.S. And people are willing to pay another dollar a pack to get this brand versus other brands.

Early on this was found to be misleading. And so there was a settlement with the FTC in the year 2000, and a settlement with the states' attorneys general in the year 2010 requiring disclaimers if they wanted to continue using the words "additive free" and "organic."

We conducted an experiment on this. And as far as we saw, it was actually the first experiment to test these disclaimers. And, again, that's after 15 years of them being around.

And we used this ad. This is an actual ad and we made modifications of it to experimentally expose people to different

claims, and the presence or absence of a disclaimer. We found that the positive health implications of the claims were not compensated for by the disclaimers.

This has real world implications. A recent study and a PATH survey found that 64 percent of smokers of American Spirits believe their cigarettes are less harmful than other brands. So, 64 percent of American Spirit smokers think their cigarettes are safer.

And this is not what everyone thinks about all their cigarettes. Only 8 percent of people, of smokers of other brands had this belief.

So this suggests that there are real implications here of decades of disclaimers not being effective. And I think this is an important cautionary tale.

We wanted to look at why disclaimers fail. We conducted a qualitative analysis study where we did focus groups and we asked people about this particular ad. We found that people

-- well, also just to mention, with focus groups, of course, about half the work I do is qualitative, half is quantitative. They both have important uses.

With qualitative research it's important as a way of understanding the different kinds of responses. You want to be wary of making generalizations about prevalence or the strength of different people's opinions because those can be cherry picked.

So, again, looking here at the types of responses people had, some people didn't notice the disclaimers at all. They were distracted by the ad. As you can see, this particular ad has two disclaimers and a Surgeon General's Warning and some other fine print, that's all kind of in black and white at the bottom. It's a very colorful top half that people are distracted by.

Some people ignore disclaimers. Some people discount them, and some people distrust them. We've had people say things to the effect

of, well, maybe the government makes them put that on there, and who knows if it's true or not.

And, also, people can misinterpret disclaimers. We had some people who saw these disclaimers and thought it was talking about the possible addictiveness product -- possible addictiveness of this product, not the harm.

Importantly, what we found about this ad fits very well with what the other decades of research about disclaimers have found in the reviews, that disclaimers are often not noticed or, if they are noticed, they can be misinterpreted.

Some of the specific problems with disclaimers include using "no" or "not" phrasing. And, again, this goes back to not repeating the myth and not reinforcing the wrong information and memory. It also requires more cognitive effort to process, a no statement.

Longer text results are problematic. Studies have shown that shorter communications

are more likely to be believed than longer communications. And disclaimers are often long.

Disclaimers often use a less legible font and in a smaller size. And they're often in a less prominent location than the claim.

Also, they may be absent from some communications. It's not always the case that a disclaimer accompanies the claim.

As some examples from today's application, this is one of the proposed draft ads for the VLN brand. You can see that it clearly communicates the claim. The claim is three words long: 95% less nicotine. And it is in very large print.

The disclaimer is at the bottom-left of the ad away from the face. And we know that people tend to naturally be attracted to people's faces, so in a less prominent location. And that disclaimer, as you see, is 16 words long. It's in smaller font -- smaller print. It's over a graphic image, and it includes, a not statement.

So, the evidence would suggest that this is not likely to be an effective communication.

As I said, most people see a print ad for about 2.2 seconds. An online ad is often seen for even less time, maybe .7 or .9 seconds. This is proposed as a social media ad. And, of course, it would not be 15 feet tall, it would be whatever size it would be on the iPad.

This is another proposed ad. It has a number of the same problems. And, again, these are all specific, evidence-based concerns as to reasons why we think these disclaimers would not be effective.

I will also point out that this particular ad happens to be laid out in a way that the word not is hard to see because it's blocked by the person's, the light on the person's hand. So, at first glance this is easy to read as, less nicotine does mean safer. That's problematic.

Also, as I said, disclaimers do not

always accompany the claims. So, these are some of the proposed in-store advertisements for the brand. And as you will notice, they clearly show the claim, they have no reference to a disclaimer.

The company has also stated in their marketing plan that for their online advertisements and their social media advertisements, due to space limitations they may not have space for the disclaimer.

So, in summary, campaigns are likely to be effective. We think there's ways that we could make those work. It's a very promising direction. Inoculation is a fascinating approach to consider because, again, if we can get the people before they get, before they're really developed into a misperception, we can provide them the correct information from the beginning. And that may be the best approach to this problem.

Disclaimers are unlikely to be effective. We have decades of data about their

effectiveness and ineffectiveness. We know that they are generally not effective. We know that they are specifically not effective for tobacco ads. And, therefore, I do not recommend them.

In conclusion, there is a widespread false belief that nicotine is the carcinogen in cigarettes.

There is a common misperception that VLNC cigarettes are safer to smoke than other cigarettes, and again, that's if they are smoked in a similar way.

An evidence-based communications campaign is worth exploring.

And disclaimers are unlikely to be effective.

These are my references.

And I'd like to thank my collaborators and colleagues on this project. And I'll end it there. Thank you.

CHAIR MERMELSTEIN: Okay. Thank you, Dr. Byron.

Can I ask just a quick -- I'll take

the chair's prerogative -- a quick follow-up question --

DR. BYRON: Sure.

CHAIR MERMELSTEIN: -- before we move on.

So, from your conclusions you would say that the disclaimer that's proposed is not effective, but perhaps an information campaign prior to it coming out would be effective. Is that a campaign that you would say should be run all the time? And does it matter who makes that campaign?

DR. BYRON: Our research at the University of North Carolina has shown that source is an important aspect of any communication. Whether it should be run all the time, you know, I wouldn't necessarily run it today if there is not going to be a product on the market that's advertised as being low nicotine or there's not going to be a nicotine reduction policy.

Certainly in advance of a nicotine

reduction policy it would be appropriate.

And does that answer your question? Or was there one more part to it?

CHAIR MERMELSTEIN: Well, I mean, in some ways one potential implication of what you're saying is, well, instead of putting a disclaimer have a campaign.

DR. BYRON: Right. It would be important that the campaign is not promoting the product but conveying the correct information to the public to prepare them to understand what this product means. And I would say that that's quite different from an advertisement promoting a product.

CHAIR MERMELSTEIN: So, keeping them separate?

DR. BYRON: Yes.

CHAIR MERMELSTEIN: Okay. Thank you.

All right. We'll have a general discussion. We're going to move on to our next speaker.

Next we have Dr. Alexander Persoskie

from the FDA.

DR. PERSOSKIE: Hi, everybody. I am Alex Persoskie, and I am a social scientist at FDA. And I will be presenting FDA's preliminary evaluation of public understanding of the proposed modified risk information.

So, let's start with an overview of what I'll be presenting today. First I'll describe the statutory requirements that the applicant has to meet regarding consumer understanding of the modified risk information. Then I'll describe the main components of consumer understanding that FDA is evaluating.

Second, given that the applicant is proposing to market VLN with information about reduced nicotine content, I'll provide you with some background information about consumer misperceptions of nicotine and the role of nicotine in causing tobacco-related diseases.

Third, I'll describe the proposed modified risk labeling and advertising for VLN cigarettes.

And then, finally, I'll describe the evidence that the applicant submitted regarding consumer understanding of the modified risk information. And I'll describe FDA's preliminary evaluation of this evidence.

The Food, Drug, and Cosmetic Act contains two requirements for consumer understanding of the modified risk information.

First, given that the company is proposing to market VLN cigarettes as a reduced exposure product but not a reduced risk product, the applicant must show that consumers will not be misled into believing that the product is, or has been demonstrated to be less harmful, or presents or has been demonstrated to present less risk of disease than other tobacco products.

Second is a more general requirement. The labeling and advertising must enable the public to comprehend the modified risk information and understand the significance of the information in the context of total health

and all tobacco-related diseases.

Before moving on to the next slide I'd just like to note the public health reasons why we're evaluating these standards regarding consumer understanding.

The reason why the public's understanding of the modified risk information is important is because it may have implications for who uses VLN cigarettes and how people use them. We're seeking to ensure that people would be correctly informed about the products' risks and how to use the products to reduce our nicotine consumption.

This is the question I'm preparing you to discuss today: Does the labeling enable consumers to accurately understand the addiction risk of using the products? And does the labeling enable consumers to accurately understand the disease risks of using the products?

To evaluate consumer understanding we considered the sources of information listed on

this slide.

First is the proposed modified risk advertising and labeling itself, which I'll show in a moment.

Second is the applicant's research, which includes a large quantitative experiment and several smaller qualitative studies that provide context for the quantitative findings.

And third is the peer-reviewed literature on consumer understanding of nicotine and low nicotine content cigarettes.

Let's now touch on the components of understanding that FDA is evaluating to determine whether people understand the proposed VLN claims. In other words, what are the key concepts that the public needs to understand?

We distilled these concepts down into two components:

First, we consider people's understanding of the products' addiction risks. Will people understand that VLN cigarettes are less addictive than other cigarettes, and

similarly addictive as NRT?

Second, we consider people's understanding of the products' disease risks. Will people understand that VLN cigarettes are just as likely to cause diseases as other cigarettes if they're smoked in the same way as other cigarettes?

Previous research has found that the U.S. public has misperceptions about nicotine, incorrectly believing that nicotine is the substance that causes most of the health risks from smoking, such as lung cancer. Accordingly, previous studies have found that many people perceive low nicotine cigarettes as less likely to cause tobacco-related diseases, even when smoked like other cigarettes.

We're sharing these data now. And we want you to keep these results in mind because we're about to go into the results specific to the products under review. Those results raise important questions we need you to discuss about consumer perceptions related to low nicotine

cigarettes and disease risk.

This slide shows results from two prior studies of consumer perceptions of nicotine and low nicotine cigarettes. The pie chart on the left shows the results from a study in which U.S. adult smokers were asked to compare the lung cancer risk from smoking either normal cigarettes or cigarettes with much less nicotine.

They were told to assume that a person smokes the cigarettes for 30 years. As shown, approximately half of people responded that the lung cancer risk would be lower for the cigarettes that contain much less nicotine.

Similarly, the bar chart on the right shows the results of another prior study. In this study, smokers came into a laboratory and smoked three different types of cigarettes: their usual brand cigarette, a very low nicotine content cigarette that was described to participants as having very low nicotine content, and a very low nicotine content

cigarette that was described to participants as having average nicotine content.

After trying each cigarette, participants rated the likelihood that they would get various diseases if they smoked that type of cigarette at the same rate that they smoked their current cigarettes.

The bar chart here shows perceptions of risk of lung cancer. As shown, smokers perceived a lower risk of lung cancer for the VLNC cigarette when they were told of its very low nicotine content compared to the usual brand cigarette and compared to the VLNC cigarette that they were told had average nicotine content.

Results were similar for perceptions of other disease risks.

These studies suggest that there is a risk of people misinterpreting information about reduced nicotine content to mean that VLN cigarettes are less likely than other cigarettes to cause diseases.

In the context of these misperceptions, this slide shows how the applicant proposes to disseminate information about the product's very low nicotine content on the product labeling.

The front side of the pack is on the left, and the back side of the pack is on the right.

This pack is for the non-menthol version of the product.

There is also a white and green version of the pack for the menthol version, which is not shown here.

The labeling includes the three proposed claims: 95 percent less nicotine; and helps reduce your nicotine consumption, both on the front and the back of the pack; and greatly reduces your nicotine consumption is on the back of the pack.

The front of the pack also includes a voluntary warning, the statement on the small box at the bottom.

The voluntary warning provides additional information related to the claims. It states nicotine is addictive. Less nicotine does not mean safer. And all cigarettes can cause disease and death.

Note that there is no information on the pack about how one would have to use VLN to reduce their nicotine consumption.

The applicant also proposes to disseminate the claims in advertisements. They proposed to use advertising channels, including a branded website, print ads, digital ads, direct mail, email, social media, brochures, point of sale ads, and earned media.

The applicant submitted a large number of proposed advertisements. They also submitted an image library with hundreds of photographs that the applicant stated they would use to periodically refresh and update the ads.

This slide shows two examples of adds that would appear in print magazines with predominantly adult readership. Note that in

these ads and some of the others, some of the modified risk claims are displayed in very large salient font, whereas the voluntary warning is shown in small font with lower contrast.

For example, in these two ads the voluntary warning is shown just above the surgeon general's warning box.

Also, although not shown here, there are additional issues with some of the other proposed ads and images.

First, as noted in the FDA backgrounder, some of the other proposed ads include imagery that could potentially appeal to youth. For example, this includes images of young models.

Second, FDA has identified additional modified risk claims in some of the advertisements, as also described in the backgrounder. The applicant did not submit any studies of the proposed advertising in the application. We don't have specific questions for the committee about the ads, but we still

wanted to make a note of these issues.

Let's now consider the research that the applicant submitted on consumer understanding. The applicant conducted a large online quantitative experiment. Participants were randomized to view either a VLN cigarette pack or a Marlboro Gold cigarette pack.

As shown on this slide in the top row, for products assessed participants rated the addiction and health risks of VLN or Marlboro Gold. For comparison, they also rated the addiction and health risks of using various classes of tobacco and nicotine products, including convention cigarettes in general, e-cigarettes, NRTs, and snuff.

The second row on this slide shows the constructs assessed. This includes perceived addiction and health risks. For addiction, for example, people rated what they believe is the risk of being addicted to each product, and the risk of being unable to quit each product.

For health risks, for example, people rated what they believe is the risk of getting lung cancer, heart disease, and mouth or throat cancer from using each product.

The bottom row on this slide shows information about participants. Participants in the study were all adults, including current, former, and never smokers. As shown, current smokers were divided into those intending and not intending to quit. Former smokers were divided into past year quitters and long-term quitters. And never smokers were divided into young adults and adults overall.

Participants who were assigned to view and rate VLN cigarettes were provided with modified risk information about VLN. This slide shows the modified risk information that participants viewed.

First, the survey itself provided participants with some information about VLN. It stated that VLN stands for very low nicotine, and said it was a new tobacco product currently

in development.

It stated that VLN are made from a tobacco plant that's been altered to contain much lower levels of nicotine than the tobacco used in traditional cigarettes.

Second, the pack labeling for VLN contained the proposed modified risk information that I showed on a previous slide. This included the three claims plus the voluntary warning in a box on the front of the pack.

The study also tested two alternative versions of the pack labeling that varied the wording of the second claim. Instead of helps reduce your nicotine consumption, the alternative version stated either helps you smoke less or helps reduce your urge to smoke.

The findings from these other two conditions were similar to those in the condition with the proposed labeling. Because findings were similar I won't further discuss these other two conditions in the presentation. But I wanted to let you know that these other

alternatives were indeed tested.

Also, note that there was another condition in the study called the VLN no claims condition. In this condition, participants were supposed to view the VLN pack with none of the three proposed risks -- the three proposed modified risk claims. However, there was an error in the study programming, and participants in that condition did view one of the three modified risk claims. Thus, we excluded the VLN no claim condition from our presentation here and we used the Marlboro Gold condition as the control condition.

Finally, also note one other aspect of the study design. The study included no conditions that could be used to test the effect of the voluntary warning. Thus, the study doesn't allow us to understand whether adding the voluntary warning on the packs helps to mitigate misperceptions of the modified risk information, whether it has no effect, or whether it exacerbates misperceptions.

Let's now look at the results, starting with perceived addiction risk.

As mentioned previously, we seek to evaluate whether the proposed labeling would enable consumers to understand that VLN cigarettes are less addictive than other cigarettes and similarly addictive as NRTs.

In the study, people were asked: taking into consideration everything you know about product, indicate whether you believe -- indicate what you believe is the risk of each of the following long-term or lifetime addiction-related issues because of smoking or using the product.

People were asked about VLN as well as other products.

This figure shows perceptions for the outcome being addicted to product. The results were consistent for the other five addiction risks that were assessed.

This figure shows perceptions among adult current smokers intending to quit. We

focus on this group for simplicity, however, results were generally consistent across the other smoker groups.

In the figure, moving from left to right, conventional cigarettes in general were rated as highest in addiction risk, followed by Marlboro Gold cigarettes in blue, and snuff.

E-cigarettes were perceived as less addictive than those products.

Finally, VLN cigarettes and NRTs were perceived similarly and as least addictive out of all the products that were rated, but still slightly above the midpoint of the 5-point scale.

Let's now look at results on perceived health risks. As noted previously, we seek to evaluate whether the proposed labeling would enable consumers to understand that, if smoked in the same way as other cigarettes, VLN cigarettes are no less harmful than other cigarettes.

In the study, people were asked:

taking into consideration everything you know about product, indicate what you believe is the risk of each of the following long-term or lifetime health-related issues because of smoking or using the product.

This slide shows the results for the outcome serious illness. But results were consistent for the other 17 health risks that were assessed.

As before, for simplicity we focus on results among adult current smokers intending to quit.

In the figure, moving from left to right, Marlboro Gold and conventional cigarettes were rated as similarly likely to cause serious illness. Snuff was rated lower, followed by VLN cigarettes in yellow which were rated similarly to e-cigarettes, and higher than NRTs.

Findings for the other smoker groups which are not shown here were similar but less dramatic. People in all smoker groups perceived VLN as less likely than Marlboro Gold and

conventional cigarettes to cause health risks. However, in the other groups the difference between VLN and other cigarettes appeared somewhat smaller than among current smokers intending to quit.

This slide shows perceptions of some additional health risks for each of the three cigarette products that were assessed. Conventional cigarettes are in gray, Marlboro Gold is in blue, and VLN is in yellow.

The health risks shown are lung cancer, emphysema, mouth or throat cancer, and heart disease. Again we show results for current smokers intending to quit.

As shown, for each health risk conventional cigarettes in general and Marlboro Gold were perceived very similarly, while VLN cigarettes were perceived as substantially lower in risk.

So, the question that emerges is how to interpret these differences in risk ratings. On one hand these results were consistent with the prior findings on misperceptions of nicotine

and low nicotine cigarettes. Thus, perhaps the voluntary warning that the applicant proposes to use on the pack labeling was ineffective, and people incorrectly believed that the very low nicotine content would confer benefit even if people smoked VLN cigarettes in the same way as other cigarettes.

On the other hand, it's also possible that when answering these questions about health risks participants assumed that because of the very low nicotine content they would smoke fewer VLN cigarettes or would not smoke VLN cigarettes for a long duration.

As we noted previously, participants did appear to understand that the very low nicotine levels in VLN cigarettes would make the product less addictive than other cigarettes.

Because of how the study item was worded, it's difficult to adjudicate between these two possibilities. As shown at the bottom of the slide, the question stated: taking into consideration everything you know about the

product -- which for VLN, presumably, includes expectations about how it would be used.

However, the question also specified that it was asking about long-term or lifetime risks, which perhaps means that participants should have been assuming long-term usage of VLN.

So, just to spend another minute to really emphasize the questions regarding these lower health risk ratings for VLN cigarettes, possibility A is that the lower risk ratings reflect a misunderstanding because participants assumed that they would use VLN cigarettes the same amount as other cigarettes when rating the risks.

Possibility B is that the lower risk ratings for VLN are potentially accurate because participants assumed that they would smoke fewer VLN cigarettes or smoke for a shorter duration.

As mentioned, the way the risk perception items were worded makes it difficult to decide between the two possibilities that I

just mentioned. However, the applicant's quantitative study also included open-ended items that can potentially help us determine what participants were thinking when they rated VLN as lower in disease risks than other cigarettes.

Specifically, the study asked participants open-ended questions about how they would describe VLN cigarettes to a friend or family member and what they see as the benefits and the risks of VLN cigarettes. Participants responded by typing their open-ended responses in a text box.

Here we show some example responses from the question about how they would describe VLN cigarettes to a friend or family member. Unfortunately, the responses to these open-ended questions don't clearly support one possibility over the other. Some responses suggested that participants understood.

For example, the response in the green bubble stated that the health risks remain

the same despite the reduced nicotine content.

Other responses suggested uncertainty, such as in the orange bubble, which stated that it is not clear whether risk levels are reduced in VLN cigarettes.

Other responses suggested confusion about the disease risks, such as in the red bubble, which states that VLN gives you the same feeling as smoking without all the harmful effects.

Finally, given that these questions were open-ended, many responses cannot be interpreted to determine whether the participant understood the health risks. For example, the response shown in the blue bubble simply states that VLN is a cigarette with less nicotine. Thus, responses to these items didn't clearly support one possibility over the other.

The applicant also conducted qualitative research on consumer understanding of the modified risk information. This research included focus groups and in-depth interviews

with individual respondents, including smokers and non-smokers. These studies ask participants about the health risks of VLN after reviewing various claims and voluntary warning statements.

Unfortunately, as with the open-ended items from the quantitative study, the findings from the qualitative research did not shed light on why people rated VLN as lower in health risks than other cigarettes in the quantitative study.

For example, the response in the green bubble here suggests that the participant believed that VLN would be less harmful to one's health because people would not smoke as much.

In contrast, the response in the red bubble suggests the opposite. That is, the person appeared to think that VLN were less harmful than other cigarettes when smoked in the same way, therefore people would want to smoke them more frequently.

I know these responses and the open-ended responses on the previous slide came up during the committee's questions for the

applicant this morning. I just wanted to note that I don't believe the company submitted information to FDA about the procedure used to code these responses, such as whether they used a systematic coding scheme and multiple coders plus a measure of the reliability or validity of the coding of the qualitative responses.

Perhaps the company can comment on their coding procedures during the discussion if the committee is interested in hearing more about that.

Thus, overall, questions remain about the extent to which the proposed labeling would enable the public to understand the health risks of smoking VLN cigarettes.

In summary, we looked at two main aspects of consumer understanding of the modified risk information: understanding of addiction risks, and understanding of health risks. The evidence indicates that the proposed labeling would enable the public to accurate perceive VLN cigarettes as less addictive than

other cigarettes and similarly addictive as NRTs.

However, results on perceived health risks were mixed. Adults perceived VLN cigarettes as moderately to very likely to cause tobacco-related diseases, but less likely than other cigarettes to cause diseases.

Based on the study submitted, it is unclear whether people perceived VLN as less likely to cause diseases because people believe they will smoke fewer VLN cigarettes, because they believe they will smoke for a shorter duration, or because they believe the very low nicotine content allows them to smoke VLN cigarettes in the same way as other cigarettes without incurring the same health effects.

This brings us to the fourth question we would like you to discuss based on your expertise.

Discuss whether the labeling enables consumers to accurately understand the following effects of using the products: the addiction

risk, and the disease risks.

Thank you for your attention and for sharing your expertise and opinions regarding this application.

These are our references. And I will leave this up for discussion.

CHAIR MERMELSTEIN: Great. Thank you.

So, we have a nice set of afternoon presentations. And what we want to consider now are a couple of different items.

First is whether the labeling enables consumers to accurately understand the following effects. Let's start with the first one, which is addiction risk.

That one seems to be from several lines of evidence here that consumers do understand the addiction risk. Other thoughts about that?

DR. BIERUT: So, I just want to add something here which is individuals' addiction risk is not all equal.

CHAIR MERMELSTEIN: Uh-huh.

DR. BIERUT: And we know this very well from genetic studies. And response to nicotine differs quite a bit from individuals. And we know that variation on nicotinic receptors and on nicotine metabolism drives differences in our nicotine -- in our addiction to nicotine. And this also drives lung cancer and other diseases.

So, in part, the biology underlying this and our difference in our biology is really, I think, not known in the general community and not known in general in the scientific field outside of the people who are doing this work in genetics. And that is something really driving this kind of whole thing here, why we're reducing the nicotine, because of this addictive quality and we vary in our risk of addiction.

CHAIR MERMELSTEIN: That's an excellent point.

Other thoughts about that particular

point? Oh, go ahead.

DR. WARNER: A different point.

I just wanted to note when you look at these specific claims -- and by the way, the last two presentations I thought were really helpful and very useful -- but when you look at these claims, I'm taking from the first presentation, number two, "helps reduce your nicotine consumption" is less dramatic than number one. And apparently would have sort of less impact, but on the other hand would imply or infer less of a health risk benefit, if you will.

But what I was struck with earlier today is the claim that it's 95 percent less nicotine is only true in the event that you're switching entirely to this product. And we go back to that dual use question. So that makes it a little confusing as to how to interpret what's going on here.

I mean, the labeling probably would not be accurate for the dual user in terms of

the dual user's understanding.

CHAIR MERMELSTEIN: Okay. So let's stick first with this question which is do they, do consumers accurately understand the effects on the addiction.

How about, which I think we've briefly discussed, I think there's okay consensus, what about disease risks? A little more complicated question here, I think, which is -- do consumers understand?

Yes, Dr. Donny.

DR. DONNY: So, this is a bit more of a question and it follows on Dr. Warner's comment.

Is it best to view this question and thinking about it in terms of the risk of the product or the risk of the product as it's likely to be used? I think that in general it's the latter that we're supposed to be focusing on. And I think it complicates things with a modified exposure application that is intended to reduce disease risk through reducing

addiction because it assumes a pattern of use.

So, one, the product itself may not be safer, and that is a misperception that people could have, on the other hand, if they're accurately perceiving that reduced addiction is likely to occur, then maybe they should be factoring in the likelihood that they would use the product in their estimate. And when we think about being misled, that's the standard at which we should be comparing.

And I don't know for sure which one it is, but it seems to me quite different.

CHAIR MERMELSTEIN: Yes, I think partly what we want to do is assess this within the context of what we think is likely and how it's going to be used.

You know, I think that -- Oh, Dr. Bierut, go ahead.

DR. BIERUT: So, thinking about how it's likely to be used and what's going to happen, I want to go back to the first presentation by Dr. Byron after lunch, which was

how is this messaging going out, I think is really the key question here.

I imagine that people may ask health care providers, what about this? Should I need to -- you know, is this good? Is this bad?

I see so many points of education that need to go out for us to, if I can use the word innoculate, I think that was the whole idea of kind of getting out in front of the message.

So this is a really important point here of how do we think it should be used, going back to the switching completely, the dual use. I think we're highly likely to have dual use. But if dual use eventually leads to single use of the product, which eventually leads to quitting, that's actually good.

If dual use leads to prolonged smoking, that's bad.

And so I think we really need much more than just what's on this path to try to protect the overall public of what's going to happen here.

CHAIR MERMELSTEIN: I think from Dr. Byron's presentation he also gave us some, you know, sort of a field -- some opportunities here. I mean, I think a couple of his take-home points were that accurate information is important. So that what we want to do is provide consumers with accurate information, that that's important, and that there is an education, and so being able to convey what is accurate to whether it's completely switch, and indeed that it does contain 95 percent. And the message about 95 percent being specific is also an important part.

But we're in the context of a lot of misperceptions out there already. And I think the opportunity that he perhaps alluded to is the need for a campaign right now in the context of any of these products making a difference, and that we have to think about who should be conveying some of this information and how that information gets conveyed.

But I think his presentation led me

to think that there are some opportunities here that we should take advantage of.

Dr. Ossip first and then -- Is Dr. Ossip on the phone?

DR. OSSIP: Yes, thanks.

We have some evidence in front of us that I think is what really what we have to work with at this point in terms of these products. And the two sets of evidence that we have is going with historical evidence from the research that's been done outside of the applicant.

And then the second would be the research specifically done by the applicant. What we saw from these two really helpful presentations -- and thank you to both of the presenters -- is that although I agree there are some opportunities from Dr. Byron's presentation that are intriguing and very nice evidence-base to them, there currently appears to be a misperception relative to health risks of very low nicotine cigarettes.

From the studies presented by the

applicant, I'm interested in hearing more about the methodology so that we can more adequately interpret what it is we're seeing. I think Dr. Persoskie said if we were interested it might be a question to ask about their methodology for the qualitative coding. And as someone who does both qualitative and quantitative research, I am very interested in that.

Also , methodologically there are some questions that I have. One is I think the study specifically asked subjects to look at maybe it was the packs, I forget, or it was a page that showed the packs, but they were asked specifically to look at this. So, based on what Dr. Byron presented, this may be very -- their interpretation may be very different from the way they would interpret it in real world use in the way it's likely to be marketed, what they would see, what they would read, how they would process that, and how they would interpret it.

And, again, we see gaps in not getting perceptions, not having data to look at

from youth relative to these particular products.

CHAIR MERMELSTEIN: Okay. I know that Sally had a question. I'm wondering if first, though, would it be helpful if we just gave Century 22 an opportunity to explain more about their methods and to answer these questions, and then we'll get to yours.

MS. TROTTER: Thank you for the question.

In terms of our coding process, and we've been doing this now for 54 years, our coding is executed by an operator-assisted coding platform. It's called Language Logic.

In terms of the process, our internal team, they receive an initial output of some of the verbatim statements to kind of get a feel for exactly what is being said. From that point they create a code frame. That code frame goes back to the provider. And then that provider goes through the process of coding all of the data.

They return that back to us and then we run the tables on, on -- and they are tested and they are also available. And the documents were disclosed to FDA.

CHAIR MERMELSTEIN: Dr. Ossip, did that help address your question?

DR. OSSIP: So, is there a single coder then, did I understand you to say?

MS. TROTTER: I'm sorry, I didn't quite hear?

DR. OSSIP: Ultimately, ultimately there's a single coder?

MS. TROTTER: Oh. There is, yes.

Now, there may be multiple people working on a study, but it's consistent for multiple people.

CHAIR MERMELSTEIN: Sally?

DR. OSSIP: So, do you have any, you know, validation or inter-rater reliability or anything on the particular coding?

MS. TROTTER: We, we can certainly provide, provide some general information about

that.

CHAIR MERMELSTEIN: Yes.

DR. OSSIP: Thank you.

MS. HERNDON: I want to go back, Dr. Mermelstein, to your observation that Dr. Byron's presentation gave us an interesting opportunity. And I think relevant to the question here. It's an opportunity, if at some point we're moving in this country to a standard, a new nicotine standard in cigarettes, to really follow the advice of the research that he provided to begin to educate consumers about addictiveness, and risk, and health risk.

From a public health practitioner perspective, one of the things in the bigger scheme of things and that was highlighted in the Surgeon General's Report are some other opportunities. We have the Tips From Former Smokers Campaign, which is one of the most effective campaigns to tell people why they need to quit.

And I think we're also experimenting

a little bit, and FDA is doing some of this, with interjecting messages about how to quit. There are other states like Minnesota that are doing some of this, too. And, you know, campaigns like Every Try Counts.

And so some of the research that we heard about today and some of the evidence from the recent Surgeon General's Report, which I haven't gotten all the way through yet but I'm working my way through, that just shows only about a third of smokers really are getting the message that NRT is effective and efficient, and when used in combination therapy or decline, you know, success rates really go up.

So, thinking about campaign opportunities of continuing the hard press on Tips From Former Smokers with some messages about how to quit, I think is the really --

CHAIR MERMELSTEIN: Sure.

MS. HERNDON: -- timely opportunity here.

CHAIR MERMELSTEIN: Of course.

Dr. King.

DR. KING: Yeah. So, first I would say how excellent those two presentations were. For me those were the most helpful of the entire day and it warms my cold black heart when, you know, science is discussed. Lest we forget that the S in TPSAC stands for science.

So, that being said, I think to answer this question for me, based on the science that was presented from both, I don't think we can say that the labeling allows consumers to accurately understand the effect on disease risk. And what was particularly telling for me was the Dr. Byron slide where it showed how nicotine is described, how it affects perceptions, and the addictiveness in nicotine content were going up but cancer risk was going down.

So, disease risk, that's cancer risk. And so it shows that you've got an issue here in terms of how the public interprets it. And that's concerning to me.

And it is compounded by the fact that the only science testing certain -- has been certain places, particularly on the product. And so, in the real world what the implications would be for some of these ads is concerning.

And the one that we were shown by Dr. Byron, quite frankly, was absolutely egregious, with the word "not" highlighted in white on the palm of the hand so you could barely see it. The fact that that got through is very concerning to me. But if that's just an example of what's to come, I think we need a lot more science in terms of what's going to be most effective.

And we have to remember that if we're talking about what the potential benefit of this thing is on public health, and based on all the science I've seen so far today, I'm just not convinced the benefit is there. Even if it's a null, that's still not a benefit, and that's the charge.

CHAIR MERMELSTEIN: Doctor -- Oh

wait, Dr. Apelberg is jumping in.

DR. APELBERG: Sorry. I just wanted to comment that nothing has gotten through. We're in the process of the evaluation for the --

DR. KING: Yeah. I'm just saying that the program that was presented to the committee is a little concerning to me, that something like that would be a standard that we're asked to review. I think it speaks to the comprehensiveness and the thought put into the application in general.

DR. APELBERG: And could I just, since I have the mic, also ask one other question to the committee.

Dr. Persoskie talked about two possible interpretations of the health risk perception findings. And I'm curious about the committee's thoughts on that, whether there is evidence that can be brought to bear to help sort of make, make sense of that, or just, you know, general comment on that topic?

CHAIR MERMELSTEIN: Dr. Thrasher, were you going to address that one at all or were going to address that next?

DR. THRASHER: I can get around to it if you want me to.

CHAIR MERMELSTEIN: Okay.

DR. THRASHER: I mean, I guess it's hard to get in the line-up and make sure you're kind of responding to what people said earlier.

One of the comments that I had around the qualitative focus groups and Dr. Ossip's question about how it is that these, I guess there were, like, 17,000 open responses that were coded. Is that about right?

And so, you know, people at FDA have identified those who indicate understanding. There's some that are associated with uncertainty, some that are associated with confusion, some that are kind of inconclusive in terms of your ability to understand what people actually took away from the message.

And when I heard the applicant, or

what I saw the example quotes that they presented, they were all in the kind of complete understanding camp. And but then when I see FDA's side I'm seeing a little bit of all four or those categories, only one of which is understanding.

And so, I guess my follow-up to Dr. Ossip's question would be if these were coded in a way that's useful for us, you know, what's the breakdown in terms of the percentage of people in each of those different categories? And are we really saying that, you know, more than 75 percent of people provided responses that indicated clear understanding? Or kind of where are we with that? Because I felt like we had two different stories going on.

The other thing that speaks a little bit to Dr. Apelberg's comment, and it's certainly consistent with what Dr. King said earlier for me, is that I don't think that we're going to be able to correct misperceptions with packaged messaging of the type that we saw here

today. And the marketing that would accompany it could potentially reduce the potential benefit of that messaging or positive upside of that messaging.

I think we would need a campaign, that's why I agreed with Dr. Byron's presentation about that. I assume that's beyond the scope of what the applicant is going to be doing. And I don't think that we can rely -- say that we can rely on FDA to provide that campaign before the market, the product would be launched. And so, that's concerning to me.

My thought after having gone through this, and more direct response to Dr. Apelberg, is that I -- and in the context of all the previous research on how it is that perceptions of addiction are pretty tightly correlated with perceptions of risk, I'm seeing the same thing when I'm looking at what the applicant presented here today.

The extents of the impact on beliefs about addiction may not be quite as strong as

what we're seeing for the perceived risk, but it's certainly in the same direction, and it's certainly a reduction in perceived risk. So that's concerning to me.

Those are the three comments to try and bring it back to him. Thanks.

CHAIR MERMELSTEIN: Okay. One of those was a question posed to Century 22 --

DR. THRASHER: Yeah, I mean just to kind of help contextualize a little bit more what was said earlier about how they actually did code those -- those comments. And can we have some sort of a feel for what people are saying when they're given the opportunity to describe their understanding of the messaging?

MS. TROTTER: So, we're happy to go back and code those comments as correct versus incorrect, to provide some more meat on those bones, if that's what I'm understanding your --

DR. THRASHER: In general, yeah, at the kind of the crudest level. Because, like I say, you all are just showing the quotes that

show correct understanding, we're seeing others that suggest that there's incorrect understanding or confusion.

MS. TROTTER: Well, and to that point, we were also trying to understand why there would be, you know, a lower risk than, say, conventional cigarettes. And that's -- pulling those verbatims was that's what helped us understand the context of that.

Speaking about the ones that specifically were in the presentation, some of those -- in fact, I believe all of those actually came from our qualitative interviews. And throughout our qualitative interviews we heard that same sentiment. So, you know, I know it's lower in nicotine, but I get it, this is not good for you. This is not better for you.

So, it was clear, at least through that qualitative interview process, that people understand that once we put that additional voluntary warning on there.

Did that answer your question?

DR. THRASHER: Not really. But, I mean, again, in the end what you said initially was what it is that I would be looking for --

MS. TROTTER: Sure.

DR. THRASHER: -- as a response. And obviously you haven't gone through that kind of a systematic analysis of the open responses that people provided. Thanks.

MS. TROTTER: And we're happy to do that.

CHAIR MERMELSTEIN: So, just back to Dr. Apelberg's question, which was there were two possibilities that were posed. One is that participants assumed that they would use their VLN cigarettes the same amount, and then when they made their products and that their health risks are therefore inaccurate. Or that they assume that they would use less of the cigarettes compared to other cigarettes when rating the product, and their health risk ratings are potentially accurate.

That second assumption requires a lot

of mental calculations and tends to be less likely when participants are at risk. That's my, you know, giving my opinion. Because that takes a few levels of cognitive inferences and stepping for somebody, that is often rare to see in response to a survey.

Dr. Donny?

DR. DONNY: Yeah. And I think it's even more complicated by the fact that in this particular case you're talking about dual use as being the most common outcomes. So now you're asking them to compute some -- yeah.

CHAIR MERMELSTEIN: So, it would be a lot of to think that their risk ratings are potentially accurate and that they did a lot of consideration of a lot of factors at once and made some mental calculations.

Dr. Hatsukami?

DR. HATSUKAMI: I just want to point out that I think we have to learn the lessons from the light cigarette experience. And what we learned there is that it's not just the

labeling, the packaging, the advertising, it's also the sensation, the sensory effects of the smoke.

And when you smoke the very light, the very low nicotine content cigarettes, the sensory aspect is really quite different. And so I think it would be important to actually take a look at the interaction of those effects and to make sure that there wouldn't be the misperception from the sensory aspects that these are lower in disease risk.

CHAIR MERMELSTEIN: Right. That's a very good point. It's a good point about potential rebound.

Dr. Ossip on the phone, you had a question?

DR. OSSIP: Yes. Yes, thank you. It's actually a comment.

I wanted to reiterate Dr. King's statement that I think was a very nice summary of what we've seen so far, and I think as well of what we've heard since then, which is based

on what we have in front of us we really can't give a clear answer to this question. But if we were to go with what we've seen and what the prior research has shown, the answer to these would be -- the answer to the interpreted disease risks would be no, that they're not accurately understanding it.

And a part of this is, by some of the questions that have been raised about the methodologies that are used and how they -- which I think have only been partially addressed.

And also, I think a very good point was made about that this is how consumers are interpreting what they're seeing on the packs, is very important. There are ways to make that, the messaging more visible and more understandable.

That will have only a certain amount of effect, and the impact will ultimately be determined by multiple sources, like whether there's a communications campaign ahead of the

release of the product, how these products are marketed by the company, which I think will really be crucial and will be very different from if we were to be measuring understanding in that context relative to the context of the very carefully controlled study, and what populations we're looking at. And, again, we see that lack for youth.

And these are, these are really important issues because these will influence whether people uptake, how they use them, whether they switch versus quitting, whether they potentially, like youth would use this as a starter product to lead to other product.

So, it's a complex issue. And I would just -- I'm concerned about this. I think this is, you know, really a complex question that's being answered that has very important public health implications. And there are more questions than answers with what we know so far going in the direction of misunderstandings.

CHAIR MERMELSTEIN: Sally Herndon?

MS. HERNDON: This is going back to kind of a minute detail that I wanted to ask the two researchers here at the table about from earlier this morning. But you brought up the different and the difference in the perception of these products.

Did you all find any compensatory behavior related to ventilation holes with these products? And what kind of sensation or nicotine consumption, how that might have varied, or was it the same as any other cigarette?

DR. DONNY: So, we -- in one of the trials we tested a less ventilated version, not the one that's proposed here. The one that's proposed here is, I believe has single-row ventilation that's similar to the you could say NRC102/103s.

We didn't see much of an effect in terms of behavioral effects going to a more ventilated -- or a less ventilated product. We did not.

We've also looked at cigarette butts, which will in part tell you how smoke is passed through and deposited within the filter, and to date haven't seen much there either.

So, I think to the extent to which we have data related to that, I don't think we've seen much.

And then Dr. Hatsukami is doing more work on ventilation. I don't know if you have any thoughts about this.

CHAIR MERMELSTEIN: So, let me try to bring this back to some sort of -- we've been all around, this has been a great discussion, but to some cohesive point.

This is a product that's on the market, correct? And so what the application is for is how marketing may -- what kinds of messages to have a modified exposure.

So, in the hope here and the whole concept behind very low nicotine cigarettes is that it -- yes, you're correcting what I'm saying. Yes, it's not yet on the market.

DR. OGDEN: Just a correction. It's been authorized to be on the market.

CHAIR MERMELSTEIN: Right.

DR. OGDEN: You know, PMTA, but it's not on the market yet.

CHAIR MERMELSTEIN: It's not on the market yet, but it can be on the market.

So, this discussion is not whether the product should be on the market or not, but rather how is it marketed, in the sense of what's the messaging around that. Is that correct? Okay.

So the hope with a very low nicotine cigarette is, in some ways, that smokers -- current smokers would potentially switch to that, and that becomes a potential road off of combustible cigarettes.

So, the question is, are any of -- in the context of that, and yes, we have the context of complicated marketplace now, the applicant is asking for -- are these messages and these claims on balance potentially helpful

or less helpful to the overall public health, that might perhaps encourage people to use these not for the wrong reasons but to use them as a way off.

And we heard today that exposures may indeed be less with these cigarettes, but the nicotine content does indeed seem to be substantially less, biomarkers are less. We have questions about, though, whether those would be realized in real life because of dual use issues, not because of the product itself, but because people have options available and they may be less satisfying.

So are any of the messages out there likely to perhaps encourage people to use these in a way that might accrue health benefits? And are these helpful messages when we think of it?

So I think that's the context of what we're trying to sort of decipher here and give some opinions about. And it's complicated based on what some of the messages perhaps are accurate but may lead consumers to have other

perceptions.

Dr. Weitzman?

DR. WEITZMAN: I think that's very useful. The only qualification I would put is the other side of the equation that there's no data presented about whether or not this messaging will influence the uptake by youth.

CHAIR MERMELSTEIN: Yes, we don't have that. We have other, just, assumptions and inferences that we can make about that, but we have not seen specific youth data yet.

DR. DONNY: Yeah. And just to extend that a little bit there, I think it would be really useful if we also saw data that spoke to the -- we got a lot about potential misperception of risk, goes with the potential for reducing nicotine, but we didn't talk about the degree to which labeling and providing that information could also have benefits. And I think it's important that we weigh both sides of that equation for all populations.

CHAIR MERMELSTEIN: Right. And I

think that Dr. Byron's presentation, you know, a couple of important messages from that is the importance of accurate information and that consumers should know what's in a product or get some accurate information to learn. So that there is some benefit for consumers getting educated about nicotine content.

Now, not everything can be packed on or should be packed on one product and one label.

MR. ZELLER: Just three more reminders to Dr. Mermelstein's very helpful framing of this.

Number one, assume no product standard, as we said this morning.

Number two, assume no campaign would proceed were this to be authorized. We take Dr. Byron's presentation seriously, understand its relevance were there to be a product standard, but assume no product standard, assume no campaign.

And then the third reminder is, were

there to be an authorization for this, it would be time limited. It's not as if, were there to be an authorization, that would be the end of this forever and a day. By law there's a maximum amount of time that whatever claim would be authorized could remain in the marketplace. Then the sponsor would have to come back to get it renewed. Just want to remind the committee of those conditions and parameters.

CHAIR MERMELSTEIN: And just a quick follow-up before Dr. Wanke.

And that there's post-market surveillance required as part of that.

MR. ZELLER: Right. There was for the PMTA. And, again, assuming that there were an authorization here, it would come with conditions, commitments, and restrictions.

CHAIR MERMELSTEIN: Okay.

DR. WANKE: And I think that's a helpful reminder. For the third point, about the idea that it's time limited, I want to remind us of, again, the lessons from light or

mild type labels, that even when those were taken off, even just a color on a pack could elicit the memory and the preconceptions that people now have. And I think that once you for five years have a product out there, it encourages misperceptions, that even removing the labels later the misperceptions might still remain.

CHAIR MERMELSTEIN: Yes.

DR. TWOREK: And I just wanted also to remind people that the length of an order does not have to be five years. That would actually be the maximum length.

CHAIR MERMELSTEIN: Five years in today's marketplace is a really long time. Things happen fast.

So some thoughts, just in terms of keeping the big picture in mind of what the --

DR. WARNER: I actually think Mitch's comment is very provocative in a way, but also reassuring in another way. I think what you're saying is, if these claims are approved, that

there is an experiment, and that it's not the end of the world if the experiment goes bad because you can stop it.

But we don't know that. I mean, it can still be bad in the longer run, it could be good, and then we could learn some things here that are positive. And maybe, well, Laura was saying, mumbling to me at one point, that maybe these people misunderstand the risks associated to claims, but they'd be right the way it would actually work out, because they would in fact smoke less. And maybe that would be beneficial.

I am struck though, and I go back to this, I am deeply disappointed that we did not have any consumer perception research that used the kinds of ads that they want to use, the marketing, so we could actually see how the marketing would have affected consumers' perceptions.

And then I thought of one other thing. I mean, they did, partly did answer this, if we have T21 nationally, then in fact

you can get at least the 18 to 21 year olds without any complications because those are "adults." I used to own a couple of them that age, and I'm not sure I'd say they were really adults. But legally they're adults --

CHAIR MERMELSTEIN: Legal age.

DR. WARNER: They're legal age, that's right. And they are the first age that could buy tobacco products.

Now, it's still not going to tell us anything about the underage kids. And maybe we do need to see that. I just would -- I think if we do end up including that this is an okay experiment to take place, I think that we're doing it without very useful information underlying that conclusion.

CHAIR MERMELSTEIN: Mitch.

MR. ZELLER: Just one clarifying point. Were there to be an authorization here, it would not be an experiment. It would be because the agency felt that the statutory standard was met.

Having said that, Congress, in its wisdom, said for these kinds of claims they can be for a maximum of five years. And so, in any scenario where there was an authorization, number one, it would be time limited. Number two, it would come with conditions.

And if there were questions still in need of answering that didn't put us into the camp of saying no to the application, we still felt that we were in a position to say, yes but. And we need to see some real world evidence on X, Y, or Z, and that could come with an authorization.

But the threshold notion from the Center's perspective is there would be no authorization for this or any similar application if we didn't think that the statutory standard that Congress set and the law could be met on the basis of the evidence that we had in front of us and that you have all been questioning and grappling with today.

CHAIR MERMELSTEIN: Dr. Ossip first

and then Dr. Bierut.

Is Dr. Ossip on the phone?

DR. OSSIP: Yes. Thank you for that, for that clarification.

So, I think just based on everything we've heard, I would be very concerned about the three -- about having the three exposure claims presented in the way that they are presented now on the ads that we've seen. I think we need to see evidence back from the way they would actually be used as promoted to the public.

And I do think we need data on use among whom we would be very concerned if there were uptake to youth it even potentially, as it were, or potentially as a starter product. There were less concerns about sustained use, but potentially as a starter product and perhaps in ways we can't even perceive yet.

CHAIR MERMELSTEIN: Dr. Beirut?

DR. HATSUKAMI: I think there has to be some kind of information provided to consumers because why would use these cigarettes

in the first place. And so there has to be some information.

But there are some major gaps. I think one of the gaps is that we really don't know how these smokers are going to use these products when they're given minimal instruction in terms of their use. And so the studies that Dr. Donny and I have conducted were really quite different than what's going to happen on the real marketplace.

So, I do think we need a little bit more information. I'm not really quite clear that the study that 22nd Century did actually was conducted in a way that would reflect what people are going to be doing in the marketplace. So I think that's one concern.

It just sounds like the disclaimer itself is not going to be sufficient. That's what Dr. Byron has mentioned. And so I think there probably needs to be more research done in terms of what might potentially reduce their misperception of disease risk. Because I'm not

totally convinced that the disease risk in fact is reduced by the evidence that we have seen.

So my feeling is that, yes, something needs -- there needs to be some labeling, but currently there isn't any sufficient evidence to indicate that this labeling might have a public health benefit. And, in fact, there might be public health risk.

CHAIR MERMELSTEIN: Dr. Bierut.

DR. BIERUT: What I'd like to do is just kind of summarize my thoughts about where I am with this.

So, this product is approved currently. And so what do I think is the risk to youth? I, looking at the epidemiologic data of combustible cigarette use still going down, which is good, even in this very dynamic space, I'm very hopeful that it will continue to go down. And I don't think that this product will change that.

I don't think that former smokers are going to switch over to this product. It's a

combustible product and it doesn't have the nicotine in it. And I just, again, believe that the nicotine is a strong driver of the addiction process.

So now we're looking at the current smokers thinking of all these tobacco products out there, and not knowing that this product has low nicotine -- you know, why shouldn't we tell them it is a low nicotine product? I think they should know that it is a low nicotine product.

The concern we have is, you know, there's this danger that may occur by telling them that it's a low nicotine product. But I think the consumers should know it.

And one of the reasons that we think that it should move forward is because of its potential, if it is -- if there's a complete switch of reducing dependence, of encouraging more quit attempts, and then having an individual quit.

So, you know, overall, to err on the side of giving people information is good. It's

the question of how do we balance this information so that there isn't additional risk.

And I'm trying to think of, for the current smoker, what is the additional risk that that individual has. And I think of, you know, I think our risks for the former smokers and never smokers is higher, but I'm not sure I see current smokers smoking more cigarettes per day, which I think is really the risk that we're looking at.

And so that's kind of how I'm balancing this.

CHAIR MERMELSTEIN: Great. Thank you. Very helpful.

Dr. Ossip, you had one more comment?

DR. OSSIP: Yes. I agree that I think it's that we would be inappropriate not to let people know that these are reduced nicotine products. My comment before was that that's really the overwhelming message right now. And from what the best I can tell from looking at the evidence, even with all the problems, is

that there are concerns that people are misperceiving that as conveying, conferring some other health benefits that are not the case just by the fact that it's a reduced nicotine product. So it becomes communicating that in what context.

When you ask what the question, what the risk would be for current smokers, I think the risk -- and I think Dr. Warner had mentioned this -- is that they would, if they perceived this as a less harmful product using it in an equivalent way to current cigarettes, or in moving to dual use, thinking, well, maybe I'll reduce my harm a little bit, that they will move to dual use instead of quitting entirely.

I do have a question because we have seen some evidence from the studies from Dr. Hatsukami, maybe Dr. Donny's group, some other groups, that when people use these products in research that they may be more likely to quit, or some percentage of them will quit. And that seems like a potentially useful outcome. And,

in fact, a useful outcome if that happens.

What is the line between communicating a message that would get them there and making a therapeutic claim? I mean, to me when I look at this it looks like something that, given the evidence we've seen, it would make maybe more sense to make the case that this should go through a therapeutic review process and actually be able to promote it as a potential cessation tool, you need to show it's somehow better than NRT, or equivalent, or whatever will go with that review process and that it works. But within this review process what is -- where is that line between moving people towards understanding what needs to be done to maximize this chances that they can use this to quit and making an actual therapeutic claim?

Is there a sweet spot there? The current messaging certainly doesn't do that, although it's been talked about as a benefit, a potential benefit.

CHAIR MERMELSTEIN: Okay. I'm going to just see if our FDA colleagues want to comment on that question.

MR. ZELLER: Any evidence that's available from the literature or from what the company submitted that showed that there actually was some quitting, even if that wasn't a primary outcome that was intended in any particular study, is evidence that we would obviously consider in our deliberations.

I think for purposes of the committee's considerations, and certainly for the Center's, I take the point that there is another pathway available under a very different standard of safety and efficacy for a product like this. But we are dealing with this on the tobacco side of the house under the standard and the statutory provisions that we laid out for the committee at the beginning of the day.

And really most appropriate to think of this within the world of MRTP, and in this case, an exposure reduction claim. Having said

that, any evidence that there was quitting in the application or in the relevant literature is something that we would take onboard and consider as well.

DR. OSSIP: May I clarify a question -- a little bit on that?

CHAIR MERMELSTEIN: Okay.

DR. OSSIP: Okay. So within this particular review pathway, you know, we've talked about -- there's been discussion here about how we hope it would lead people to quit. I mean, why would people switch to it? Because either they're perceiving that it's less harmful or it may be a step down to quitting. I mean that's -- I'm not sure what the other rationale would be to do it.

So is there any wording that's appropriate in the claims that would be made, or the marketing, or that might affect consumer perceptions that would move them in that direction that would be allowable under this review pathway, that would put them in a

position of being able to view this as a potential step down to quitting?

MR. ZELLER: I think that for the sake of the committee's deliberations you need to look at the claims as have been submitted, the claims in the labeling and proposed in the advertising.

If the committee has additional thoughts related to quitting we will -- we're happy to hear them. But it's kind of a snapshot in time. The application is in. The claims are what the claims are. Were there to be a marketing authorization, there are other conditions and parameters, commitments that could be put around a marketing authorization.

But I understand what you're saying, Dr. Ossip. But for purposes of your deliberations think of the claims as is.

CHAIR MERMELSTEIN: Okay. First Dr. Warner and then Dr. Duffy, then Dr. Thrasher.

DR. WARNER: So, in response to that, Mitch, I knew -- I understand that, and I agree

with you that that's what we have to face here. If there is a possibility that these claims are not going to be approved, it might also be useful to 22nd Century to hear what kinds of claims the committee thinks might be approved. And I don't want to spend the whole day on that.

But as an example, if I look at the claims in front of us I think, number one, "95 percent less nicotine" unqualified by some statement that says "if you smoke only these cigarettes" is possibly wrong, especially if there's a lot of dual use. And if people interpret it as saying they're getting rid of these nicotine if they use these while they're using other cigarettes, it's inaccurate.

So, there is language that could be adapted there that I personally would find that I'd be much more comfortable with.

Number two, it says "helps reduce your nicotine consumption." Something like "can help you reduce your nicotine," and so on. I have to say after Dr. Byron's presentation, and

it's consistent with what I've observed elsewhere, the voluntary warning strikes me as much more as a legally protected disclaimer for the company.

So somebody says, well, I thought this was being sold as a much healthier product, then say, no, we told you it wasn't. Particularly with what we saw on some of those ads up there, nobody is going to pay any attention to that, no smoker is going to pay any attention to it.

I was reminded of the adds that we see for pharmaceuticals on T.V. all the time where they'll, you know, tell you what good things it does and then they'll put on some nice music and pretty people and they'll tell you your right arm's going to shrink, it's going to drive you berserk, and so on and so forth. They wouldn't be doing that if those messages were being communicated to the public. It's a CYA kind of measure.

And that's what I think this

voluntary warning is. That's not to say it's a bad thing to have. I don't think it's going to have any useful effect.

I don't feel that we've heard the appropriate kind of evidence to draw the conclusions that we need to say that these warnings -- or not, excuse me -- that these labels are appropriate. We don't know how they would be interpreted by enough important people.

Having said that, I'm very sympathetic to the notion that it wouldn't be altogether bad for people to know that these are substantially lower nicotine cigarettes, and that some people would probably interpret that in a way that might ultimately be a positive. I think without that they're not going to be able to sell these at all. I mean, there's probably no point in trying to market it.

And you have the extra irony, by the way, that they'd have to have a label on it, a mandated Surgeon General's Warning saying this cigarette contains nicotine and it's addictive.

So I don't know where you go with that but -- I mean, I'm sympathetic to the product and the concept behind it. I don't feel that the evidence presented here has answered questions that are important to me.

CHAIR MERMELSTEIN: Okay. Dr. Duffy, then Dr. Thrasher, then Dr. Evans.

DR. DUFFY: Taking off on your point, Ken, I think I agree. I feel like it would be a disservice to the public to not tell them. It would be dishonest to not let them know that this is a lower nicotine product.

I mean, what is the alternative? To put nothing? Have people not know? I mean, that doesn't make sense to me.

But -- and I know you said, you know, don't look at the ads, just look at the words. But it's very hard for us who work in this field, who know that when those ads are accompanied with the words it's a whole different message that gets relayed.

And so I don't know, you know. I'm

sympathetic as well to the industry in that I think the public should be told. But I would want to know in what context and in what way that information is given to them. And I think it's good, it should be given to them in a way that we can evaluate it, that makes sense that it's not going to do harm, for example, to you if there's some of the other, you know, concerns that were brought up today.

But I think they should know. I mean, I think it should be labeled in some way.

CHAIR MERMELSTEIN: Dr. Thrasher.

DR. THRASHER: Yeah. I mean, I think I'm sensing the tone is pretty much in alignment here across the members of the committee. I guess in terms of next steps what I would be looking for would be some kind of systematic evaluation of the best ways to communicate instructions for use, the best ways to communicate the concept of switching completely to this product will result in 95 percent less exposure to nicotine.

And then, similarly, I'd be looking, I'd be trying to understand kind of alternative ways of communicating this concept that it is equally risky to other cigarettes. The package that we evaluated today does not allow us to do that. And I would feel more comfortable making recommendations if I saw some reasonable alternative strategies in front of me and data to support them. And then from that, those strategies, pick the ones that seem most promising.

And I don't see that here at all. And, again, I think that's going to be an important component for someone like me at least to get on board with the concepts going forward.

CHAIR MERMELSTEIN: Dr. Evans.

DR. EVANS: I just have a clarification for FDA and listening to the committee's concerns about real world use data. But I just want to clarify that you would expect to see and evaluate that in post-market scenario?

DR. THRASHER: Yeah. I mean, I think that, like we mentioned before, there is, you know, an important aspect of post-market that involves surveillance and requiring companies to conduct studies to ensure that products continue to be a, you know, benefit to population or be appropriate to promote public health.

But as Mitch said earlier, I mean, we need to be able to show that the standard has been met to authorize products under this pathway to begin with. So we have to have enough compelling evidence that, you know, that standard has been met. And that includes understanding how the product may be used when it's on the market with the claims.

CHAIR MERMELSTEIN: Okay. I think we've heard a lot of what I thought would be a good roundtable. I think most people have had a chance to express their thoughts about the questions that we've been asked to discuss today.

Any other comments about them?

(No response.)

CHAIR MERMELSTEIN: I think we've heard some excellent presentations. I appreciate the work from Century 22 in putting together a very comprehensive package and a nice presentation, and being able to be responsive to our questions during the day.

And our speakers throughout the day were exceptional and really very helpful in setting the stage. So, I think just in the last few minutes, what you heard from the committee is that we're all pleased with this concept of the very low nicotine cigarettes. We'd love to see them get out and be successful. And I think there is also good sentiment that consumers should be -- oh, should know, you know, they shouldn't be -- information shouldn't be withheld, you know, from this decision. And there is some value to that.

I think the greater concern is more of not promoting or continuing to promote misperceptions that are already out there. It's

not up to one product to be able to overcome misperceptions that are already there, but not to enhance them and to further ones that may well be there. And there may be other data that would be a little bit more helpful in guiding future messages for this product and make it of greater appeal to smokers so that it might have some potential way to get them off combustibles.

So, I think you've heard a variety of opinions, but some consensus. Other thoughts from anybody?

MR. ZELLER: Well, just on behalf of the Center, I want to thank all the participants, the committee, for a robust and excellent discussion, the company for coming in with its data, making the presentation, the public speakers, the FDA presenters, Dr. Byron.

Welcome to our world, everybody. This is what we deal with. And this is a really important process to do out in the open, literally for all the world to see, not just for the people sitting around the table or in

audience in the room. This is what Congress wanted when it came to these kinds of claims for these kinds of products. And I'm just talking about tobacco products generally.

These applications need to be made public when we accept them for filing and review. And we need to take each one of these applications to this committee for just this kind of discussion.

So on behalf of the Center, we are enormously appreciative of everybody that participated and contributed to the process and to our thinking, and to the chair as well for an excellent job of presiding over these deliberations.

So, thank you, everybody.

CHAIR MERMELSTEIN: Thank you. I did not mean to shut off discussion. I thought we had come to a, you know, a stopping point here. Is that -- any last thoughts before we adjourn then?

DR. BIERUT: Happy Valentine's Day to

everyone.

(Laughter.)

CHAIR MERMELSTEIN: Very nice.

Thank you all, again. Really appreciate your continued attention here.

Thank you.

(Whereupon, the above-entitled matter went off the record at 2:35 p.m.)