UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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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January 25, 2018
8:00 a.m.

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

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M E E T I N G

(8:07 a.m.)

DR. HUANG: All right, good morning. I think we'll go ahead and get started.

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

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will

refrain from discussing the details of this meeting with the media until its conclusion.

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

Now I'll turn it over to Caryn Cohen.

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

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

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

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

The purpose of today's meeting is to discuss modified risk tobacco product applications submitted by Philip Morris Products S.A. for the IQOS system with Marlboro HeatSticks, IQOS system with Marlboro Smooth Menthol HeatSticks, and IQOS system with Marlboro Fresh Menthol HeatSticks. Accordingly, this meeting is categorized as one involving a particular matter involving specific parties.

Based on the categorization of this meeting and 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, Willie McKinney, and David Johnson are participating in this meeting as non-voting representatives. Dr. Bailey is acting on behalf of the interests of the tobacco growers. Dr. McKinney is acting on behalf of the interests of the tobacco manufacturing industry. And Dr. Johnson is acting on behalf of the interests of the small business 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. McKinney is employed by Altria Client Services. And Dr. Johnson is employed by the National Tobacco Company.

We ask that you please do not approach the head table at any time during the meeting.

And I'll remind you that there's no use of flash photography or TV cameras during the session of the meeting, and that you silence your cell phones.

Our press contact here today is Michael Felberbaum, and he is in the back of the room if you have any questions for him.

Thank you very much.

DR. HUANG: Thanks, Caryn.

And now we'll do the introduction of Committee members. And again, I'm Phil Huang. I'm the Health Authority and Medical Director with the Austin Public Health Department.

DR. GIOVINO: Hi, I'm Gary Giovino with the University of Buffalo School of Public Health and Health Professions.

DR. MERMELSTEIN: I'm Robin Mermelstein from the Institute for Health Research and Policy at the University of Illinois at Chicago.

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

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

DR. WANKE: Kay Wanke, National Institutes of Health, Office of Disease Prevention.

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

DR. McLOUGHLIN: Good morning. I'm Kris McLoughlin. I'm from SAMHSA, the Substance Abuse and Mental Health Services Administration, and I'm part of the Office of the Chief Medical Officer.

DR. JOHNSON: Good morning. I'm David Johnson. I'm with National Tobacco, and I'm representing the interests of the small tobacco manufacturers today.

DR. BAILEY: Good morning. Andy Bailey, University of Kentucky, extension tobacco specialist, and I'm here representing tobacco growers.

DR. McKINNEY: Good morning. I'm Willie McKinney, Vice President of Regulatory Sciences with Altria Client Services, and I'm representing the interests of the tobacco industry.

DR. FAGAN: Good morning. Pebbles Fagan, College of

Public Health, University of Arkansas for Medical Sciences.

DR. WEITZMAN: Good morning. I'm Michael Weitzman from NYU Medical Center and the College of Global Public Health at NYU.

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

DR. REES: Good morning. Vaughan Rees from Harvard Chan School of Public Health.

DR. BLOUNT: Hello. Ben Blount, U.S. Centers for Disease Control and Prevention.

DR. HECHT: Steve Hecht, Masonic Cancer Center, University of Minnesota.

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

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

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

DR. HUANG: Great. And again, welcome, everyone.

I do want to make a few comments regarding the schedule for this morning. We're going to start out with our Open

Public Hearing session, and each of the public speakers will have 3 minutes to make their presentations. Then, at the end of the Open Public Hearing session, we are going to have 20 minutes for PMI to respond to some of the questions from yesterday. And then we'll take a break, and then we'll come back for the Committee discussions.

So we'll go ahead and start now with the Open Public Hearing session. And so I think the speakers will be up here on the screen, if you can come on up.

MS. LOCKHART: All ready. My name is Cheryl Lockhart. I'm from Charleston, West Virginia, and I own two brick-and-mortar vape shops. I'm an ex-cigarette smoker of 25 years. I've not had a combustible cigarette in 3 years. I'm not only speaking as a shop owner, but as a mother and a grandmother.

As a citizen of West Virginia, a state with one of the highest smoking rates in the nation, I know the effects smoking has. I have conversations every day with customers who talk about how smoking impacted their health and how their life has changed since switching to electronic cigarettes. I hear how customers breathe better and have more energy. They're excited because they don't smell bad, and they don't get sick all the time.

When I explained to some of my customers that I would be speaking to you today, the response I tended to receive in some form was why are they spending time on heated tobacco products when we know that vaping works? Why aren't they listening to us? I don't want to lose access to my favorite flavor or device. When are they going to fix this?

To all of those questions, my answer is always I don't know. But what I do know is that the Committee and the FDA will take a step in the right direction by approving this application. It's time to recognize that we are living in the 21st century.

This market needs innovation and competition. There's no reason to stop a product like IQOS from coming to the market with scientifically accurate claims. Whatever decision it makes, the FDA must follow this decision with real structural reforms that ensure that technology that we know has been working in the U.S. -- vaping -- is not strangled by enormously expensive regulations that take away the ability of consumers to access flavored e-liquids and devices.

In the end, I doubt that I will carry this product in my shops. But as an American, I know that adult smokers deserve the right to access it. Let's help America quit smoking. And

if you haven't already, check out a documentary, *A Billion Lives*, at abillionlives.com.

Thank you for your time, I appreciate it.

DR. HUANG: Thank you.

Our next public speaker is Craig Jones with Privis Health.

DR. JONES: Good morning. My name is Craig Jones. I'm the Chief Medical Officer for Privis Health. It's a company that works on population health in a care management platform. Prior to that, I was the Executive Director for the Vermont Blueprint for Health for 10 years, and prior to that, the head of the Division of Allergy and Immunology at Los Angeles County USC Medical Center. In each of those jobs, I have been involved in building population health initiatives, care management initiatives, completely dedicated to improving the health of populations in areas in the inner city of Los Angeles and statewide in Vermont.

Right now, what I'd like to tell the Committee about this morning is a population health initiative that we're working on and planning with the Applicant, PMI, so that as we introduce new products to the market, we really can understand the impacts and the changes that these types of products have on population health.

So the components are very straightforward. We have a care management platform that assists primary care settings and other providers with delivering the best team-based care possible for all conditions, including tobacco cessation.

We would offer that platform to primary care centers and settings such as health centers. They would have the opportunity and our assistance at reorganizing how they deliver care, which is something that we've worked on through all my different projects. They could use the care management platform, and at the same time we'd be aggregating large population-level data, both from use of the system as well as from the medical record, the electronic medical record.

The advantages, the impacts of the program, fairly straightforward: Providers are able to organize and deliver better team-based services and work with community providers, mental health centers, a whole array of different types of providers with a shared care plan.

The back end, we're aggregating data that can be used to study the population impacts for all conditions. Not just for tobacco cessation, but it includes tobacco cessation. And one of the key aspects of this is a new clinical pathway for tobacco cessation that would include risk modification as one

of the options for people who are unable to quit.

So this project that we're working on with PMI is an important advancement and really begins to answer the call for meeting large, real-time, population-level data to understand how our different initiatives and interventions are working.

Thank you, Committee, for the opportunity.

DR. HUANG: Thank you.

Our next speaker will be Gregory Angelo with Log Cabin Republicans.

MR. ANGELO: Thank you, Mr. Chairman and esteemed members of the Committee.

Log Cabin Republicans is the nation's premier organization representing LGBT conservatives and straight conservative allies of the LGBT community. As an organization with a national constituency largely composed of LGBT individuals, a cohort proven to be more than twice as likely to smoke combustible tobacco products compared to our peers, Log Cabin Republicans implores you to consider the value of IQOS heating products as vehicles that encourage smoking cessation and step-down alternatives to traditional cigarettes.

Combustible tobacco is responsible for the deaths of 30,000 LGBT individuals each year, twice the number caused by

complications related to an HIV-positive diagnosis.

In fact, those smokers undergoing antiretroviral therapy to treat HIV are now far more likely to die from their cigarettes than from complications of the virus. It's an alarming finding, to be sure, considering the LGBT community is burdened by disproportionately high rates of both tobacco use and HIV. These risks are heightened for transgender women, as smoking while undergoing hormone therapy dramatically increases the risk of blood clots.

Strides in HIV-related healthcare have only been possible because of harm reduction approaches to the disease embraced by healthcare professionals over decades of research, prophylactics as well as recent breakthroughs in pre-exposure prophylaxis, otherwise known as prep medication. As a result, HIV diagnoses among gay and bisexual men have increased less than 1% in the last 5 years, while life expectancy has jumped to 85 years.

Unfortunately, America's approach to kicking tobacco has adopted a far less effective tactic of advising complete abstinence, a method which only about 6% of smokers -- in which only about 6% of smokers find success. It's little wonder the LGBT community is particularly resistant to antismoking

campaigns when messaging continually fails to address how the pressures of being gay and living with trauma, violence, and alienation can create and sustain a consistent relationship with tobacco and cigarettes.

It is clear the tools to address the harm done by traditional tobacco products are readily available to us today. Log Cabin Republicans encourages you to quit the habit of making perfect the enemy of the good and embrace IQOS as a positive, less harmful alternative that encourages smoking cessation. I say this as the President of Log Cabin Republicans and as a former smoker.

Thank you for your time.

DR. HUANG: Thank you.

Our next speaker is Damon Jacobs.

MR. JACOBS: Hello, everyone. Thank you so much for your time this morning. My name is Damon L. Jacobs. I'm a licensed marriage and family therapist in New York and California States, as well as having proudly served the LGBTQ community for most of the last 25 as an HIV prevention specialist, and it is with that frame that I stand here asking you and asking this Committee to proceed and allow IQOS to be considered on the market as a less harmful smoking product.

And as my colleague Gregory mentioned, there are numbers behind this. We are communities disproportionately affected by smoking. We have 30,000 related smoking deaths every year, according to the CDC. But we have also shown a proven track record, a really demonstrated track record of adapting harm reduction strategies to modifying risk and changing behavior, and there's no greater evidence that I can share with you than the CDC's own announcement in February of last year of the unprecedented drop in new HIV infections in this country. The data came out for 2014. It showed an 18% reduction in new HIV infections in the year 2014, and much of the reason for that is being the combination of harm reduction strategies, that when you put condoms together with treatment as prevention with pre-exposure prophylaxis, then you get people bought into harm reduction strategies, you get people who have choices and options, and you want to get behind that and change their behavior to bring down these epidemic numbers.

I know, I believe, I am firmly convinced that we can see the same trajectory with smoking deaths as well, that given a plethora of harm reduction options, including cessation, including medications, including vaping, and including IQOS, that we have this unprecedented opportunity before us to see

smoking numbers decline in the LGBT community and to see the mortality numbers come down the way we have seen HIV death numbers as well.

Now, I know that there are people in this room and many, many people outside this room who hold the belief that people should just quit or they should abstain or just say no. But I could tell you, from being on the other side of the therapist's chair for, again, most of the last 25 years, people do want to quit, they do want to stop, they do want to save their lives, they do want to save their lungs. But unfortunately, it is not always easy to just say no, that the grip of this addiction is often very, very powerful, and as my colleague Gregory mentioned, the effects of trauma and alienation and violence often lead people to return to the drug that they understand that works.

With IQOS there is an opportunity to help people take care of themselves, address mental health issues but not lose their lungs and their lives at the same time.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Alex Clark with the Consumer Advocates for Smoke-Free Alternatives Association.

MR. CLARK: Good morning. And thank you for the opportunity to speak with you today. My name is Alex Clark, and I'm the Executive Director of the Consumer Advocates for Smoke-Free Alternatives Association. We are a 501(c)(4) nonprofit consumer organization with a membership of more than 200,000 consumers from all walks of life.

I'm here today to express CASAA's support for PMI's MRTP application, as we agree that IQOS marketing should accurately inform consumers of the relative risks of using this heat-not-burn tobacco product. CASAA believes that consumers deserve honest and accurate risk communication about the products they use so they can make informed choices.

However, our support for PMI's application is not without concern. Specifically, we draw attention to the statement that "Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related disease." In our written comment we provide a footnote to this statement expressing our objection to the use of the term "tobacco-related disease."

To echo the recent statements made by Director Zeller and Commissioner Gottlieb, CASAA believes that we -- regarding nicotine, CASAA believes that we must update the language we

use to discuss the harms of smoking. Broadly referring to the health consequences of smoking as tobacco-related harm misinforms the public by wrongly implying that all tobacco products carry the same risks as smoking. It is imperative that we have a constructive conversation about the relative risks of nicotine delivery products and consistency in our communications about the risks of consuming different tobacco products.

To underscore this point, the other statements that PMI is seeking approval for are consistent among one another in their focus on the fact that IQOS reduces the production and exposure to harmful and potentially harmful constituents.

PMI is not seeking approval to market IQOS as an alternative to low-risk products like smokeless tobacco, vapor products, or other nicotine -- or other smoke-free nicotine products. Therefore, marketing claims should not reference an outdated and politically motivated understanding of tobacco-related harm. IQOS is a lower-risk alternative to smoking, and marketing statements should narrowly focus on this fact.

CASAA strongly recommends that PMI amend their proposed marketing language to read "smoking-related diseases" and that FDA allow this small but vital change.

We also question the wisdom of PMI's self-imposed prerequisite that a consumer must be a smoker in order to purchase IQOS. It is unclear from the application materials whether or not IQOS might provide a protective or a deterrent effect for at-risk never smokers or former smokers who might relapse.

CASAA believes that enforcing a smoker test may ignore a small, but not insignificant, group of consumers who are, for whatever reason, contemplating starting smoking and should have access to low-risk products instead of feeling that smoking is their only option.

Again, thank you for the opportunity to speak with you today, and we urge the Committee to issue a favorable recommendation to FDA regarding approval of PMI's MRTP application of the IQOS system. Thank you.

DR. HUANG: Thank you.

Our next presenter is Julie Gunlock.

(Off microphone comment.)

DR. HUANG: Oh, no. Scott Ballin. Sorry.

MR. BALLIN: Good morning. I worked in the tobacco control arena for many decades and have been particularly interested in issues pertaining to FDA regulation of tobacco.

Today we are in a new era. On July 28th of last year, Commissioner Gottlieb and Director Zeller announced some long overdue strategies for reducing the devastating disease and death caused by the deadly cigarette. It includes working to reduce the nicotine levels in cigarettes while at the same time making significantly lower-risk products available to smokers.

Our tobacco and nicotine policies have been at a crossroads for a number of years, and given the rapidly changing technological, innovative, and competitive environment, we are finally beginning to see some serious discussions about what a more modernized regulatory framework can and should look like. Consideration of products like IQOS is just a piece of this new visionary puzzle, which calls for the reassessment of how best to regulate the growing spectrum of products.

My comments are in ways, many ways, less about IQOS and more about how FDA, the public health community, researchers, manufacturers, consumers, and TPSAC can help move the ball forward.

Here are a few essential elements to consider:

1. All tobacco and nicotine products should be regulated by the FDA based on the risks, relative

risks, and intended uses.

2. Serious consideration should be given to significantly reducing the levels of nicotine in cigarettes, but only as a part of a comprehensive tobacco harm reduction strategy.

3. FDA processes for the review and approval of science-based reduced risk products should be reconfigured and streamlined, and that consideration be given to setting workable, less bureaucratic product standards.

4. Consumers and the public should be given complete, truthful, and accurate information about the risks and relative risks of the products by both the public and private sectors, and that includes the FDA.

5. Adults should have ready access to alternative, non-combustible, lower-risk products that are consumer acceptable.

6. Good science, regardless of who is conducting it, should be driving policy and regulatory decisions and efforts.

7. Greater attention should be undertaken to

encourage and support innovation and technology in both the public and private sectors. And

8. There needs to be ongoing civil engagement between all stakeholders.

My bottom-line message to TPSAC, to CTP, and all of the stakeholders in this room is that a significant opportunity exists for implementing new strategies for reducing the 480,000 deaths caused by the deadly cigarette.

FDA needs to be doing what it can to establish a more enlightened and flexible regulatory framework that can meet the needs and expectations of consumers, stimulate innovation, and advance public health goals.

I commend the leadership of Commissioner Gottlieb and Director Zeller for moving this ball forward. Let's make sure we all keep our eyes on their vision.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Julie Gunlock with Independent Women's Forum.

MS. GUNLOCK: Good morning. Thank you for allowing me to speak this morning. My name is Julie Gunlock. I'm a Senior Fellow at the Independent Women's Forum, which is a research

and educational institution in Washington that is run and staffed entirely by women. Perhaps it therefore makes sense that I'm going to focus my remarks on women and specifically the fact that women have a far more difficult time than men quitting traditional combustible cigarettes.

I'm sure you're all aware of the study that was published in the *Journal of Neuroscience* by researchers at Yale University that found that when men smoke, the number of nicotine receptors in the brain increased; but that wasn't true for women, who while smoking had the same number of nicotine receptors as nonsmokers.

The results suggest that, neurobiologically, men are more responsive to the nicotine in cigarettes, whereas women tend to be rewarded more by the cues of smoking, like the smell and taste of the smoke. And as a woman, I would add this very non-scientific observation that it might also be the appetite-suppressing qualities of the cigarette.

So why does this relate to the matter at hand? Well, as you know, currently the FDA only approves nicotine replacement therapies such as patches and gum to help people quit smoking. Clearly, this study demonstrates that women need treatment options other than nicotine replacements, such as those that

help replace other cravings, like the taste and smell and the hand-to-mouth habits associated with smoking.

Similarly, researchers at the University of Montreal found that women's menstruation cycle increases neuroactivity related to cravings which often hamper a female's attempt to quit traditional smoking -- traditional cigarettes. Obviously, you all know that men don't have menstruation cycles, so they don't deal with the monthly cravings for ice cream.

Other studies have shown women have much more severe symptoms of withdrawal than men and that women are more likely than men to begin smoking again when faced with anxiety.

In an interview with National Public Radio, a professor of psychology at Yale School of Medicine explained that women often report smoking is helpful in reducing negative mood; it helps in enhancing positive mood and managing the stress of everyday life. She said that they look to cigarettes, traditional cigarettes, to help them with those difficult situations, and as a consequence, it is often more difficult for women than men to give up cigarettes.

Clearly, the FDA and this Committee does not intend to punish women simply for their gender, but that is precisely what is going to happen if women are limited to smoking

cessation products that biologically cannot provide them with the help they need to quit traditional cigarettes.

For this reason, my organization, the Independent Women's Forum, myself, and many women, I suspect, would urge this Committee to approve new and innovative e-cigarette products like IQOS that will help women quit smoking.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Naomi Lopez Bauman with the Goldwater Institute.

MR. ZELLER: Just a statement for the record, from the Center Director and the Office Director: Men have daily cravings for ice cream.

(Laughter.)

MS. LOPEZ BAUMAN: Good morning. My name is Naomi Lopez Bauman, and I'm the Director of Healthcare Policy at the Goldwater Institute, a public policy research organization based in Phoenix, Arizona. The institute is a national leader for a constitutionally limited government and is respected by the left and right for its adherence to both principle and real-world impact.

Thank you for the opportunity to testify in favor of FDA

approval for the modified risk tobacco product application being sought by PMI for their heat-not-burn tobacco products.

According to a report by the U.S. Surgeon General, smoking causes 87% of lung cancer deaths, 32% of coronary heart disease deaths, and 79% of all cases of chronic obstructive pulmonary disease, commonly known as COPD. Also, smoking is responsible for every third cancer death and also contributes to cancer treatment failures.

Recent studies reveal that the presence of harmful or potentially harmful constituents, which number in the thousands, are significantly lower than combustible cigarettes and may have the potential to reduce the risk for smoke-related diseases.

There is also evidence supporting the benefit of switching from combustible cigarettes to heat-not-burn through the reduction in nicotine delivery.

Simply put, there are thousands of chemicals delivered to one's body through smoking. Some have been demonstrated to be harmful while others are believed to be harmful. IQOS has been shown to reduce these harmful or potentially harmful constituents by 90 to 95% compared to combustible cigarettes.

In addition to the potential impact of reducing the number

of smoking-related deaths in the U.S., which now total about 480,000 per year, another important benefit of allowing for a lower-risk alternative to combustible cigarettes will be found in taxpayer savings for public healthcare programs.

Medicaid now accounts for more than one-quarter of state budgets, when counting federal and state funding, compared to 11% in 1988. It is estimated that more than one-quarter of adult Medicaid enrollees are smokers. Smoking-related diseases among Medicaid enrollees now account for about 15% of total program spending. It is estimated that more than 60% of the nation's total healthcare expenditures that are related to smoking-related illness were paid by taxpayer resources.

As states seek to provide innovative and bold new approaches to patient wellness and taxpayer-funded programs, these types of heat-not-burn products will be important tools in states' ongoing efforts to promote patient wellness while protecting precious taxpayer resources.

For these reasons, the Goldwater Institute urges this Committee's recommendation for approval.

Thank you for your consideration.

DR. HUANG: Thank you.

Our next speaker will be Will Cohen with the Vape a Vet

Project.

MR. COHEN: Hello, and thank you for letting me speak. My name is Will Cohen. I'm a social worker, a public health researcher, and a Ph.D. candidate in epidemiology at Arizona State University School of Social Work.

About 7 years ago I started the Vape a Vet Project when I was working with the City of Phoenix, specifically in veteran services. I noticed that all of them smoked, and a common line we would give them is wait before you smoke, or if you smoke, if you're going to go into an interview. The reason for this is it can be off-putting.

Well, we had to come up with something that was better. I had quit smoking at that point using vapor products, and I started handing out my old products, things that I had used that had helped me that I was no longer using anymore. So eventually I formed Vape a Vet Project, which collected these items and gave them to veterans. Now, over the course of 7 years, we have helped approximately 80,000 veterans who were former smokers, who were no longer smokers.

All we ask here today is that if the science shows that this product is indeed safer, that it is indeed a lower-risk product, that we be allowed to communicate that information to

our clients in the correct manner. If the science shows that this product is something like 90% safer, I want to be able to communicate that information to the tens or hundreds of thousands of veterans that are contacting us every day, asking for a product that can help save their lives.

Tobacco products are endemic to the military and, in fact, the United States military is the only organization that ends up paying for tobacco twice. These products are subsidized on base, they're cheaper to buy them at the PX, and then the military pays again for the harmful effects of tobacco.

Products like the IQOS system allow us a spectrum of tools that we can use specifically with the Vape a Vet Project, but in organizations all across the country, to help and assist veterans with getting off of tobacco products. The fact that we have the availability to provide different products is only a bonus to public health and, specifically, to an unfortunately underserved population in our society.

When I'm contacted by a veteran, I want to be able to accurately and correctly relay the information about the safety, the benefits, and the risks of these products. So when the FDA determines the language that can be used in this application, please let that language reflect the actual

provable scientific risks and benefits so that we can relay that information as well.

Thank you. Have a good day.

DR. HUANG: Thank you.

Our next speaker is Jeff Stier with the National Center for Public Policy Research.

MR. STIER: Good morning. I'm Jeff Stier, and I notified the FDA I'm with the Consumer Choice Center. So thank you for making that correction.

I'm a Senior Fellow at the Consumer Choice Center. I speak on behalf of adult consumers who believe they have the right to make informed choices based on the best currently available science. That's why I applaud the FDA for embracing the continuum of risk as one of the central tenets of its new comprehensive approach to nicotine.

As Commissioner Gottlieb and Director Zeller wrote in the *New England Journal of Medicine*, the Agency needs to do more to protect Americans. In particular, we must shape a regulatory framework that reduces their use of combustible cigarettes.

One of two primary parts of the strategy includes "recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public

health." This Committee has been tasked with addressing questions that can help inform the Agency as it considers this first major test of that approach.

I was impressed with the degree of rigor and the analysis of the many studies presented in support of the application yesterday. As is always the case, each study type has limitations. You did a good job of exposing those limitations yesterday. Even with the limitations and uncertainties addressed at length, taken on a whole, the toxicological, cell culture, animal, human clinical, and behavioral studies all point in the same direction, the direction we'd expect when comparing a noncombustible tobacco product to the deadly cigarette.

I believe the Agency and, not incidentally, the public would be well served from additional curiosity and questions from a perspective regulators don't consider often enough. What are the costs of being too cautious? What if we consider the cost in human lives of each additional day consumers are prevented from choosing an obviously less harmful alternative to cigarettes?

You do your job when you ask "what if." We heard a lot of "what ifs" yesterday. But what if the FDA is right and

noncombustible tobacco products can replace cigarettes to the benefit of public health? What is the cost to public health if we wait for just one more study in an ever-elusive search for absolute certainty about the future?

What if the already impressive switching numbers we've seen in other countries so far are not a best-case scenario but are only a worst-case scenario, only the tip of the iceberg as the world looks to the vaunted U.S. FDA for trusted guidance? I can tell you, consumers and regulators throughout the world are indeed watching.

What if estimates of 90,000 fewer deaths over 20 years in the U.S. alone are far too low as they are based on a very conservative estimate in an effort to satisfy even the most skeptical regulator?

And what if a large sentiment of adult smokers -- a large segment of adult smokers want to enjoy tobacco and nicotine but don't want to take on more risk than necessary?

I conclude. What if consumers have more common sense than some give them credit for?

DR. HUANG: Thank you.

Our next speaker is Erika Bliss with Equinox Primary Care, LLC.

DR. BLISS: Hi. Thank you so much for letting me speak today. As you said, my name is Erika Bliss, and I'm a practicing family physician, and I've been in practice for about 17 years, and this application is really important to me as a practicing doc because I encounter patients, not every day but very frequently in practice, who have tried and tried and tried to quit and just can't do it.

And up until now, all I've been able to offer them is, you know, nicotine replacement or medications, some of which are poorly tolerated by people, sometimes unaffordable to them, or cognitive behavioral therapies or just urging them to quit. And, you know, for some of these folks, it's just not effective, and all I can do is keep encouraging them to keep trying.

The IQOS product and the concept of heated tobacco as an alternative to smoking combusting tobacco is -- to me, would be such a great tool to have in my toolbox. The tragedies I see on a regular basis of people's -- the disease profiles they have because of smoking, it's painful to watch, and it's painful to not be able to offer them something else that would help them.

Just in the last 4 years, I've had three patients die of

incurable lung cancer, all of whom desperately wanted to quit smoking and found it impossible to do so. I have patients with very severe COPD who couldn't quit until it was too late, and now they're at home on oxygen at the age of 50, unable to function. I have people who have caused themselves chronic kidney disease and have been put on dialysis because they couldn't quit smoking. I wish I had gotten to them years and years and years ago and had had some success.

But I understand them because I also smoked when I was young. I was one of those dumb teenagers who picked it up and thought it was cool and got addicted even though my mother smoked and I hated it, and she developed emphysema before I started smoking. So I understand how easy it is to start and how hard it is to quit. I had to work very, very hard to quit smoking. My patients are always shocked when I tell them that. But, you know, it's -- I really appreciate what they go through.

I think the research is very, very compelling, and one of the things I think we're not that great at in this country is -- as a public is understanding relative risk, and I think the FDA could do a huge public service here by helping us all understand that you have to consider relative risk and harm

reduction. It's not always black and white; there's not always a perfect solution.

I rarely find the perfect solution for my patients for anything. It's always a matter of balancing risks and benefits, and this would be yet another tool in my toolbox to help them understand how to manage those risks and benefits when they're not able to quit smoking entirely.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Robert McClure with the James Madison Institute.

DR. McCLURE: Good morning, members of the Committee. Thank you for this opportunity to be here. My name is Dr. Robert McClure, and I serve as the President and CEO of the James Madison Institute in Tallahassee, Florida.

For those of you unfamiliar, JMI is Florida's oldest and largest policy think tank, and our mission is to advance the principles of limited government, free markets, and economic prosperity in the Sunshine State and here in Washington, D.C. We've been educating policymakers and our regulatory bodies, along with the public, for more than 30 years.

Through JMI's Center for Economic Prosperity, we have been

steadfast in our belief that whenever possible and practical, 20th century regulatory systems must adapt to 21st century technology and not the other way around. We've seen technology overtake regulation time after time in the entertainment industry, in the healthcare arena, and in transportation, and in almost every case the advances of technology have forced regulators to catch up. The tobacco industry is not unique in this respect.

This regulatory issue before you is both important on its own as well as in a broader context of how the Food and Drug Administration seeks to impose regulations on the states, that affect millions of consumers and taxpayers in states like Florida.

Public health issues regarding smoking have been widely documented over decades. It is in the national interest of public health to provide consumers with less harmful alternatives to traditional cigarettes and truthful information about those alternatives so that we can make -- so that they can make informed decisions about the products they may use.

Research is clear that reductions in the smoking population have both individual and societal benefits. A healthier population is less likely to consume healthcare for

chronic conditions like emphysema and asthma as well as more deathly illnesses such as heart disease and lung cancer. Lowering demand for healthcare services will help to create a better trajectory for overall healthcare costs.

Currently, more than 40 million Americans continue to smoke despite the evidence of its impact. Innovation and technology are filling the gaps that have been desperately needed for years.

Specific to this, numerous numbers of technology have been developed showing promise in other countries using patented heat-not-burn technology. Based on the use of these products by a diverse global consumer base and available science before the FDA and available to the public, we believe it is an important threshold of evidence necessary for Agency approval.

In my home state of Florida, data indicates that about 15% of our population smokes traditional tobacco products, roughly three million Floridians. Reducing that number by just 10% through newer, safer, and innovative products means 300,000 Floridians are reducing their risk of heart disease, cancer, and years of costly medical treatments.

It is within this context that the James Madison Institute encourages granting of the modified risk marketing order.

Thank you.

DR. HUANG: Thank you.

(Off microphone comment.)

DR. HUANG: That's it. All right, got it. Where are we?

MR. MANUPPELLO: Good morning. Thank you for the opportunity to --

DR. HUANG: Hold on. Let's see, is this right?

MR. MANUPPELLO: Oh, do you want me to --

DR. HUANG: Please.

(Off microphone comment.)

DR. HUANG: That's right. Okay, Joseph Manuppello, People for the Ethical Treatment of Animals. Right person?

MR. MANUPPELLO: Okay, good morning.

DR. HUANG: Okay.

MR. MANUPPELLO: And thank you for the opportunity to present these comments.

PETA's interest in tobacco product marketing applications is simply that no more animals be made to suffer and die in order to bring new tobacco products to market.

In its application, Philip Morris reports results of three animal experiments: two 90-day inhalation toxicity tests and one systems biology study. These experiments used more than

400 animals. The inhalation tests employed nose-only exposure. Rats were immobilized in glass tubes only slightly wider than their bodies, connected to an inhalation chamber and exposed to cigarette smoke or IQOS aerosol for 6 hours each day for as long as 137 days, about one-fifth of their natural life span. These tests are for IQOS products only. An even greater number of animals was used in tests of earlier versions of these products.

For a 2011 FDA workshop on the scientific evaluation of MRTP applications, Altria Client Services submitted an extensive assessment of one of these earlier versions, an electrically heated cigarette smoking system which was completed by Philip Morris USA in 2006. These experiments used approximately 1,100 animals, including 650 mice for a skin-painting experiment. And there's no reason to think that this is even close to a full tally of the animals used to develop IQOS.

On a more positive note, Philip Morris also reports the results of three in vitro toxicity tests and five in vitro systems biology studies. Philip Morris researchers have pioneered 21st century toxicological methods, including the use of reconstituted human bronchial epithelium exposed to whole

smoke at the air-liquid interface to measure patients and biological pathways.

More recently, these researchers have developed a framework for the in vitro systems toxicology assessment of e-liquids.

We are grateful for these widely applicable achievements, and we sincerely hope that Philip Morris will continue to support and expand these efforts.

We ask TPSAC to advise that no more animals be used to test the IQOS system and its components. There's no scientific justification for conducting additional animal tests.

In its report, *Scientific Standards for Studies on Modified Risk Tobacco products,* the Institute of Medicine correctly observed that preclinical assays are fundamentally incapable of demonstrating that new tobacco products are less risky than existing ones. Instead, the role of preclinical assays is to identify especially risky products that should not be tested in humans, as well as products that have a reasonable potential for use risks.

Philip Morris has already demonstrated this. It reports the results of eight clinical studies with smokers. The results of these studies show that exposure to IQOS aerosol

produced significantly less toxicity than exposure to cigarette smoke and did not introduce new risks.

Thank you.

DR. HUANG: Thank you.

I do want to point out that after this speaker, we will go back to Speaker Number 6. So now we'll hear from David Williams, Taxpayers Protection Alliance.

MR. WILLIAMS: Thank you, and good morning. On behalf of Taxpayers Protection Alliance and our members and supporters across the country, I would like to make the following statement to TPSAC in support of approving the modified risk tobacco product applications. This was submitted by Philip Morris's IQOS.

Now, we submitted a longer statement, and I won't read the longer statement. I'll keep this to 3 minutes, or 2 minutes and 48 seconds now.

This morning I want to mention a few items. Let me first state that I will be mentioning IQOS quite a bit, but this is far beyond IQOS. This is about what the FDA can do with innovation and embracing innovation for taxpayers and consumers.

TPA appreciates the FDA's efforts to reexamine processing

times in accordance with the 2009 Family Health and Smoking Prevention Act. Bringing safer tobacco products to the market expediently will undoubtedly offer significant health benefits for consumers.

The Tobacco Act's intention was not to prevent but protect users and the public from the risk of using tobacco. In line with those goals, we believe that PMI diligently incorporates those principles of consumer safety throughout the IQOS decision process.

Time frames will discourage future ambitions of creating safer tobacco products while ultimately depriving users of the ability to take advantage of a lower-risk alternative.

Congress clearly intended for the FDA to develop rules and processes designed to bring reduced risk tobacco products to market in order to diminish the harm to public health caused by conventional cigarettes. FDA should provide a path for ultimately allowing manufacturers to disclose or claim this reduced risk to consumers if it is shown to be a scientifically sound claim.

Other countries have welcomed IQOS to their markets. In a couple of weeks, the Winter Olympics start in South Korea. Americans will travel to South Korea, and they will see South

Koreans using IQOS. There's no reason why consumers in this country shouldn't have that same option. Every adult smoker in America has the right to know that IQOS is not just interesting technology but could be the innovation they have long sought as a way to live a healthier lifestyle.

Now, let me just wrap up by saying that obviously this is a very professional issue that we're talking about with Taxpayers Protection Alliance. It's also personal. When I was a kid, my father smoked three and a half packs of cigarettes a day. Think about that, three and a half packs a day. That's 70 cigarettes a day he smoked. Obviously, he is no longer with us. And it's a shame because his team is in the Super Bowl next week.

I only wish that these products would've been available 40 years ago. And the FDA and TPSAC has the opportunity to make these products available to today's generations and future generations.

Thank you.

DR. HUANG: Thank you.

The next speaker is Gregory Conley, American Vaping Association.

MR. CONLEY: Good morning, and thank you for allowing me

to testify a little late. My name is Gregory Conley, and I currently serve as the President of a nonprofit called the American Vaping Association. I am here this morning to encourage the Committee to recommend approval of Philip Morris's MRTP application for IQOS with all claims sought by the Applicant, including reduced risk exposure as well as reduced disease risk.

For 7½ years I have been an advocate for tobacco harm reduction, with most of my activity dealing with the new technology of vaping, which helped me quit smoking and has helped millions of smokers around the world quit.

But unfortunately, over that same time, I've also seen the relative risk perceptions of vaping among both smokers and nonsmokers plummet, thanks to campaigns against these products, thanks to uncertainty being pushed by campaigners against these products.

Despite this, it is still the number one quit smoking tool in America, and if public health had chosen to embrace these products rather than push them out, that number would be better today.

But I am not so naive to believe that vaping or snus is the solution for all smokers. Smokers need choices. Some

smokers will try snus, and it won't replicate the feeling that they get from a cigarette. The same problem can be had with vaping; they miss the taste of tobacco. IQOS can solve this.

But watching the Committee yesterday, I had the same and similar feelings as I did watching the prior TPSAC Committee assessing General Snus' MRTP. There seems to be a reaching, a looking for any particular reason to disapprove, to recommend disapproval of this application. I would encourage you to please do not think of this through the lens of what can we do to stop this product from coming to America, as it has in 30-plus countries, but think about the lives that could be saved.

My hope is that the court system eventually recognizes the absurdity of this. There is a truth tax in America on telling the truth about tobacco products, and unfortunately, the number one selling cigarette company in the world, the one with the most money and the most resources, they will be likely, possibly the first to get this approval. Meanwhile, innovators and small businesses, medium-sized businesses, they don't stand a chance.

So it shouldn't be this hard to tell the truth. Please recommend approval of this application so we can get past this,

so we can start saving lives with IQOS, but also so we can start making changes to this Agency so that it's not just the Philip Morrises of the world that are able to tell the truth.

Than you.

DR. HUANG: Thank you.

The next speaker is Bill Godshall, Smokefree Pennsylvania.

MR. GODSHALL: I'm Bill Godshall, Founder and Executive Director of Smokefree Pennsylvania, which has campaigned to reduce cigarette smoking since 1990 by reducing secondhand smoke exposures, reducing cigarette marketing to youth, holding cigarette companies accountable, and increasing cigarette taxes.

Since 2004 we've also informed the public that cigarettes cause more than 99% of all tobacco-attributable morbidity, disability, mortality, and healthcare costs, and that smoke-free alternatives are below 2 on the continuum of risk in which cigarettes are 100 and NRT products are 1.

We've also advocated keeping all low-risk, smoke-free alternatives legal to manufacture, market, and use, which is why we opposed the tobacco-controlled Marlboro Monopoly Act that was negotiated and agreed to in 2004 by Philip Morris, Robert Wood Johnson Foundation-financed Matt Myers, and then

GlaxoSmithKline lobbyist Mitch Zeller, which banned sales of all new smokeless tobacco products more than a decade ago.

We also opposed Josh Sharfstein's unlawful cigarette-protecting 2009 FDA e-cigarette import ban, and Mitch Zeller's 2016 cigarette-protecting deeming rule that banned sales of all new vapor products 18 months ago, banned truthful health claims for vapor products, and bans all vapor products in the near future unless the deeming reg is significantly changed.

For disclosure, neither I nor Smokefree Pennsylvania have ever received any funding from the U.S. Department of Health and Human Services or from any tobacco, drug, or vapor company, so we have no financial conflicts of interest.

Recent studies indicate that Marlboro HeatSticks and IQOS are about 90% less harmful than cigarettes, but far more extensive scientific and empirical evidence has consistently found snus, moist snuff, dissolvables, and vapor products are about 99% less harmful than cigarettes.

So why is FDA considering approving MRTPs for Philip Morris Marlboro products that appear 90% less hazardous than cigarettes after FDA recently banned the sale of vapor products that appeared 99% less harmful than cigarettes? And yet, they've already helped millions of Americans quit smoking,

which FDA and CDC refuse to acknowledge, and have helped cut youth smoking in half since 2010.

And why has FDA refused to accept 367 PMTAs but is considering PMTAs for Marlboro HeatSticks? A key reason is because Philip Morris and Altria spent hundreds of millions of dollars lobbying to enact the 2009 tobacco-controlled Marlboro Monopoly Act and imposed FDA's 2016 deeming rule because both policies protect Marlboro cigarette monopoly and Marlboro HeatSticks from market competition by thousands of small smokeless tobacco and vapor companies that can't afford 100 million dollars to submit PMTA and MRTP applications.

If FDA approves MRTPs and PMTAs for Marlboro HeatSticks, Philip Morris and Altria will spend hundreds of millions of dollars more to protect their Marlboro HeatStick monopoly by lobbying to keep vapor products banned, including the Cole-Bishop bill they're pushing in Congress right now.

DR. HUANG: All right.

MR. GODSHALL: Before creating another multibillion Marlboro monopoly, the FDA should rescind its disastrous deeming rule that bans millions of lifesaving vapor products and begin to truthfully inform the public that all smoke-free tobacco nicotine alternatives are far less --

DR. HUANG: Okay.

MR. GODSHALL: -- hazardous than cigarettes.

DR. HUANG: Thank you.

MR. GODSHALL: Thank you.

DR. HUANG: Our next speaker is Carrie Wade with R Street Institute.

MS. WADE: Hello. I'd like to thank the FDA and the CTP and TPSAC Committee for inviting us to give statements on the present IQOS MRTP application.

I think PMI did a great job yesterday demonstrating the reduced risk of IQOS compared to combustible cigarettes, and I think the TPSAC Committee did a great job considering the unanswered questions that remained.

My name is Carrie Wade, and I'm the Director of Harm Reduction Policy at the R Street Institute here in Washington.

For now, our two main interest areas are opioid and tobacco harm reduction. Considering the staggering number of tobacco-related illnesses that occur each year, I think that tobacco harm reduction has potential to have the most impact on health and welfare of our populace. I think this because despite 30 years of public health campaigns targeting smoking and attempting to decrease the smoking rate in this country,

smoking continues to kill 480,000 people per year. Clearly, an abstinence-only approach to smoking isn't working, and a harm reduction approach could have better benefits.

Unfortunately, in 2013, 50% of U.S. adults believed that e-cigarettes are as harmful as combustible cigarettes, and in 2015 this number was 74%, meaning 74% of people thought that e-cigarettes were as harmful as combustible cigarettes. Nobody would ever switch if they really thought this, so we'll never see the benefits of these reduced risk products if people don't know that they are safer.

But we know that labels work. Studies consistently show that warning labels affect smoking behavior change and quit attempts, and that specific warning labels detailing toxins further reinforce the health risks that are associated with smoking. We know that health warning labels are a major source of information and reduce the disparities of access to this information. This is why I think it's so important that reduced risk labels are able to clearly state the lower risk compared to combustible cigarettes. MRTP labels indicating the risk reduction probably have the greatest impact to assure people that they're using a safer product.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Mario Lopez with the Hispanic Leadership Fund.

MR. LOPEZ: Good morning. My name is Mario Lopez. I'm President of the Hispanic Leadership Fund, a nonpartisan advocacy organization dedicated to promoting public policy that strengthens liberty, opportunity, and prosperity for all Americans.

On behalf of our members across the country, I'm here today to support authorizing the modified risk tobacco product applications published on June 15th, 2017.

As the previous speaker reminded us, 480,000 people die every year in the United States due to smoking and smoking-related illnesses, cost over $300 billion yearly, including medical expenses and lost economic productivity, all according to the CDC. But despite massive public campaigns and other large-scale and costly efforts in recent years, millions of Americans will continue to smoke.

In this context, we would like to thank Mr. Zeller for some of his recent comments highlighting that alternative methods of delivering nicotine "could be incredibly helpful to curtail cigarette smoking." After all, he noted, it's not

nicotine that causes disease and death. Shouldn't we be thinking about various forms of nicotine delivery?

We agree with Director Zeller's assessment as well as the FDA's own comment in the tobacco deeming regulation in the *Federal Register* on May 10th, 2016, stating that "FDA believes that the inhalation of nicotine without the products of combustion is of less risk to the user than the inhalation of nicotine delivered by smoke from combusted tobacco products."

Also, just last month, the United Kingdom's Food Standard Agency's Committee on Toxicity issued an important statement on noncombustible products, concluding that they "are likely to be less risky than smoking conventional cigarettes."

The FDA recognizes that harmful or potentially harmful constituents are the likely causes of smoking-related diseases. Indeed, the tobacco combustion that takes place during cigarette smoking, where temperatures can reach 1,600 degrees Fahrenheit or higher, breaks down tobacco into harmful chemicals. Heating tobacco without combustion, however, produces an aerosol that contains lower levels of toxicants compared to cigarette smoke, as the aerosol is not the result of the chemical reactions that result from combustion.

The MRTP application in question features a patented

system that eliminates 95% of toxic chemicals that are present in cigarettes, as well as about 70 cancer-causing chemicals present in tobacco smoke.

The public health benefits are simply too great to ignore. The FDA has an opportunity to recognize the realities and science involved in comparing methods of tobacco consumption and allow consumers to use products that will substantially lower the negative effects to their health.

The Hispanic Leadership Fund respectfully urges TPSAC to recognize the merits of approving the modified risk tobacco product applications in question.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Julian Morris with the Reason Foundation.

MR. MORRIS: Thank you for permitting me to speak to you today on a subject of great importance to the millions of Americans who currently face disease and the likelihood of an early death as a result of smoking cigarettes.

I'm Vice President of Research at Reason Foundation, an independent research organization that has published extensively on the risks posed by combustible cigarettes and

the importance of permitting access to less harmful alternatives.

Make no mistake, smoking causes disease and death. Over 30 million Americans currently smoke. Of those who continue to smoke long term, about half will die from smoking-related diseases. The majority of smokers in America have tried to quit. Unfortunately, most attempts fail.

For smokers unwilling or unable to quit through other methods, one option may be to switch to a substitute that replicates much of the experience of smoking but releases far fewer toxicants. That is where the new class of heat-not-burn tobacco products comes in.

PMI's IQOS heats tobacco without combustion, producing a tobacco-flavored vapor containing nicotine but no smoke. The effectiveness of IQOS in delivering nicotine while reducing exposure to the harmful constituents of smoke has been confirmed through experiments and clinical trials by PMI and by independent researchers such as Dr. Konstantinos Farsalinos. The UK government Committee on Toxicity recently investigated two heat-not-burn products, PMI's IQOS and BAT's glo, and came to similar conclusions.

Nearly 4 million adults in 30 countries have switched from

cigarettes to IQOS. In Japan, the only country where IQOS is sold nationwide, IQOS accounts for nearly 10% of the tobacco market after little more than a year on the market, and cigarette consumption has fallen dramatically.

IQOS evidently appeals to current smokers in other countries. Surveys also suggest that this is true for U.S. smokers. So, by contrast, surveys suggest that IQOS would not significantly appeal to never smokers in the U.S. This suggests that there are large net gains to public health in the U.S. from allowing IQOS onto the market.

Smokers not only want less harmful products like IQOS, they also want reliable information about the relative risks. Healthcare providers also support such an approach. This is the purpose of an MRTP.

It is important to avoid misleading consumers into thinking that alternative products are without any risks at all. However, available scientific evidence suggests that IQOS use is significantly less risky than smoking combustible cigarettes. Restricting adult smoker access to this important information poses a greater risk than allowing it.

There are also safeguards that limit the risk that an MRTP might lead to misinformation. It's time limited, and it may be

withdrawn in light of new evidence.

In evaluating this MRTP application, we encourage TPSAC to adopt the test that has been successful for centuries in civil cases, i.e., the preponderance of evidence, and permit valuable information to be shared with inveterate smokers who are currently at risk of premature death and disease.

As such, we encourage you to recommend approval of the MRTP in this instance and, where questions exist, to work with the Applicant reasonably to resolve those questions.

Thank you very much.

DR. HUANG: Thank you.

Our next speaker is Gregory Connolly with Northeastern University School of Law and Bouve School of Health Sciences.

DR. CONNOLLY: Thank you very much for coming here. It's an enlightening experience, I have to say.

Okay. We've been studying tobacco products for about 15 years with an NCI grant and more recently focused on abuse liability of novel tobacco products such as IQOS. And I think the question before this panel -- and I would say take this question seriously. In 1970 the drug oxycodone was approved by FDA, perhaps with sufficient, perhaps with insufficient information, and today we're suffering from the unintended

consequences of that approval.

I think we have to ask ourself the question, is this a reduced nicotine delivery device or is it a device that's taking a psychoactive substance and using high technologies, like my iPhone here, which we're now reporting behavioral dependence among children who become conditioned by the iPhone, and placing that psychoactive substance in a manner which the manufacturer, through high technologies, informatics, can control the very modulators that affect abuse liability through greatly reinforcing the patent of nicotine delivery and where the user becomes a passive user? I can think of no other agency than FDA, with the exception of Abilify, which was approved with a very simple sensor a few weeks ago or a few months ago by CDER, that is allowing this to occur.

Now, if you say it's okay to take high technology and allow a manufacturer to control the delivery of a drug and not the user, you are making a precedent for FDA that has significant impact on this Agency and the health of Americans.

What affects abuse liability? The patent of delivery, the unit dose, a brief high exposure, speed of delivery, puff intervals with no nicotine, and then scheduled reinforcement. That's exactly what IQOS does with its device.

Could I advance? Could someone advance that slide?

Here's a look at it. Now I'd ask people in the room, can you, after yesterday -- raise your hand if you can't -- can you tell me what the two circuit boards with the 34 or 35-plus chips do? Have you reviewed the patents? Has Philip Morris submitted the identification of the chips, what their function is?

Next slide, please.

Can anyone tell me, in the room, after yesterday, except Philip Morris, what this device does, where the tobacco weighs about 0.01% of the total device?

DR. HUANG: I'm sorry, we do have to --

DR. CONNOLLY: And I'm going to complete by saying I think that this device is tied to what has been published by FDA in the *New England Journal of Medicine*.

DR. HUANG: Okay, thanks.

DR. CONNOLLY: That is Philip Morris should agree to a standard --

DR. HUANG: We need do need to wrap up your testimony.

DR. CONNOLLY: -- to lower the nicotine addiction in Marlboro and then let this product go.

DR. HUANG: Thank you.

DR. CONNOLLY: And I would ask Philip Morris today to raise your hand --

DR. HUANG: Okay.

DR. CONNOLLY: -- and say we collectively agree to lower the addictiveness of Marlboro Lights in the next 10 years.

Thank you very much, speakers.

DR. HUANG: Thank you.

DR. CONNOLLY: And I am glad to be in the room today.

DR. HUANG: Thank you.

MR. BLAIR: Good morning. To my knowledge, I'm the only Paul Blair testifying here today.

(Laughter.)

MR. BLAIR: And in that capacity, I am the Strategic Initiatives Director at Americans for Tax Reform, which is a taxpayer advocacy organization based in Washington, D.C., and founded in 1985.

By way of background, for the last 5 years I have handled ATR's portfolio of work on tobacco harm reduction at all levels of government in the United States.

Today I'm here to express our support for granting the MRTP applications sought for IQOS products. We support granting the applications for three reasons.

First, both the available science and common sense indicate approval is appropriate. Lighting tobacco on fire produces harmful chemicals that have negative consequences when inhaled. The evidence suggests that the IQOS product reduces the harmful and potentially harmful constituents by 90% and carcinogens by 95% when compared to combustible cigarettes. It also shows that young adults who have not smoked cigarettes have little to no interest in using IQOS, while current smokers have considerable interest in the products.

Second, innovation will save more lives than excise taxes or regulatory prohibition, not only to 4 million adults around the world who already use IQOS, but countless more have sought out other reduced risk products in their attempt to quit smoking. Though excise taxes on tobacco are extremely lucrative business for government, they aren't particularly effective at getting smokers to quit. New lower-risk products will prove to be a significant tool for harm reduction and the reduction in smoking rates across the U.S.

The simple and accurate messages PMI seeks to deliver to consumers will be an extremely powerful tool in the fight to reduce smoking rates, far more powerful than inaction, additional taxes, or annoying regulatory schemes.

Third, hundreds of billions of tax dollars annually can be saved as a result of products like IQOS. More than 100 billion dollars a year in public spending is the result of cigarette use on programs such as Medicaid, Medicare, and Veterans Affairs health programs.

Low-income individuals are more likely to smoke in the U.S., meaning that products like IQOS, when truthfully marketed to smokers, may not only benefit the country's most vulnerable populations but may save American taxpayers significant sums of public expenditures on healthcare programs as a result of improved health if smokers can make the switch. This would free up invaluable resources for other public health programs, education, infrastructure. The list goes on and on.

In conclusion, it was clearly the intent of Congress to pave a pathway forward with the approval and truthful marketing of new reduced risk products.

The science suggests that this product is less harmful and will benefit American consumers who will be empowered to make informed decisions about the products that they do or do not use. American consumers are not dumb. Equipped with accurate information and an abundance of choices, many will make the switch away from cigarettes.

It is for these reasons that we at Americans for Tax Reform strongly urge the Committee to give a positive recommendation to the FDA for the MRTP applications sought by PMI for IQOS.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Lauren Lempert with the University of California, San Francisco.

MS. LEMPERT: Good morning. I'd like to highlight some of the key scientific findings that we've detailed in UCSF's written comments, which I hope you'll read.

First -- whoops, here we go. Okay. So, first, we show that the applications fail to demonstrate that IQOS, as actually used by consumers, significantly reduces harm to individuals.

As a preliminary matter, the applications only compare IQOS to conventional cigarettes, and we question whether a more appropriate comparator product should be e-cigarettes, which are actually more similar to IQOS and possibly less harmful.

But even compared to conventional cigarettes, PMI's own data supports a conclusion that IQOS is no different from conventional cigarettes in terms of their effects on 23 of 24

biomarkers of potential harm.

Also, we show the applications fail to evaluate many other possible health effects from IQOS, including harms to endothelial function as measured by FMD, immunosuppressive effects, pulmonary and liver toxicities.

Importantly, we also point out that they failed to report on potential harms from the full range of all 93 harmful and potentially harmful constituents and other potential toxins that may not be found in conventional cigarettes.

Next, we also show the applications failed to show that IQOS, as actually used by consumers, will benefit the population as a whole, considering both users and nonusers of tobacco products. A fundamental omission is that they failed to consider the appeal to or the effect on youth, adolescents, and other nonusers. But, in fact, our recent experience with e-cigarettes shows that young people are more likely to use novel products like IQOS concurrently with conventional cigarettes.

Also, we show they failed to demonstrate that the proposed labels and warnings will not mislead consumers, especially youth, or that they understand the need to switch completely to get the purported benefits. In particular, the modified

exposure claims are likely to be misunderstood as modified risk claims.

In addition to these substantive problems, we found the process unfair because the public did not have time to fully consider all the studies and amendments that were only recently posted. For this reason, we think TPSAC should not take final action until they and the public have had time to adequately consider the full and complete application.

Finally, all the problems we've addressed concerning the MRTP applications apply as well to the premarket applications for IQOS. Permitting IQOS to be marketed with or without modified risk claims is simply not appropriate for the protection of public health as required for both PMTAs and MRTP applications.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Patrick Hedger with FreedomWorks Foundation.

MR. HEDGER: On behalf of millions of FreedomWorks activists nationwide, I offer these remarks in support of Philip Morris's modified risk tobacco product application for IQOS because of the unique opportunity it presents for FDA to

exercise regulatory responsibility. This is key to ensuring regulated industry's continued investment and innovation leading to not only safer tobacco products but better food, drugs, and cosmetics as well.

There are three pillars to responsible regulation: congressional intent, clarity and consistency, and rejecting the nirvana fallacy.

First, all regulation is a delegation of congressional authority. Thus, regulators must adhere to the intent of the law. The law is the Family Smoking Prevention and Tobacco Control Act of 2009, and it explicitly states the goal of Congress, and therefore FDA, is to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products.

In the near decade since, 0 of the 35 products submitted to the MRTP process have been approved. How could this possibly meet the definition of effective oversight as Congress intended? Can I call myself an effective parent because my children don't cause any trouble simply because I don't have any?

With this in mind, this Committee must consider how its recommendations will impact FDA's compliance with the very laws

which empower the Agency. What's clear is Congress did not task FDA with directing insurmountable hurdles to MRTP approval. As much as some may wish this were the case, it is not, and it is not anyone's prerogative to circumvent the law in order to create a de facto ban.

Next, approval of this application would ensure FDA is being clear and consistent. Last July, Commissioner Gottlieb said we must recognize the potential for innovation to lead to less harmful products. We applaud this approach. But actions speak louder than words. This Committee must understand that denial of yet another MRTP application in the new light of this promise would undoubtedly chill investment in new and better products.

Finally, responsible regulation means rejecting the nirvana fallacy. This fallacy occurs when impossible perfect outcomes are weighed against a possible good one. This "just quit" approach isn't working. In 2011 the CDC reported that only 6% of smokers successfully quit while over 30% expressed no interest in trying to quit. Philip Morris has presented extensive data demonstrating IQOS to all but eliminate byproducts versus a regular -- harmful byproducts versus a regular cigarette, and IQOS has been approved by public health

regulators in such advanced nations as Canada, Germany, Japan, and the United Kingdom. It may not be a perfect solution, but this Committee cannot weigh a post-IQOS approval scenario against a fictitious world free of tobacco use.

FreedomWorks is cognizant and concerned about the public health impact of smoking. We also strongly believe in the ability for adults to make choices for themselves, so long as they do not harm others. We believe the approval of Philip Morris's IQOS MRTP application is the only outcome consistent with these positions. If FDA is serious about utilizing industry investment and safer nicotine products and its public health strategy, as it should, considering the expressed intent of Congress --

DR. HUANG: All right.

MR. HEDGER: -- MRTP approval must be more than a mirage.

DR. HUANG: Thank you very much.

Our next speaker is Jeff Fortenbacher with Access Health, Incorporated.

MR. FORTENBACHER: Thank you very much for allowing me to present today.

I'm going to take it from a level that's way up here to one that's kind of down at the grass roots. I actually come

from -- I'm not with a very big organization. Access Health is a program that's been operating for about 17 to 18 years here that truly offers lower-income -- community health coverage to lower-income workers in our community, and as we've done that, we've had a very unique approach. One is we started off very much with a population health management approach and really where everybody actually has a health coach and everybody is, again, encouraged and given the support and tools necessary to what I call reach their optimal health.

Over the years, what we've found with our population -- again, we're Midwest, again, a very industrial area that we come from. Smoking is very prevalent, and our population being lower income, 60% typically, when they come in, smoke. We have, again, a very active program which requires everybody to go through smoking cessation. We want them to get educated about what's happening within them and what their choices and options are.

Over the years, we've typically been able to get about a 30% cessation rate with that, but we still have 70% of the individuals that smoke. We truly understand that we need to meet the individuals where they're at and then, from there, support them in moving toward better or more optimal health.

We're still leaving 70% of our people still smoking. Some reduce, but again, some basically still continue to do it.

So over the years, again, we do it consistently, but we need more tools, understanding that we're failing with about 70% of our population. Yes, we're working on other areas with them. Again, this product and products like these are key and essential for us to keep these members engaged. We again looked at empowerment and these individuals, and every encounter that we have with an individual needs to be empowering.

This population, again, as it relates to trying to quit and not being able to quit, feel very disempowered. This would be a perfect tool, in a sense, in our box to be able to continue to engage them and move them in a more appropriate direction.

Thank you.

DR. HUANG: Thank you.

Our next speaker Daren Bakst with the Institute for Economic Freedom, the Heritage Foundation.

MR. BAKST: Thank you very much. My name is Daren Bakst, and I'm a Research Fellow at the Heritage Foundation. The views I express today are my own and don't necessarily

represent the official position of the Heritage Foundation. And I do appreciate the opportunity to speak today.

From the outset, I would stress that the best available science should certainly inform the scientific decisions made by this Committee. However, this also means that emotion, dislike for tobacco companies, the precautionary principle, and other unrelated issues should not inform or influence any scientific decision or, for that matter, any decision before this Committee.

While some people might question what it will mean for TPSAC to grant the applications, I think the more important question is what would happen if TPSAC doesn't grant the applications or otherwise provides unfavorable recommendations to the FDA regarding these critical alternatives to smoking.

Unfavorable recommendations could undermine the Agency's regulatory plan to address the harm from tobacco. The FDA apparently has embraced tobacco harm reduction as evidenced by its regulatory plan on tobacco-related disease and death.

Most importantly, unfavorable recommendations could have a significant negative impact on existing smokers. For the many smokers who want to quit using cigarettes, there's now genuine hope that this goal can be achieved because of the many

innovative products being developed by private companies. This includes the heat-not-burn products that are the subject of the modified risk tobacco product applications at issue today.

These products more closely mimic the act of smoking, thus providing a very appealing alternative to cigarette smokers who may find that other products such as e-cigarettes just don't work for them. Increasing choices for consumers means having a greater chance of identifying those products that will appeal to an even greater number of cigarette smokers who want to stop smoking.

The IQOS products have already had an impressive record of getting cigarette smokers to switch to this less harmful alternative.

There are certainly potential concerns, such as the use of these products by children. However, these products can and should be made available to smokers whilst still addressing any legitimate concerns, if any, which might exist regarding use by children.

Further, the companies offering important alternatives should be able to inform the consumers of the many benefits of these products and, for that matter, the risks that these products could provide. But not being allowed to provide this

information, that's actually itself misleading to consumers. To not take this approach, for a lack of a better phrase, it would be throwing the baby out with the bathwater.

Yet, the Agency should be commended for embracing tobacco harm reduction and recognizing that cigarette smokers should not be faced with an all-or-nothing proposition -- smoke cigarettes or stop smoking -- without the use of viable alternatives to make cessation feasible.

DR. HUANG: Thank you.

MR. BAKST: This Committee should knock down the barriers --

DR. HUANG: Thank you.

MR. BAKST: -- and not create unwarranted obstacles. Thank you.

DR. HUANG: All right, thank you.

Our next speaker is David -- sorry, Graham Boyd, the Tobacco Growers Association of North Carolina.

MR. BOYD: Thank you very much for the opportunity to present today. I'm the Executive Director for the Tobacco Growers Association of North Carolina, and ours is an organization that represents more than 2,000 farmers who are directly engaged in the business and livelihood of growing

tobacco.

Per the 2009 Family Smoking Prevention Act, it was explicit that FDA has no authority over the farm. Yet, our remarks today are to remind you that your actions do trickle down in terms of impact on the farm.

Given the fact that farmers are simply suppliers and not manufacturers of cigarettes or any other tobacco-related products, it might seem curious why we, as an organization, would ask for the opportunity to speak today. I would expect, and have observed, that much of the commentary before you is focused on health-based regulation, technology, and science and concerns related to smoking. Again, we are not experts in any of these specific areas, and we don't engage in the health debate on smoking any more than too much fat in our diet or lack of exercise.

Our remarks this morning from a farm perspective are based on economics. So I would remind you that the policy decisions that you make as an organization have direct impact at our farm level.

North Carolina is the largest tobacco-producing state in the nation, and for the last half century, the crop value has, on average, annually been worth more than a billion dollars at

the farm level. In addition to that are thousands of jobs and tax revenue.

I will remind you, in fact, that FDA, through user fees, this year will collect over $600 million.

So, in the past decade, we've recognized a decline in demand for U.S. tobacco, and a lot of this can be attributed to a shift in where that tobacco is being sourced -- offshore -- and in our view, inferior tobacco ingredients.

So as you move forward, and the technology advances for this industry, reduced modified risk products, such as IQOS being discussed today, may become a reality. Now, we understand that IQOS uses a third less tobacco by weight or by volume compared to a conventional cigarette, so it might be curious why would an organization representing farmers support technology adoption that uses less tobacco. The fact of the matter is we aren't assured with any guarantee that current cigarettes have any U.S. tobacco in them. What we know is we're having a state of decline, and we're losing volume to offshore producers.

So we would leave you with the following statement, that we support the approval of IQOS in the United States market and we would ask the FDA to stipulate that such products are

manufactured in the United States and are inclusive of a high percentage, if not entirely, of U.S.-grown tobacco. And why is that? Ours is the most highly compliant, highest standard of premium leaf in the world, already subject to a tremendous amount of government oversight at the federal and state level.

This is an economic obligation and opportunity for us and at the same time a way to provide consumers, adult consumers, assurance that they're using the best quality products available.

DR. HUANG: Thank you.

MR. BOYD: So my appeal is to support the American farmer.

DR. HUANG: Thank you very much.

The next speaker is David Dobbins with Truth Initiative.

MR. DOBBINS: Thank you for the opportunity to address the Committee. We'll discuss three issues. First is our concern about the strength of the Marlboro cigarette brand and marketing HeatSticks under the Marlboro brand.

We see cross-brand marketing in many product portfolios in the food and beverage industry. One need only look at Coca-Cola and Doritos. The conventional wisdom is this cross-brand marketing increases consumption across the entire portfolio. Indeed, we have observed part of investor

enthusiasm for IQOS is rested on the belief that it will potentially grow the market share of all Marlboro products.

The FDA's summary to TPSAC notes that cross-brand marketing may be a potential incentive for current smokers to try the product when they might not try less similar devices like e-cigarettes. However, this may have other effects.

Marlboro is the most popular cigarette brand in the United States. Unsurprisingly, it is also, by far, the most used cigarette brand amongst youth. PMI has provided no data on how Marlboro branding might affect IQOS and Marlboro cigarette uptake by youth, and given that the large majority of lifetime smokers start as youth, this is no small oversight.

We're also concerned about issues of dual use. PMI's data from its international whole offer test show substantial dual use in every study market, with more common dual use -- with more common exclusive use in Asian markets.

Our own consumer studies in Switzerland and in Japan have shown that in Japan there was more interest in the product due less to health concerns than the cultural concern for the comfort of others. Swiss smokers were far less interested. They found the product unsatisfying, cumbersome, and complicated to use. We were not surprised to see the less

success of exclusive use in this market.

Lastly, we want to take on the notion that's been expressed here, that reduced harm products added to the nicotine market will themselves be silver bullets to end the tobacco epidemic. The dual-use data belies this, but I would also point to the recent conclusions of the National Academies of Sciences, Engineering, and Medicine on e-cigarettes. That report models the public health impact of a hypothetical reduced harm product that is 90% less harmful than a conventional cigarette. Assuming 15% of the smokers switch completely to the new product with no new cigarette initiation as a result of an increase in overall interest in nicotine products, the committee concluded that lives saved over 35 years would just be 1.1% better than baseline. A more conservative assumption, a 10% switching and 5% new initiation, shows a benefit of 0.7% better than baseline.

We encourage the Committee and the FDA to recognize that while bona fide reduced harm products that meet modern notions of consumer safety may be a tool at reducing morbidity and mortality from tobacco use, they must be regarded as part of a more holistic approach, not a solution by themselves.

Thank you.

DR. HUANG: Thank you.

The next speaker is Hank Campbell with the American Council on Science and Health.

MR. CAMPBELL: Hello, I'm Hank Campbell, the President of the American Council on Science and Health. We are a 501(c)(3) whose mandate is to separate health threats from health scares for the American public, and in the 40 years of our existence, there is no health threat that compares to smoking. With 40 years of history being against cigarettes, it's difficult to be succinct, and I'm a guy who can't even order lunch in under a thousand words, but I have promised to be brief and so I will.

When I first came to the American Council on Science and Health, I was very much in the quit-or-die camp. I am like a lot of people in this room; I am a child of two smokers, and my hope is that 40 years from now no one in a meeting like this will be able to say such a thing.

But in order for that to be possible, we have to make realistic harm reduction and smoking cessation techniques viable. And that's why even though we've been against smoking for 40 years, we are in support of these sorts of tools for options for people who want to quit.

I developed compassion when I became the President of the

American Council on Science and Health precisely because I had access to millions of data points. I had a chance to talk to smokers, and there are very few who are just recreationally going to do this and they like it and they don't know the risks. I mean, I believed it was an IQ test when I first became the President of ACSH, and now I recognize that there are other issues that are involved. So if we're going to separate health threats from health scares, we don't want to take a hypothetical concern about what might happen in the future and use that to offset the very real harm that's occurring for a lot of people.

In my written statement, there are three concerns and three benefits, and if we're talking about hazard versus risk -- and that's how, if we're going to inform Americans about these issues, we always have to separate hazard, risk, absolute risk, relative risk, things like that, so that they can make these informed decisions.

Dr. C. Everett Koop was on our advisory board because we have long maintained that smoking is a pediatric disease. If we stop it at young people, you don't see people at age 30 taking up smoking; it's just very rare for that to happen. But the risk of taking up something -- if I have a choice between

someone taking nicotine from this kind of product versus a cigarette, I'm going to take this every single time.

In conclusion, we've been proud of the work we've done in causing smoking to plummet, right? That's been the hallmark of our basic success, but we want that decline to accelerate, and so, for that reason, we are asking for MRTP approval for this product.

Thank you.

DR. HUANG: Thank you.

Our next speaker is Matthew Myers with Campaign for Tobacco-Free Kids.

MR. MYERS: Thank you. I appreciate the opportunity to be here today.

First of all, I'd like to be clear about something. This is not really a debate about whether or not products will truly reduce risk and reduce the number of Americans who die from tobacco use. I think that's a uniform goal here. It is really about the scientific standards that will be applied in the conditions that they'll be worked.

And a quick caution from our point of view, and that is we've been there before with light and low tar cigarettes. We shouldn't make the same mistakes again. This statute was

designed to provide precise standards which should be followed and followed rigorously. We support them under those circumstances.

We'd like to point out in our comments three important questions which we believe have not been adequately answered.

First, the data on dual use from the studies that were presented yesterday is concerning. The cross-country comparisons demonstrate wide variabilities. We need to be very cautious in looking at the conditions that led to certain types of use in different countries. We shouldn't automatically assume they apply here. We should understand what will happen here, because if it's high levels of dual use, it doesn't matter how much safer the product is.

Second, Philip Morris has truly not met the burden of demonstrating that its products will not be attractive to youth. It's really inexcusable that a company, which is the most successful company marketing cigarettes to kids in the United States and around world, says it doesn't deal with young people in this circumstance. The most important issue is we have to understand that, and asking adults what kids are going to do is not the way we're going to find out the answer to that question.

Nor can we assume, as was represented yesterday, the fact that we have laws against selling to kids. Is that adequate protection? If that was adequate protection, we wouldn't have had an epidemic of youth tobacco use for the last 50 years in this country.

There's also a particular concern that hasn't been the real focus in that, and that is the appeal of this product, not the claims necessarily, but the product itself. This looks more like an Apple product, both in name and design, than you could imagine.

You know, it isn't a coincidence that this product looks very similar to the most popular product among youth in the United States, e-cigarette product in the United States: JUUL. It is high tech, it is sleek, it is designed in exactly the way that will appeal to young people. And JUUL now has over 40% of the e-cigarette market. Reports from schools all across the country demonstrate that as a result of the design and how this product is marketed, it has taken off in social media around children.

When we look at population effect here, I think we have to take a look at the product and those kinds of issues with regard to it.

Third, despite the statements and the sincerity expressed yesterday --

DR. HUANG: I'm sorry, we do have to --

MR. MYERS: I'll be one sentence. There is a real serious reason to be concerned about the marketing goal of Philip Morris International, despite it claims that its goal is to see a reduction in cigarette use. Your corporate policies are directly inconsistent with that. If you look at what they do, not what they say, it means that the only way we'll protect our kids is if FDA doesn't stop.

Thanks.

DR. HUANG: Okay, thank you very much.

Our next speaker is Becki Gray with the John Locke Foundation.

MS. GRAY: Good morning. Thank you for the opportunity. My name is Becki Gray, and I'm the Senior Vice President of the John Locke Foundation. We're located in Raleigh, North Carolina.

The John Locke Foundation is a state-based free market organization that was created in 1990 as an independent nonprofit think tank that would work for truth, for freedom, and for the future of North Carolina. We are committed to

individual liberty, limited constitutional government, freedom, personal responsibility, and the freedom that comes with choice. We're particularly interested in the public policies that promote individual liberty and personal responsibility. In that vein, we are pleased to offer these comments in support of the modified risk tobacco product application for the IQOS system.

According to the Centers for Disease Control, 480,000 people die from smoking traditional cigarettes every year in the U.S. It is the leading preventable cause of death and disease. Tobacco harm reduction products offer consumers a choice outside of these traditional combustible cigarettes, a safer, less harmful choice, a choice that saves lives.

The market has produced alternative vaping products, nicotine-reduced cigarettes, patches, and gums for consumers who are either trying to minimize the health risk or quit tobacco use altogether. Philip Morris International offers the latest innovation. Its research, investment, and development have generated new products offering another way to reduce the health risks of tobacco use.

The IQOS system of tobacco delivery uses a heated noncombustible technology. Extensive research, which has been

presented to you, indicates that the IQOS system offers a lower health risk alternative with an experience that consumers found satisfying. The product is offered for sale in over 20 countries around the world. Consumers are responding. Choice has created a growing market and a safer alternative.

Other comments have focused on the extensive evidence and research indicating that the considered product is safe, offers fewer health-related risks, and lowers health-related cost associated with tobacco use.

Our interest lies in the realm of consumer choice. For consumers who choose to smoke, having a reduced risk product available to them gives them a viable, less harmful option. This would allow consumers to take control of their tobacco use in a safer manner.

Regulation that limits choice and pushes consumers towards more harmful options does nothing to promote public health and safety. As you consider approval of the modified risk tobacco product application, please consider consumer choice and freedom.

The John Locke Foundation encourages the Committee to recommend to the Food and Drug Administration to support emerging technology and consumer choice and approve the

modified risk tobacco product application sought by Philip Morris.

Thank you so much.

DR. HUANG: Thank you.

Is that the last of our speakers?

UNIDENTIFIED SPEAKER: Yes.

DR. HUANG: Okay. All right. So we now have a strict 20-minute follow-up from PMI.

DR. GILCHRIST: Good morning, Mr. Chairman, members of the Committee, members of FDA, and Director Zeller. We really appreciate the opportunity to come back to the podium and clarify a few points that came up in the discussions yesterday and to reiterate some of the key findings from our submission.

We recognize that no single study can demonstrate, in a premarket assessment, that a tobacco product presents less risk of harm than cigarettes. The strength of our assessment approach is that we've conducted multidisciplinary studies to develop evidence across the entire causal chain of events that links smoking to disease. All of our studies, including clinical trials with smokers, have consistently and coherently demonstrated that switching completely to IQOS can reduce the risk of tobacco-related disease and presents less risk of harm.

Manuel explained yesterday, over the past decade we've published more than 30 peer-reviewed publications describing our assessment studies and over 150 publications describing the approaches and methods we used. These peer-reviewed papers and studies were published in journals such as *Nature Biotechnology*, *Toxicological Sciences*, *Food and Chemical Toxicology*, and the *Journal of Translational Medicine*.

The citations for these peer-reviewed papers and studies are in Section 2.7 of our application. We also provided to FDA today a copy of an article summarizing our indoor air quality assessment that was the subject of a question yesterday.

Now let's turn to the question of whether reductions in exposure from switching to IQOS can be overcome by smoker puffing behavior, which was a question that arose.

This simply isn't possible because of the IQOS technology. The IQOS aerosol contains 90 to 95% lower levels of toxicants than cigarette smoke. This leads to almost 95% of the reductions in exposure to toxicants induced by smoking abstinence. Significant reductions were seen across gender, race, and also HeatStick gradient tested.

While the toxicant yield of cigarettes increases in line with intensity of puffing behavior, with IQOS the heat control

technology has decoupled the delivery of nicotine from that of toxicants. This prevents puffing behavior from influencing toxicant yield in a way that could overwhelm the benefits.

We've confirmed this by testing IQOS across a wide range of puffing regimes, and we consistently see significant reductions in the formation of toxicants. In other words, IQOS, as actually used by consumers, consistently achieves significant reductions in toxicant exposure, and this is confirmed by our clinical reduced exposure studies.

In addition, biomarkers of potential harm showed beneficial changes compared to smoking. Moreover, we've presented these changes in comparison to cessation, which is recognized as the gold standard for risk reduction.

Our studies focused on the main diseases that account for more than three-quarters of smoking-related mortality. It should be noted, though, that the same mechanisms involved in these diseases are also relevant to other smoking-related diseases. Our studies show switching to IQOS reduces impact on these mechanisms by 90 to 95% consistently and coherently.

Yesterday you requested data on complete switching. That's 100% IQOS use. In our premarket and postmarket studies, we saw that many adult smokers switched completely and didn't

dual use with other tobacco and nicotine products.

As you can see from this slide, the majority of exclusive IQOS users in our actual use study in the United States completely switched to IQOS. By the end of the study period, of the 8% that demonstrated exclusive use by Week 6, 75%, that's six out of eight, had switched completely. That would translate into nearly 2.5 million U.S. smokers abandoning cigarettes completely.

Based on postmarket data from outside the U.S., we've observed even higher levels of complete switching, and we expect to observe similar dynamics here in the United States.

This slide shows that between 47 and 68% of IQOS users have completely switched. Our data show that for many, dual use is a transitional behavior and an opportunity to encourage even further complete switching to IQOS.

With FDA's authorization, we'll be able to reinforce the important message of complete switching in order to ensure that this transitional phase is as short as possible.

Let me move now to one issue that's relatively straightforward to clarify: misuse.

While it was mentioned that 5% of participants in our premarket actual use study lit and attempted to smoke

HeatSticks like cigarettes on a regular basis, this is not the case. Our data show that around 180 HeatSticks were lit throughout the study out of a total of about 137,000. This is 0.125% of all the HeatSticks that were used. Our hypothesis is that this occurred simply out of natural curiosity because there was no continual misuse.

Of course, appropriate understanding of the product and product messages will facilitate proper use and complete switching to IQOS.

In developing our comprehension assessment program, we consulted with experts in the field of consumer comprehension, including in the area of over-the-counter drugs. Across our six qualitative and quantitative studies, we've consistently seen that both smokers and nonsmokers understood IQOS and our messages, and we achieved these results after only one single exposure to the messages.

As Sarah outlined yesterday, PM USA's commercialization plans will reinforce product messages to support awareness, trial, and complete switching. This will include one-to-one communications and repeated exposure to product messages that are important to support complete switching.

In overseas countries, we've put in place the

infrastructure to be able to provide adult consumers with multiple options to reach our support teams whenever they have a question or a need. This is all to support full switching from combustible cigarettes to IQOS.

To give you a perspective, our contact centers for the Japanese market employ over 500 personnel and handle hundreds of thousands of inquiries every single month.

Here in the United States, all of this, of course, will be complemented by postmarket surveillance to monitor actual use, consumer behavior, and potential unintended use by nonsmokers and former smokers with FDA's input and oversight. FDA also has the authority to impose conditions or to modify the order, which will be time limited.

Today there are 40 million men and women who smoke in America. The objective is to move as many American smokers as possible away from cigarettes to a product that presents less risk.

We outlined the results of our population health impact modeling, which showed that more than 90,000 smoking-related deaths could have been averted within 20 years of introducing IQOS. Yesterday a question was raised about the significance of this number. Let's put this in the context of the perfect

solution, which is cessation.

If, instead of switching to IQOS, all of those people quit tobacco altogether, instead of 90,000 pure smoking-related deaths, there would have been about 100,000 in the same time frame. This is because the benefits of risk reduction grow over time. Of course, without IQOS, the 90,000 smoking-related deaths averted would increase dramatically over time.

Without an alternative like IQOS, most of the 40 million American men and women who smoke will simply continue to use cigarettes. With IQOS, meaningful change is possible, and IQOS presents a compelling opportunity. It is consistent with FDA's stated strategy of regulating along the continuum of risk. It's not a perfect solution, but the statute doesn't require perfection. It calls for change and progress. It enables real-world solutions for America's smokers that are better than the status quo.

Thank you. Mr. Chairman, we'd be happy to take any further questions that the Committee may have.

DR. HUANG: Okay. Dr. Giovino.

DR. GIOVINO: Thank you, Dr. Gilchrist. So Dr. Gregory Connolly of Northeastern University raised an issue of the chips in the system and what -- how many chips are there?

Like, is there a technology in there that it would be good for the Committee to know about it? Is there a technology that could potentially control behavior in ways that we don't understand?

And, you know, I've been reading a book called *The Hacking of the American Mind* by Robert Lustig, and he describes how iPhones work, and I'm just concerned that this might be similar. So please --

DR. GILCHRIST: No --

DR. GIOVINO: -- let us know.

DR. GILCHRIST: -- I can reassure that there's no technology in there that's intended to manipulate in any way what is delivered from IQOS. And, in fact, we take deliberate care and control to ensure that IQOS cannot be manipulated.

And, of course, FDA has all of the information related to the device and the controls that we have put in place within the application and has the ability to order manufacturers to check that everything is manufactured according to the correct procedures and protocols.

And, of course, in a postmarket setting, FDA has the ability to oversee all of the product use patterns and understand what they are and be able to act if they believe

that there is anything happening. But, of course, it wouldn't be in our interest to do something like that. We're absolutely committed to making IQOS a success. We will not put a foot wrong.

DR. HUANG: Dr. Wanke.

DR. WANKE: Thank you. I actually take to heart Dr. Giovino's question, because yesterday it was my understanding that the technology really was limited to heat sensors, sensors that were controlling the temperature, and asked, but clearly not directly enough, to have a better understanding of other features or functions.

So one of the things that I think would be useful would be having a better understanding of what that technology does. It seems like a lot of technology in order to just control heat sensor feedback loops.

And so I think it would be very helpful for us to understand, you know, have a better understanding of what the components are and what they do and what the capacity is and the functionality of the system itself, because I'm realizing, in the presentation yesterday, we saw and could see the external components, but we never had that opened up, we never had pictures presented to us, and we never had an explanation

of what all those components can do.

DR. GILCHRIST: Could I have Slide 1 up, please?

So here is what's inside the holder -- inside the charger, the IQOS charger. You can see that there's a cradle to hold the holder inside. There's the electronic circuit board and a large battery. The battery is simply there to provide sufficient energy for 20 HeatSticks to be used during the day without having to recharge. The electronics in this particular component in the charger are there to control the recharging cycles to recharge -- to control how the battery is recharged in a safe way to ensure that nothing goes wrong in terms of recharging.

Inside the holder -- I'm not sure if we have a slide with the cutout of the holder as well, please. Slide 1 up, please. So this is what's inside the IQOS holder itself. Again, you can see the vast majority of it is battery. So at the end of the holder you have the heating blade there, which is what needs to be controlled by the software. And the software on the control electronics that you see here is designed to carefully measure and monitor and control tobacco temperature on an ongoing, continual, real-time basis.

DR. WANKE: Does it control anything other than

temperature? Puffing parameters?

DR. GILCHRIST: No, it's monitoring puffing, so it's monitoring, when you saw the dips in the chart that I showed yesterday, it's monitoring to see when those happen because it uses that to help count the number of puffs and uses that to automatically switch off once 14 puffs have been reached, if that comes within the 6 minutes.

DR. WANKE: So is that a complete list of what the capacity of that technology is doing, what the computer technology is doing or the chip technology?

DR. GILCHRIST: It is also monitoring the charging of the battery within the holder as well. And I think that's it.

DR. WANKE: That's a complete list?

DR. GILCHRIST: Yeah.

DR. HOLMAN: Do you want to mention the cleaning function?

DR. GILCHRIST: Yes. Sorry, thank you. You're better than I.

There's a self-cleaning function, so it will count the number of sticks that have been used, and after the 20th stick, it will initiate an automatic cleaning profile, which happens when the holder is docked back into the charger, and it basically acts a little bit like the self-pyrolysis in a

kitchen oven, where it takes the temperature up to get rid of any dirt, tobacco, residual tobacco that's on the heater blade so that you can quickly brush it off and you have then a clean device.

So the software is counting how many sticks have been taken and managing that whole process and ensuring that it happens only when the holder is inserted within the charger.

DR. HUANG: Actually, I have a follow-up question, also, on the design. It was presented, and I think it was probably Dr. Connolly also, on the similarity to the product, the e-cigarette product, and if you had some of the marketing data on attractiveness to youth. I mean, it is certainly a sleek design, and do you have some information on appeal of the product design or how that was formulated?

DR. GILCHRIST: So, first of all, IQOS is not an electronic cigarette. It is subject to different regulations to electronic cigarettes. In fact, it's subject to the same regulations that apply to combustible cigarettes, and those are considerable. So restrictions on advertising, age restrictions for purchase, and so on and so forth. So that's what applies to IQOS, not the regulatory regime that applies to a product like was mentioned in the public comment period. So that's

first of all.

Now, we recognize that there's a careful balance that we have to walk between making this product unattractive to unintended audiences, but at the same time making it attractive to the intended audience. We all use technology in our lives; we all have products that are innovative and high tech. So we worked very carefully to ensure that the product would be intuitive and useful to the smoker and easy for them to switch to. We were very mindful that we shouldn't make it attractive to unintended audiences, but at the same time we shouldn't make it ugly for smokers because then they simply will not switch, and our goal is to switch as many of them as possible completely from cigarettes to the product.

DR. HUANG: Okay. And I am being reminded that we have 1 minute and 20 seconds left in this section.

Yes, Dr. Mermelstein.

DR. MERMELSTEIN: Just a follow-up about the technology, so there are two parts to the question. The first is how is puff related to temperature? So does puffing behavior change with temperature if it regulates the temperature?

And is there a learning so that you can help facilitate how people learn to use the device with the chip and with

temperature? Is there even an internal feedback mechanism that helps facilitate optimal utilization for smokers to get their delivery of nicotine?

DR. GILCHRIST: Okay, so the first part of your question, the relationship between puffing and temperature, so Slide 3 up. So you can see on the chart that I showed yesterday, the dips in temperature that occur that are marked with the arrows that come out from the word "puff." So those are puffs, and what you can see is those puffs actually decrease the temperature of the tobacco.

Because combustion is not occurring, you don't have that flare of temperature that you get in a combustible cigarette when you bring oxygen into the system. In fact, it's the reverse. The cool air that's brought in with a puff cools the temperature down, and the heater has to work to bring it up to the right temperature again so that you can produce the aerosol for the user to use. And this happens consistently over and over and over again through the course of the stick. So puffing reduces temperature.

The second thing you asked was whether there was any learning, machine learning if you like, with the device. No, that's not what is happening. We're doing learning in the

laboratory to understand for future versions of the device. Once we know that we have consumer feedback about the advantages and the disadvantages of the device, we're working on continually improving.

But, of course, any improvements here in the United States would need to be authorized by FDA, and we're very aware of that, and we look forward to having a dialogue with the Agency in the future, if they grant authorization of the product, of how we can bring new innovations to the product so that we can minimize any disadvantages and maximize any advantages that smokers see as we continue through learning from them.

DR. HUANG: I do appreciate your restricting your comments to within the 20 minutes.

I will ask the Committee, would you like to spend a few -- just a few minutes to ask a few more clarifying questions, or is that -- okay. So just a few more minutes.

Okay, Dr. Rees.

DR. REES: Thank you. I'm interested in smoker behavior. You know, I understand that you've taken measures to put in place a standard, though, which the product cannot be manipulated, but there's often unintended ways in which a consumer might use a product, and we've certainly seen that

with light cigarettes and the elasticity of the constituent yield with more intensive puffing. You said that it's simply not possible, but I still don't understand the mechanism by which nicotine, as you put it, is decoupled from the toxicant yield. And my expectation is that more intensive puffing would deliver a greater yield of toxicants which then, of course, would have implications for the population simulation modeling that you presented yesterday.

DR. GILCHRIST: Okay, Manuel can bring you the details on this, but the decoupling happens because we're simply not burning tobacco anymore, and by not burning tobacco, we're so significantly reducing the formation of the harmful and potentially harmful chemicals that puffing regimes that we have measured over and over again do not yield significant differences in the level of reduction that we see compared to cigarettes. But Manuel can explain a bit more the deliveries.

MR. PEITSCH: Yes, we have looked at that in some amount of detail during our process of product development obviously, because we were concerned about this relationship between puffing regime, intensity of puffing, and then obviously -- which is nicotine deliveries and would affect smoke HPHC or toxicant deliveries.

If we'll look at Slide 2 up, please, for a moment, we have noticed -- and that is known also from the literature. If you look at the red lines as well as the blue lines, which are two types of combustible cigarettes, the delivery of toxicants is actually in a linear relationship with the delivery of nicotine, and the delivery of nicotine is influenced by the puffing topography. I'll show you that in a moment.

Now, if we look at what IQOS does, what the heating technology implemented in IQOS actually does is create a relationship between nicotine delivery and toxicant delivery that is of a different nature. It can be linear, like the first one on the left where you have ammonia, acrylamide, ethylene oxide, etc., which are delivered in a linear relationship, albeit by a much lower -- at a much lower level.

Then there's a relationship that is a plateau. That means that it goes to a certain level and then plateaus off, and the relationship remains the same, remains linear.

There a few which are quadratic, but albeit at a very lower level than conventional cigarettes.

And, eventually, there are a long list of them which is basically flat, which basically says however you puff on this particular product, IQOS, you will not get an increase in

toxicant delivery.

Now, are these things relevant in the context of humans? And I would like to have Slide 1 up, please. We have looked at the actual nicotine delivery that people can actually obtain, as actually used in a consumer panel, can obtain from IQOS. And what we see is this range between 0.6 and 2.2 mg/stick.

We also showed that, in this exercise, actually the Health Canada intense happens to be the median way people use IQOS, so it is a very relevant proxy for the average use of IQOS. But because, as I showed in the previous slide, there is no direct -- there is not the same relationship between nicotine delivery, puffing regimes, and toxicant deliveries, we are in a situation where IQOS, as actually used, cannot be -- will always reduce the exposure to HPHCs, and we're not in the same situation as we would be with a conventional cigarette.

DR. HUANG: Thank you.

Okay, we're going to have three more questions. And I apologize, Dr. Ossip is on the phone again, and we did not recognize her. If you could introduce yourself, then go ahead and ask your question.

DR. OSSIP: Thank you. I'm Deborah Ossip, and I'm with the Department of Public Health Sciences at the University of

Rochester. Thank you for your presentations to all the presenters this morning.

My question is, is there the ability for this device to connect with other devices or technologies? Like someone earlier made the analogy that it looks kind of like an Apple, you know, like an iPhone. Is there the ability to connect with other devices or technologies like an iPhone or a mobile phone, other mobile devices, computers, or laptops?

DR. GILCHRIST: So for overseas markets, we have developed Bluetooth capability to be able to have the customer support service integrated with, for example, mobile phones and computers.

Now, of course, here in the United States we didn't have that functionality when we made the application, so it doesn't form part of this application. So our consumer support activities will be done without the aid of Bluetooth here in the United States, but certainly that's something that would be possible in the future and following discussions with the Agency.

DR. OSSIP: Thank you.

DR. HUANG: I'm sorry. That Bluetooth technology is tied in how?

DR. GILCHRIST: It's not for the product that's here in the United States because it was not part of our application, so obviously we're bound by the four corners of our application to the Agency. Bluetooth functionality was not part of that.

DR. HUANG: But overseas it is, you said?

DR. GILCHRIST: Overseas we have the functionality available.

DR. OSSIP: Actually, if I could do a follow-up. Could you talk a little bit about how that's used overseas?

DR. GILCHRIST: So we're using it to be able to help consumers remember, for example, when they have to clean or when they may need to reorder HeatSticks so that they don't run out and have to go back to combustible cigarettes. We're doing it to help encourage them to stop using combustible cigarettes. You know, for example, a message may come up, hey, you haven't used your IQOS device today. Have you stopped smoking, or is it because you've gone back to combustible cigarettes?

So that's the type of way that we can use it, is to help to remind people to do certain activities that they don't have to do with combustible cigarettes, like cleaning and reordering, etc., and also encouraging them to make that full switch.

DR. HUANG: So overseas, that is related to the circuitry that we were talking about earlier, or it's integrated into that?

DR. GILCHRIST: In the overseas device, but here in the United States we're stuck with the four corners of the application, and Bluetooth will not be available here. All of our customer support activity will be done through one-to-one communications, direct mail, phone calls, through some use of social media, but not with Bluetooth.

DR. HUANG: Okay, thank you.

Dr. Rees.

(Off microphone response.)

DR. HUANG: No. Oh, Dr. King.

DR. KING: So I have two questions. One is minor, and I think you'll be able to resolve it very quickly for me. So I was intrigued by the name IQOS, which you addressed yesterday and I saw in the device itself it's a little "i," but on your slides it's a big "I." So can you clarify to me which is correct; is it a big or a little?

DR. GILCHRIST: We realized this point quite late on in developing all of our slides.

DR. KING: Okay.

DR. GILCHRIST: So in the application we use, I believe, a little "i." Now, in the other countries overseas, we've used a big "I." Frankly, we will discuss with the Agency about the strong opinion.

DR. KING: But the product itself is a little "i." Yeah.

DR. GILCHRIST: Yeah.

DR. KING: So iPhone uses a little "i."

DR. GILCHRIST: Yes.

DR. KING: Yeah, that was -- yeah.

DR. GILCHRIST: And maybe I could just come back to the question I think it was Dr. Fagan had yesterday about what does it stand for, and my colleague said, well, why didn't you explain what's probably on some people's mind. It's been written in the press that it stands for "I Quit Ordinary Smoking" or "I Quit or Switched." We've seen all of those things. These are all -- I think the term is backronyms; these are things people have invented following the use of the trademark IQOS. It's not true.

DR. KING: Okay, okay.

DR. GILCHRIST: It's not what it stands for.

DR. KING: So my second question is a little more nuanced than that one, but that's interesting. Thanks for clarifying.

What's the anticipated lifespan of this product? So surely it's been on the market in Japan, from my understanding, 2 years at least. So I presume, you know, there's an anticipated -- but how long this product lasts.

And then what happens after that? Is it like an iPhone where you get a new product or -- I was intrigued yesterday, you mentioned that if the product breaks, they can send it back to you all, and that would be the only way you could get information from at least the U.S.-based device, was if it was sent back to you.

But is that the anticipated plan for as many years and they send it back to you to fix, or is it going to be new iterations, like a newfangled iPhone that will be coming out, you know, every year to keep people enticed to use the product? Can you speak briefly about lifespan, and then what's the plan for, you know, new devices moving forward?

DR. GILCHRIST: Yeah. So the lifespan of the device, it's guaranteed for 1 year, which is kind of similar to what you get for mobile phones. Now, what drives that is the battery capacity and battery performance. We know, from the mobile phone, after a year you start to have to charge it more frequently and so on. So that's what's driving the lifespan.

In terms of what happens next, next generations and so on, we already have new generations of the IQOS device on the market overseas, but of course here, because of the regulatory process and the application, we are -- we applied with a certain version of the device, and that's what will go on the market here in the United States.

But, of course, we're happy to discuss with the Agency how we can integrate upgrades to the device, improve functionality to help smokers to make the switch, for example, in the postmarket setting, and that's something that can come after authorization of the FDA.

DR. KING: Just to follow up on that, so the Bluetooth, what is the prevalence of use of that function then? In Japan, where it's currently implemented, how prominent is the use of that? The consumer base has adopted that?

DR. GILCHRIST: I don't have that data. I would need to come back to you, I'm sorry. We can try and see if we can get something for you later on this afternoon.

DR. KING: So the proportion of all people who have the devices, they're utilizing that technology --

DR. GILCHRIST: Right.

DR. KING: -- for which you could get data from that?

DR. GILCHRIST: We'll see if we can get that from my colleagues.

DR. KING: Okay, great. Thank you so much.

DR. HUANG: And I think Dr. Wanke has a follow-up.

DR. WANKE: Yeah, just a quick follow-up because I'm not sure that I understand if a component of Dr. King's question was answered. Would the intention be for consumers to send their device back? So I'm thinking about the access of data. If you're not going to be using Bluetooth, is there still a plan to get the data from the devices through a marketing strategy of having them send the device back for a reduced cost of a future device or some other way of having them send the devices back?

DR. GILCHRIST: No. The only time we extract data from the device is to understand why a device may have malfunctioned, for example. So if we get a consumer return, for example, we have oftentimes had in the earlier days a problem with blinking of one of the lights, which was an issue that was received several times.

So when we have a device returned to us, we can then look at software to understand was it the fault that we anticipated it was and in order to be able to return it to -- provide a new

device to the consumer. But that's the only time that we would extract that, just to be able to understand what was the device fault, in order to be able to provide a replacement.

DR. HUANG: Okay, thank you very much.

We will now take a 15-minute break. Committee members, please remember there must be no discussion of the meeting topic either amongst yourselves, with the press, or with any members of the audience. Thank you. Again, we'll reconvene in this room in 15 minutes.

(Off the record at 10:26 a.m.)

(On the record at 10:41 a.m.)

DR. HUANG: Okay, we're going to get started. We will begin our Committee discussion section, and before we start, Dr. Apelberg is going to give us some guidance and --

DR. APELBERG: Yeah, thank you. I just wanted to provide a few clarifications to the Committee and to the public before the Committee gets going on its deliberations.

One, just to reinforce that the purpose of this meeting is not to discuss whether this product should be authorized to come onto the market. We're separately evaluating at FDA premarket tobacco product applications to determine if that would be appropriate for the protection of public health. The

purpose of this meeting is to discuss issues relevant to the modified risk tobacco product application, so specifically to market the product with modified risk information. So that's just one clarification.

I also wanted to touch on something that -- an issue Dr. Thrasher raised yesterday towards the end of the day about some confusion around, you know, the application, including statements specifically talking about reduced risk and then other PMI Important Warnings, which, you know, stated that it hasn't been demonstrated that these reduce risk. And I just wanted to remind the Committee that FDA has before us requests under both 911(g)(1) for risk modification order and 911(g)(2), an exposure modification order, for these products, and as I presented yesterday at the beginning of the day, the standard for 911(g)(1) is that the product is actually used by consumers, reduces the risk to individuals, benefits the population as a whole, and that's to make any modified risk statement.

If that standard can't be met, what 911(g)(2) allows for is another pathway, but in that case, there are a number of things that have to be met, and there it's that modified risk information has to be limited to information about exposure,

information about levels of chemicals, things of that nature. And one of the other conditions that's laid out in the statute is that, in that case, it shouldn't -- consumers shouldn't be misled into believing that the product has been demonstrated to be less harmful or to present less risk.

So recognize there's a bit of complexity, but the questions that we've laid out for you, the first question is related, Question 1a and 1b are related to particular statements that are being requested under the 911(g)(1) pathway, and then when we get to Question 2, 2a and 2b is related to the statement that's being requested under the exposure modification, 911(g)(2), that's listed up here. And one of the statutory requirements for 911(g)(2) is even if this statement is about exposure or lower levels of chemicals, things of that nature, that it should be reasonably likely that such reductions would translate into reduced risk. This is why we've asked you the question as is.

So I hope that hasn't made things more confusing, but I did just kind of want to differentiate between the fact that there are a number of things being considered as part of this application.

DR. HUANG: Okay, thank you.

Yes, Dr. Weitzman.

DR. WEITZMAN: I have a question. Are we allowed to ask you questions to clarify issues that we might be confused about before we vote?

DR. APELBERG: Yes. Yes, you're allowed to ask us clarifying questions.

DR. WEITZMAN: Okay.

DR. HUANG: Yes, Dr. Wanke.

DR. WANKE: And I also have a question for Dr. Apelberg. So that was really useful, thank you, because that's one of the questions I was going to ask, is that I felt like I needed a primer by FDA about what the Committee can and can't weigh in on, and one of the things that I want as a follow-up question is a little bit about the messages that are being proposed themselves, because it's -- in a way, it's unusual, given the way that product warning labels are authorized is that they're developed by the government, and these are messages that are developed by the industry.

And so it appears as if we are to vote on those labels as is without necessarily the science behind how they were developed, what they were for, what the cognitive testing is, and what the reading level is, what's the public's

understanding of what they are.

And so you say that one of the goals is that it is not misleading in terms of misleading the public to understand harm differentially, but are there any other guidances that we can -- or feedback that we can give and suggesting different language or, you know, some things might be technically true but not completely true in saying that reduces exposure for some but not all characteristics.

DR. APELBERG: Yeah, I think we're hoping that for each of these voting questions, before that there's a discussion question or discussion statement, and yeah, what we would like is for the Committee to discuss these issues, to raise these, and even when Committee members are voting, we'll ask for the rationale or the reason behind their vote, and that's another opportunity to provide whatever contextual information is necessary.

And just one more clarifying point with respect to the modified risk information: It's sort of addressed in numerous questions. The first few get at, you know, the substantiation of that from a scientific perspective, but then later there's also a question about how do consumers perceive, you know, this information, what do they think about it, are they -- do they

understand it.

DR. WANKE: So is that a condition of the Tobacco Control Act, that any modified risk statements are always developed by the industry? Is there any part of the act that allows for FDA to put forth their own statements of modified risk?

DR. APELBERG: You know, at this point, the act, you know, basically lays out the criteria that FDA needs to use to evaluate an application, but it is, you know, it's up to the applicant to develop that evidence base, to develop that information, and provide it to, you know, to FDA for us to make a determination.

DR. WANKE: And develop your messages, I guess, is what I'm saying.

MR. ZELLER: You are advising, and then ultimately, we will make a decision on the claims that the company has put before the Agency.

DR. WANKE: Okay.

DR. HUANG: And then Dr. Giovino.

DR. GIOVINO: So if the Committee or the FDA doesn't think the wording is as precise as it might be, is there any sort of negotiation that might go on with the Applicant later?

MR. ZELLER: Don't concern yourself with any of the back

and forth between the Agency and the Sponsor. You're reviewing the science that has been submitted, other information that's been made available to you, the public comments that you've heard, all the back and forth between all of the members of the Committee and the company over the course of 2 days, and you are reviewing and making recommendations on the claims that they have proposed to make. If, in the context of discussing and answering these questions, you have thoughts and suggestions, that's fine, but let's not turn this into recommended changes.

DR. GIOVINO: Sure.

MR. ZELLER: You're reviewing the claims that the company --

DR. GIOVINO: Sure.

MR. ZELLER: -- has put in their application.

DR. GIOVINO: Okay, I understand that. I just needed to know what came next from you guys.

DR. MERMELSTEIN: Just one more clarification.

DR. HUANG: Okay, Dr. Mermelstein.

DR. MERMELSTEIN: So yes, we shouldn't be getting into wordsmithing; I get that. But what we are voting on is the explicit words that are there, which will make a difference?

MR. ZELLER: That's correct.

DR. HUANG: Okay. So I think let's go ahead and -- okay, Dr. Weitzman.

DR. WEITZMAN: For clarification. In risk assessment, one often -- and this is a question about risk, which appears throughout this. Being exposed to something that's potentially risky is somewhere along the line, but doesn't necessarily demonstrate that there are biologic effects as a consequence of that exposure. Am I making sense? So, for me, a question is are we voting on risk being exposure in some of these questions, or is risk demonstration of harmful effects?

MR. ZELLER: The (g)(1)/(g)(2) distinction -- and, Ben, please feel free to elaborate on this -- is the difference between a claim to reduce exposure to harmful things. The harm reduction/risk reduction claim is to reduce the harm or risk of disease. So one is -- one set is -- claims to reduce exposure to toxins, and we've broken these out by question, and the other is to reduce the risk of disease, which is where additional information in the application comes into play.

DR. WEITZMAN: Got it, thank you.

DR. HUANG: Okay. All right, so let's -- we can dive in, and to try to keep on time, we are setting a goal of 30 minutes

to take our first vote. I mean, I think once we do our first vote, we will probably -- it will get easier. But our initial goal is to try to get to that point after discussion in 30 minutes. And so we'll start. So the first --

(Off microphone comment.)

DR. HUANG: Oh, oh. Oh. Clarification. The actual voting members are from Dr. O'Connor over to Dr. Weitzman. Sorry about that. Yeah, you're supposed to be -- okay, so --

(Off microphone comment.)

DR. HUANG: Huh?

MS. COHEN: And Dr. Ossip on the phone.

DR. HUANG: And Dr. Ossip on the phone, yes.

(Off microphone comment.)

DR. HUANG: Pardon?

(Off microphone comment.)

DR. HUANG: You do not get two votes.

(Laughter.)

DR. HUANG: All right, so if we could put up the first question. So the first question is -- and this is where we're having our discussion regarding Question 1a and 1b. And so we are to discuss evidence related to the health risks of the IQOS system and the appropriateness of the proposed modified risk

information.

So the question, specific question is: Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true: "Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases."?

And then part (b) is: Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true: "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."?

So now open for discussion.

Yes, Dr. Thrasher.

DR. THRASHER: I mean, I guess for me, in some ways it's around the link between the biomarkers of exposure and then the kind of clinical outcomes in humans, and that's where I see the biggest leap of faith around the data. And I'm wondering if Dr. Hecht may be able to speak to that link in a way that helps us who aren't experts in that area feel more comfortable with the data that have been presented.

DR. HECHT: Well, there are studies that have shown --

prospective epidemiology studies, nested case control studies within prospective epidemiology studies carried out in the Shanghai cohort and the Singapore cohort that have demonstrated the relationship between specific biomarkers of exposure, namely cotinine, NNAL, and phenanthrene tetraol and lung cancer development after years of smoking. So these were samples collected from smokers and then frozen away, and then you wait 20 to 30 years until a sufficient number of cancers develop, pull them out of the freezer, and then analyze for these biomarkers.

So those three biomarkers in addition to one "biomarker of risk," 8-epi-PGF2alpha, those four biomarkers have been shown to be related to lung cancer in a couple of studies, and that's the data that's out there, and it's reasonable and it makes sense because the more nicotine you take in, for whatever reason, be it genetic or the design of the product, in a cigarette, the more nicotine you take in, then the more carcinogens you're going to take in because along with nicotine comes everything else.

And so when you look at total nicotine equivalents or cotinine, which correlate with each other very strongly, what you're really looking at is almost a substitute for a lot of

the minor constituents that are then coming in in proportion to the amount of nicotine, whereas nicotine is not carcinogenic but the carcinogens and toxicants come along with it.

So, I mean, I think it's reasonable to say that a reduction in biomarkers of exposure indicates a likelihood of reduction in risk. But, you know, there are other things going on. So without getting away from the original questions, I mean, the "biomarkers of potential harm," it's not so clear.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I think I know the answer. It's to you, Dr. Hecht, it's to the original question that I asked. Is it exposure or clinical evidence of disease? And if I understand you correctly, one could say that decreased exposure is a proxy measure for decreased risk for disease.

DR. HUANG: Dr. Blount.

DR. BLOUNT: Just a clarifying remark on the biomarkers of potential harm. As Dr. Hecht mentions, very much -- many different things going on with biomarkers of potential harm where they can be indicative either of a direct insult of a harmful agent such as oxidants in the case of F2-isoprostane, also in the case of F2-isoprostane indicative of a free disease pathophysiological process or an actual active frank disease

process.

So I think, in interpreting biomarkers of potential harm, one needs to be careful with reading too much meaning into the absence or presence of biomarkers of potential harm. But with the assumption of biomarkers of exposure to carcinogens, for example, and the assumption of a linear dose response down to very low doses, one can assume that that is reducing harm.

DR. HUANG: Actually, I'd like to take a step back just for a second because, you know, our charge is to discuss the evidence and the appropriateness of the proposed modified risk information, and going to what Dr. Wanke was saying, I mean, because one of the things that strikes me in terms of the actual statement that's been created is, okay, scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related disease.

I see it almost as two extremes in a way, that we're talking about the scenario of total switching, which is our ideal state, and if that happens, then could it reduce, can it reduce the risks of tobacco-related diseases? It's almost the lowest threshold given the highest outcome that we're wanting to say.

Did you want to follow up on that?

DR. WANKE: And I'll even add that I'm focusing in on the words "shown" and "can," so scientific studies have shown, not scientific studies imply or scientific studies suggest or -- this is showing that the risk of disease is lower. Have the studies actually shown disease is actually lower in the people who completely switch?

And also we talked yesterday about the word "can," and was it Dr. Ramazzotti who had said that there was even consideration of the word "can" versus "may," and "can" was chosen because it was a stronger -- it was perceived as being a much more definitive statement, but I don't know if "can" is the best word when the data might not be definitive. It may be "may" or "suggests that," so I'm also looking at those words in that statement.

DR. HUANG: Dr. Bierut.

DR. BIERUT: So I think the wording is very important here in what we're being asked, and I'm assuming that the FDA, in generating these questions for us, really had certain intentions.

So I'm looking at the -- well, one, I want to say that the Applicants really did a tremendous job laying out a conceptual

model and walking through that conceptual model of demonstrating evidence. But if we look at their Slide CC-71, when it looks at disease, there's a little mouse there, and there isn't a human being there, and being kind of picky about this, it is -- you know, I think that conceptually, it is highly likely that this reduces disease, but the wording in this question is, you know, "have shown," and that's a very high standard that has been asked of us. And, you know, I think it is highly likely that it will be shown, but we're being asked at this time has it been shown. And the biomarkers, I think, you know, one of the seven deadly sins is hubris, and biomarkers have led us astray before. And again, I don't think it will in this case, but this wording is very strict.

DR. HUANG: Thank you.

Dr. Fagan.

DR. FAGAN: Yeah. I'm just kind of stumbling over the words in here as well. I'm focused on this last part, which is the risk of tobacco-related diseases, and going back to Dr. Weitzman's question yesterday about why only certain diseases were focused on, and we got a response today to that related to we focused on the top ones associated with cigarette

smoking, okay.

And so my question is, and for discussion for the group is, you know, what is the relevance of the diseases that we were presented to this product? I would imagine that oral cancers, you know, laryngeal cancer, that that data might have been presented because we're talking about this product. And so I would like to hear from the rest of the Committee members, you know, for the tobacco-related diseases that were selected, are those the right ones for the product that we're being asked to evaluate?

DR. HUANG: Dr. Wanke.

DR. WANKE: And just a quick follow-up to Dr. Fagan's point is the word "tobacco-related diseases," I actually think in our public comments this morning we were cautioned against using the term "tobacco-related diseases" so broadly when the comparison is for smoking-related diseases or combustible product-related diseases, and maybe that's the accurate comparator, so that might be the accurate term here, reducing the risk of cigarette smoking-related diseases, because perhaps in comparison to say snus or to say any other non-combustibles, the risks may not have been shown to be reduced.

DR. HUANG: Right. And I think that was a comment from

one of the speakers this morning.

All right, other comments? Yes, Dr. Weitzman.

DR. WEITZMAN: Well, I need to go back. I have two comments. One is that I need to go back to the -- something I said yesterday, that there's nothing about prenatal or childhood exposure, and there are both consequences to children and there are consequences later in lifetime due to secondhand smoke and prenatal exposure. So, to me, as a pediatrician, this is somewhat misleading.

The other thing is a person who's been asked on numerous occasions to weigh in on the causal nature of associations, one needs -- research is one of the few words in the English language that means what it says, you search and you search again, and if you come up with similar findings, then you could say that you believe that something is causally related.

So the word that "studies have shown," I don't see a whole host of studies. For me, I'd feel very uncomfortable making a judgment call that what we've seen, it suggests, it implies, but I wouldn't, could not, under oath, say that what we've seen demonstrates to the scientific community that it's been shown.

DR. HUANG: Okay. I think Dr. Ossip on the phone has a comment. Dr. Ossip?

DR. OSSIP: Yes, hello.

DR. HUANG: Okay.

DR. OSSIP: Okay, thanks. I wanted to follow up on the last three comments, and I'm grappling with this. I think "leap of faith" is, you know, kind of where I'm landing, as well, but also trying to understand the parameters of what we're looking at. So when we're looking at tobacco-related diseases, however we define it, we have seen the data that the Applicant presented. There are some implications, potentially, for humans.

What qualifies as reducing the risk, how much risk, what diseases does it need to show? You know, if you reduce the deaths by three people for something that combustible tobacco causes, then that's a risk reduction, but it's not clinically meaningful. So part is just understanding what we mean by risk reduction and for whom and for what kinds of diseases.

We have seen that with some of the biomarkers that there were very little differences between the HeatSticks or the IQOS and the combustible product. There's the comparison that about 10 HeatSticks are about the equivalent of one to three referent cigarettes on a number of constituents that are carcinogenic and potentially carcinogenic. We know that there are some

numbers somewhere between 53 and 60 constituents, if I'm remembering that correctly, that were higher in the HeatSticks compared to the combustible cigarettes or the referent cigarette, I think, and so there are a lot of unknowns here. Dr. Weitzman raises the important issue of kind of the impact on younger folks.

And so as I struggle with this, I think I'm -- you know, that term "leap of faith" is really resonating for me, and maybe in combination with that, independent versus industry-sponsored studies. So that's one point that's kind of resonating, that "leap of faith" issue.

The second is it might be helpful to define, you know, like what -- it's not so much a matter of wordsmithing, but what does, from the FDA standpoint or from guidance to us, qualify as a meaningful risk reduction that would warrant this kind of a statement?

DR. HUANG: Mitch.

MR. ZELLER: Debbie, this is Mitch. We can't give you a concrete answer to that question. All we can do is refer you back to the statute and say welcome to our world as regulators. And so let me repeat the relevant language in the statute, and it's the charge of the Committee to have your discussion within

this statutory framing of this particular question. And just to remind everybody about what the statute says, we're talking about a claim, in this instance, that would significantly reduce harm and the risk of disease to individual users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

The Applicant presented evidence yesterday in an attempt to address those key considerations for this part of the statute, and now we're turning it all over to you for your discussion and deliberation.

DR. HUANG: And that's where I'd say -- I mean, you know, when I look at this -- I mean, I'm glad we're not deciding or recommending whether the product comes to market or if it's going to be available; we're being asked should this be able to be labeled and advertised as a modified risk tobacco product.

And so, you know, I mean, one of my -- first, want to do no harm and want to make sure that we are sort of certifying or recommending certification that the science is there that this is -- the evidence is that it's a modified risk tobacco product, and it's strong enough that that can be labeled and advertised in that manner.

DR. OSSIP: And if I could just follow -- I think -- thank you, Mitch. I think that the word "significantly" helps, so thank you for repeating that.

DR. HUANG: But I think also going, in terms of that it will also benefit the population as a whole, I mean, I think it's one of our responsibilities also to think of all of the implications of advertising and labeling for this product as a modified risk tobacco product.

DR. THRASHER: Can I add something on that because this is something that I struggle with as well. But as I understand it, our charge for this first question is really around the statement for people who do completely switch from combustible tobacco to IQOS. And then later on we'll get to the issue of, kind of, the broader population benefit amongst -- as it's actually used.

DR. HUANG: Although again, I mean, I think part of our charge also was to discuss the appropriateness of that formulation of the statement also or --

DR. THRASHER: I thought that was more at the end.

DR. HUANG: Well, it's here, too.

I mean, it is in the -- you know, discuss evidence and the appropriateness of the proposed modified risk information,

because that's something that troubles me a little bit is, as I started out by saying, it's taking this ideal scenario which we've seen evidence that in real-life use, you know -- and depending on your definition, it's 8% or 15% complete switching, and then saying if you have that scenario, it can reduce the risks of tobacco.

But I think that's where -- I have some problems about that language, and again, it goes back to what Dr. Wanke started out the discussion with of, you know -- I think the language was formulated as part of the proposal, but is that even the right language?

Yes, Dr. Bierut.

DR. BIERUT: I find it interesting the order of the questions that we were asked. You know, looking at Question 1 and Question 2, we've been given the hardest question, what I think is the hardest question first. And I kind of want to know, is that purposeful by the FDA? Do we have to take the test in order?

(Laughter.)

DR. APELBERG: We organized this in a way that was comparable to the way I kind of framed out, sort of, the key questions that FDA needs to evaluate so that the first two

questions really are about, sort of, before even getting into okay, the -- you know, like, what is the impact to the population; are the -- is the basic information that's being proposed to be communicated, is it defensible scientifically? You know, it's sort of like a first -- a first cut, a first threshold.

And then if it is, how do consumers understand and perceive that? What do we expect the impact to be to smokers and some of these things that people are talking about? I mean, will they use it in a way that would, you know, result in the purported maximal benefit? What is the impact to nonusers? What is this going to mean? It's a piece of the story, and that was the thinking for organizing it in that way, but we recognize that there were probably many ways that it could've been organized.

DR. BIERUT: Can we switch the order or -- well --

MR. ZELLER: I think we would prefer that you proceed in the order, but also understand the differences between 1a and 1b before you get to 2.

DR. HUANG: Maybe we should start discussion on 1b and see how that goes. So 1b: Has the applicant demonstrated that the following statement in their proposed modified risk labeling

and advertising is true: "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."?

DR. THRASHER: So I guess my clarifying question around that is that --

DR. HUANG: Dr. Thrasher.

DR. THRASHER: -- I assume that this is -- "less risk of harm" is broader than tobacco-related diseases, then. So it's meant to encompass other kinds of disease endpoints that may be unique to IQOS?

DR. HUANG: Dr. Rees.

DR. REES: And just to add to that, does this imply population-level effects or individual outcomes?

DR. HUANG: I think our charge, we're to consider both. I mean, because if it is included in the advertising and labeling, I mean -- and we're supposed to consider that broad impact.

Dr. McKinney.

DR. McKINNEY: With questions that are related to the -- to the intent of the statement, is it okay to have the Applicant respond to the harm and whether or not they meant population?

DR. HUANG: Well, it's actually -- our charge is to consider population.

DR. McKINNEY: Okay.

DR. HUANG: Correct?

Yes, Dr. Fagan.

DR. FAGAN: Yeah, I'm just going to go back to something I was talking about yesterday, which is for 1b, it says the IQOS versus IQOS system. In the consumer's mind, I don't know if they mean the same. The system is the total package that was presented to us, right? The battery, HeatStick, everything. IQOS, in and of itself, I don't know what that means to the consumer.

So in the first question, 1a, it says IQOS system, and in (b) it says IQOS, and without really understanding, you know, what that means to the consumer, if they even differentiate between these two because IQOS, in and of itself, could just be meaning the HeatStick. That's what I was trying to get at yesterday, so that's why I was asking about how do people understand the system itself. And so for me, the switching back and forth between the terminology, we know consumers get confused very easily, and so the switching back and forth between the terminology, I just -- you know, if someone has

-- I would like to be enlightened about that, if someone else has a thought or an opinion about it. I'm happy to hear what folks have to say.

DR. HUANG: Dr. Giovino and then -- oh, you're following up. Okay, Dr. McKinney.

DR. McKINNEY: Yeah, that's a great question, and I throw it out again, is it okay for the Applicant to address that question of whether or not they have data to answer your question at this point?

DR. FAGAN: Well, we asked -- I mean, we did talk about this yesterday, so I don't have an answer to your question. I'm just saying this did come up yesterday.

DR. McKINNEY: It just seems like it's an important question, and if you need an answer to the question, I mean, we can keep bouncing the question around. I just thought that if the Applicant could provide a comment.

DR. HUANG: We can ask them. If you could clarify between the IQOS system and IQOS and what was --

(Off microphone comment.)

DR. HUANG: And how does it -- yeah. Go ahead and state how you want it. How does the consumer interpret those differences?

MR. RAMAZZOTTI: So in all our studies, we didn't just present the message as it is presented before you for your reaction. Of course, we gave to all the consumers participating in the study additional information about how is the whole system, what it's composed of and how does it work, and that is this information. This, in fact, reflects the way we communicate this information to consumers in real life in the markets where we commercialize.

When an adult smoker enters one of our stores or gets in touch with one of our IQOS experts, it's put in front of the device with its own box, it is in box, it shows the charger, it shows the holder, and it shows -- it is shown, also, the HeatSticks variant that they can choose from that go together.

So, in our view, the fact that IQOS is a system and that is consistent composed of two different elements, an electronic device and a pack of HeatSticks, which are available in different variants, is very well understood by consumers.

Now, as far as the harm perception, I think there's been discussion about harm versus risk and less risk of harm, what do consumers understand. Yesterday I made a very brief remark about it.

For consumers, as we learn from our qualitative studies,

harm and risk are used rather interchangeably because they consider harm, harm of what, harm of -- generated by the risk of getting the disease or what are the diseases that are usually generated from smoking or from using tobacco is the one that we discussed, the main ones, which are COPD, CVD, and lung cancer. So there is a very linear and not -- and how can I say, a leapfrog understanding among consumers.

DR. HUANG: Okay, thank you.

Dr. Giovino.

DR. GIOVINO: Well, for Dr. -- I might come back, but for Dr. Thrasher's question, notice that the 1b says smoking -- smoke cigarettes where the other one is tobacco, and I hadn't really focused on that until we had the earlier -- so it sort of puts it in context, right, this product versus cigarettes, so it's sort of smoking-related diseases, so I don't know that they're that different. That's the only context, contextual difference I can find.

Do people believe that this means in humans, both of these statements?

MR. RAMAZZOTTI: Yes, they do because, also, when we discuss with them -- and the question that they answer in our communication studies always relates to their personal health

risk.

DR. THRASHER: Yeah.

MR. RAMAZZOTTI: All the questions are related to what is the probability that you will get this disease. Also, what is the risk that you will get this disease sometime in the future, for your own -- for yourself, not to others in general.

And then, in our scale, just to give you a little more details, there are 18 statements that relates to different kind of smoking-related disease varying from having -- for very long, all the way up to getting lung cancer, and then they have to answer from no risk to very high risk on each of them regarding themselves, personal health.

DR. HUANG: I do need to clarify, the questions to the industry should go through me, and I'll -- yes, Dr. Weitzman.

DR. WEITZMAN: To me, qualitative research is a step in demonstrating reality. I think that Dr. Fagan's question about system versus IQOS, and I think the question about harm, could easily be answered in a quantitative way, and I don't think it's been done, and I haven't heard you answer a question about either of those other than to say that it's qualitative. Do I have that correct?

MR. RAMAZZOTTI: Let me clarify. I said that what we

learn in qualitative has been then verified in quantitative. When it comes to --

DR. WEITZMAN: Did they --

MR. RAMAZZOTTI: -- the system --

DR. WEITZMAN: Okay.

MR. RAMAZZOTTI: Sorry. Can I just finish this --

DR. WEITZMAN: Sure.

MR. RAMAZZOTTI: When it comes to the system, we have explained to the consumers and given information about what is the system that works in our quantitative studies. That's what I meant.

DR. HUANG: Our timer -- just to be conscious of the time, we have now gone past our 30-minute, sort of, milestone, and we're starting to go into the other side of the territory. I want to bring us back to our charge. We are trying to vote on the first -- but then, I think that, you know, we're going -- the discussion that we have about these issues are also what's important for providing information to FDA and the discussions that we're having, and again, there are two aspects to this: the evidence related to the statement, and the risks of IQOS and the appropriateness of this proposed modified risk information.

And I mean, it sounds like some of the language that we're going to be voting on, there are certainly concerns, and we're not supposed to get into wordsmithing. But I think that that's, you know, also part of the consideration and discussion that we should have. And again, I should -- you know, the question is, is this statement, does the science show this and for this to be an appropriate statement for them to use in their labeling and advertising? Correct? Yes.

DR. HOLMAN: Can I just try to clarify?

DR. HUANG: Okay. Dr. Holman.

DR. HOLMAN: What Ben was talking about earlier, I mean, what we wanted you to do is in this question, tell us whether you think smokers, no matter how many there are, that completely switch, whether, in fact, that reduces the risk of tobacco-related disease, or in the case of 1b, whether there's less risk of harm if they were to continue smoking. A lot of the commentary, although we appreciate it and we want to hear it, we're expecting it to be captured in later questions. So, for example, how do people -- you know, how do people interpret, how do consumers interpret IQOS versus IQOS system, our expectation is you guys would discuss that under Number 5, which is talking about label comprehension and use.

And so, again, what we want to do is kind of walk through this in a very stepwise manner. Regardless of the exact wording, you know, do you think that that fact has been demonstrated adequately or not? And then, as you go through the questions, I think some of these other issues being raised, we expect it to come out in later questions.

DR. HUANG: Okay. Dr. Fagan.

DR. FAGAN: Yes, I understand that, but the wording is important, and so we're trying to get an understanding of what the words mean here and what the consumer might perceive them to mean if the consumer is going to see these statements. So it's hard to disentangle that, and I think that's what you're hearing here. And so we can only go by what's before us and try to decipher what we think this terminology here means based upon the evidence and what we think the impact will be on the populations.

DR. HOLMAN: So we get at all of these questions, and they're related, and we will obviously put together the response to all of these questions and understanding what the recommendations from the Committee are. But, again, if you look at Question 5a, it is do consumers accurately understand the risks?

So, again, our expectation is that you would discuss your concerns with the exact wording of the statement, for example, the difference between IQOS and IQOS system, on 1a and b under that question.

DR. HUANG: And, again, part of my discomfort is that the way the wording is phrased, it's setting up probably, you know, two extremes: the highest extreme of what we would like to see in terms of happening, and the lowest threshold for saying it reduces risk. I mean, we're saying not "does it"; it just says "can reduce." Well, anything, I mean, could reduce risks, and so that's where there's some concern as well.

DR. WEITZMAN: So I think I understand, but I just want to clarify for the voting members that, to me, I understand our mandate with 1a and 1b, the science, not how it's communicated, but rather do we believe that what we've seen accurately portrays what the question is, which is does this alter disease prevalence and does that translate into a population basis? I understand fully that we want to talk about language later, but to me -- and correct me if I have this wrong. Have we seen, over the past day and a half or the past day that it was presented, are we convinced that we would say that they've demonstrated what this says?

DR. HUANG: Okay. Yeah.

MR. ZELLER: Just one last clarifying point. We, I guess, haven't thought about it this way until hearing this important discussion. However you individually answer Question 1 does not limit, in any way, how you would answer Question 5.

DR. HUANG: And, actually, Dr. Ossip on the phone has a question or a comment.

DR. OSSIP: Yeah. Dr. Weitzman, I think, framed the question very nicely based on what we have in front of us: Does the science support either of these kinds of statements irrespective of the details of the wording regarding tobacco-related disease. And so is it appropriate at this time to express an opinion specifically on that, to express a position on that?

DR. HUANG: Sure.

DR. OSSIP: I know we had --

DR. HUANG: Yes, that's okay.

DR. OSSIP: I've been listening very, very carefully to the discussion and looking back through my notes, and with that question, as Dr. Weitzman framed it, my read is that it is -- it would be a premature leap to make statements about disease given what we've had presented to us right now.

DR. HUANG: Okay. Yes, Dr. King.

DR. KING: So I would reiterate that point, and I think it's important to base it on the preponderance of the science, and you know, even if you're looking at the framing, it says, you know, "Scientific studies have shown." Well, scientific studies have shown a lot of things, but that could be one study or two studies. But in public health and in prudent public health practice, you base your decisions on evidence and the preponderance of the science.

And so in looking at the framing, the underlying crux of this statement is, is it scientifically true that switching completely can reduce disease, the incidence of disease? And if you look at the point earlier that was made in the slide, which I believe it was 71, the pink portion, it says disease; the totality of the evidence isn't there to support that among humans.

So if the intent of this statement is to the scientific truthfulness of that, based on the evidence we've been presented by the Applicant, does not demonstrate that, from my opinion, based on the preponderance of the evidence that we've been given. And I think it's important to understand the quality, the quantity, and also the various individuals who are

conducting that research to make a fully informed decision about such statements like this that have such broad implications for public health policy planning and practice.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I understand that, and I resonate to that. I am conflicted, though, because there's so much wiggle room in this statement. If I was editing this sentence, as I often do, or often copy editing something that I've written or somebody else has written, I would say there's way too much wiggle room in this sentence. And, I mean, there have been scientific studies, they have shown -- I mean, the word "can" is such a wiggly word. They have the potential to reduce. Yeah, they do. They're showing a potential. So what the heck am I voting on? If I believe that they're showing a potential, I do believe that, but there's not -- and by the way, given the time frame, there would never be enough evidence. I'm just trying to be fair. There would never be enough evidence that we're used to when evaluating for a Surgeon General's report.

So I'm getting a headache because it's the wiggle room in the language, and like, I could see myself approving this, but I also could see a company running with it in ways that isn't how I understood it, and that's my concern.

DR. HUANG: Dr. Wanke.

DR. WANKE: I think those are good points, and I still -- even with the wiggle room, I'm not even sure that we've seen a demonstration for a strong "can" given that there -- of the lack of human studies. Given that the product has already been on the market for a couple of years, I would've liked to have seen more clinical studies with users who have been using 4 years and their biomarkers and health outcomes, even if there were short-term markers that say increased respiratory diseases or colds and flus and those sorts of things, does it -- even for short-term health outcomes, I would've liked to have seen that data given that the product has been marketed for a while.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I've heard Dr. Giovino's comments, and I'm just actually pleading for any other alternative thoughts that would convince me otherwise, because I'm trying to hear what people are saying, I'm trying to be very open to the perspectives. And so is there another alternative opinion that, you know, in conjunction with Dr. -- what Dr. Giovino offered, that other people may have to offer that there's something that we're not -- that we're missing? I would just like to ask for that from the Committee.

DR. HUANG: And this is the point -- I mean, I feel very much like Dr. Giovino, I mean, in that -- but I also -- I mean, I think there is certainly potential, and if you had a scenario where switching completely could -- can reduce, you know, the risk of disease and -- but I don't -- I agree that there is absent the evidence to fully show that in humans. But, again, I think the way the language is worded, it is so vague that -- I mean, that's where I think we need to -- I mean, if we have the understanding, as Dr. King was saying, is the evidence really strong enough that we can make this claim, but that's what we're talking about, though, is this, being an advertising and labeling claim, that's there -- and that's where the phrasing of language, I think, is a little inappropriate with what the evidence shows, but this is the language that has been proposed.

Yes, Dr. Mermelstein.

DR. MERMELSTEIN: I mean, the fact that we're having this discussion among all of us shows that we're all interpreting the sentence in so many different ways and focusing on different words, and for some of us who are seeing it as more wiggle room, others of us are seeing it as almost too restrictive, so I've heard on this Committee now, which means

it's really not a good statement, and it's not reflecting, perhaps, even what we view about the risks or not.

But this particular sentence is a problematic one, and we're not here to wordsmith, so I guess I'm saying maybe we should vote on this and move on then to the next ones where things -- this is advisory to the FDA, and I hope all of our votes get taken in context of the totality of our votes and the discussion and that we're all confused about the sentence.

DR. HUANG: And I would just -- I mean, I feel a strong responsibility that we get this right, that we don't want to do any harm, that we're making -- if we're saying and approving that this is a modified risk tobacco product, that it should have a pretty high threshold for us to make that statement. That's why I'm concerned about the language that's actually proposed here.

But, you know, I mean, I'm glad that we're not saying this is determining whether this goes on the market or anything like that; if it's out there and benefits people, we want to see that. But our charge is can we make this statement; are we recommending that this actually meets this standard to make this claim on labeling and advertising as a modified risk tobacco product?

And I think Dr. Ossip on the phone has a comment.

DR. OSSIP: No, you may be thinking of something from my prior comments. I haven't said anything.

DR. HUANG: Okay, thanks.

DR. OSSIP: Thank you.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Yeah. There was a lot of talk about potential, which I think is appropriate. Thank you for those comments, Dr. Giovino. And then I heard comments about wiggle room, and I'm not clear that -- I don't completely understand what is meant by wiggle room.

DR. GIOVINO: Well, I think many people interpret "can" as "does," but "can" means "are capable of," okay, but that doesn't mean actually "do." Reduce the risk of tobacco-related diseases. Does that mean some tobacco-related diseases? Because it might reduce the risk of some, but does it increase the risk of others? You know, is this going to be interpreted -- and so those are the two areas that I thought were the squishiest. Others may have other thoughts.

DR. HUANG: I guess there was a suggestion we go ahead and call the question and vote, and we will afterwards go around and explain our vote that we choose -- so are we ready to do

that?

And one thing also, there are three choices. There is yes, no, abstain. If you choose to abstain, you can explain what your rationale for abstaining is. But, again, you know, we've had some discussion, we've had some clarification, we will have an opportunity to explain your vote. Is everyone ready to vote? Okay. All right. So -- oh, here. Hold on, I have to read this.

We will be using an electronic voting system for this meeting. You have three voting buttons on your microphone: yes, no, and abstain for this one. Once we begin the vote, please press the button that corresponds to your vote. After the eight voting members have voted, the votes will be locked in, and the result will then be displayed on the screen. I will read the vote from the screen into the record. Next, we'll go around the table, and each voting member will state his or her name and vote into the record and the reason you voted as you did. Okay, so now -- huh?

(Off microphone comment.)

DR. HUANG: Oh, okay. And after everyone has done their vote, we'll call on Dr. Ossip, and she will verbally state her vote.

Okay. So now we will go ahead and begin the voting process for Question 1a. Please press the button on your microphone that corresponds to your vote.

(Committee vote.)

DR. HUANG: Okay. And now, Dr. Ossip, what is your vote?

DR. OSSIP: My vote is no.

DR. HUANG: Okay. All right, do we have the results, or how does that work? Okay, the vote is 1 abstention and 8 noes. And Dr. Ossip voted no.

Okay, we can start maybe at this end and sort of explain your vote.

DR. THRASHER: Sure. Jim Thrasher.

I can appreciate some of the comments around the language. I was trying to hold that off until the end and just kind of take it at face value as I imagine that PMI might intend for us to interpret this question. And, for me, it's all about that connection between reduced biomarkers of exposure and then biomarkers of potential harm, and what I see as being kind of a vagueness that would lead me to the conclusion that this statement would be true, as I imagine PMI intended. Thanks.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: For me, I just don't think that the science

supports the bottom line no matter how we say it. I don't think that I'd be able to, in good conscience, say that this has been really demonstrated to reduce harm.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I agree with the previous statements and would just like to add that, again, I'm just unclear on whether or not the tobacco-related diseases that we were presented with were the ones that were relevant to the product, so that's my additional comment.

DR. HUANG: This is Phil Huang, and I again have expressed my concerns with the language. I do think that there are still -- I mean, in terms of human -- showing and impact on human disease, that there is still -- the evidence is lacking.

DR. GIOVINO: This is Gary Giovino. I abstained because I think there is potential, great potential, but I don't think this message communicates it.

DR. MERMELSTEIN: And this is Robin Mermelstein. I agree with Gary that there's tremendous potential, and I just was uncomfortable with the language in this statement and felt it did an actual disservice to the potential.

DR. BIERUT: This is Laura Bierut. I also agree with the potential there and -- but I don't believe that the scientific

evidence in humans exists at this point.

DR. O'CONNOR: This is Richard O'Connor. I generally agree with what's been said, and I had a problem with the linkage between scientific studies and human disease specifically referenced within this claim.

DR. HUANG: Okay. So I guess we can move on to 1b, then. So, again, we will begin the voting process for Question 1b: Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true: "Switching completely to IQOS presents" -- yes?

(Off microphone comment.)

DR. HUANG: Oh, I'm sorry. Dr. Ossip, please, could you please explain your vote?

DR. OSSIP: Yes. Based on the scientific evidence presented, my read is that it would be premature to make such a claim.

DR. HUANG: Thank you.

Okay, so we are going with -- moving forward with Question 1b. And, again, the statement is does switching completely to IQOS present less risk of harm than continuing to smoke cigarettes? So we'll begin the voting process. Please press the button on your microphone that corresponds to your vote.

(Committee vote.)

DR. HUANG: Okay, is that right?

MS. COHEN: Dr. Ossip.

DR. HUANG: Oh, Dr. Ossip, what is your vote?

DR. OSSIP: My vote is no.

DR. HUANG: Okay. And has everyone voted now? Okay, everyone's voted. The vote is now complete and locked in. Okay. So there are 4 yeses and 5 noes on this. And we can maybe start on this side again.

(Laughter.)

DR. HUANG: Oh.

(Off microphone comment.)

DR. HUANG: Yes, okay.

DR. O'CONNOR: So I thought, in contrast to what I said, I just said a few seconds ago, I think the totality of the evidence that was brought forth supports the sort of less-specific statement that's quoted here of switching completely, and I think I'd stress that has to be the focus of harm broadly defined, and I think the evidence base, I think, was sufficient for me.

DR. BIERUT: I agree with that. I thought that the earlier exposure experiments in humans, in particular, were

demonstrating more of this scientific evidence for harm versus disease, so I'm making that distinction between those two.

DR. MERMELSTEIN: And I definitely agree with the two prior comments, and for me, also, is the judgment that continuing to smoke cigarettes is by far the greatest harm, and that's an important part of this statement.

DR. GIOVINO: I agree with all of these statements. I thought this statement had less wiggle room, and I was able to support it.

DR. HUANG: This is Phil Huang, and for similar reasons for the last vote, I have concerns about a statement just about switching completely. I do, in terms of the actual -- that is the scenario that is most likely to be able to present this scenario, but I have still those concerns with the evidence.

DR. FAGAN: I agree with my colleagues who actually voted yes because this was a more difficult question for me to answer, but I also agree with what Dr. Huang said and -- which is the reason why I decided to vote no, even though this was a very difficult question for me to answer.

DR. WEITZMAN: And I agree with Dr. Huang and Dr. Ossip that I'm still not convinced that the strength is there to make such a statement.

DR. THRASHER: Yeah, I agree with everybody, and you know, it is incredibly difficult to read into what is meant by harm here, and I guess one of my thoughts was around, you know, some uncertainty with regard to other harms that may be specific to IQOS that aren't necessarily attributable to smoking cigarettes, but I certainly struggled with it. Thanks.

DR. HUANG: Dr. Ossip.

DR. OSSIP: I think that was Dr. Thrasher who just spoke?

DR. HUANG: Yes.

DR. OSSIP: And I agree with that as well, that I'm concerned about other risks that may be unique to IQOS that haven't been presented or characterized. And so, again, I voted no because I think at this point, based on the evidence that's been presented to us, it would be premature to make such a claim.

DR. HUANG: Okay. Now we can start a new clock for 30 minutes to go on Question 2.

So Question 2: Discuss evidence related to human exposure to harmful or potentially harmful chemicals when combusted cigarette smokers completely switch to the IQOS system, including the implications of changes in exposure for long-term disease risk and the appropriateness of the proposed modified

risk information.

So (a) is: Has the applicant demonstrated that the following statement in their proposed modified risk labeling and advertising is true: "Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."?

And then Part (b) is: If the answer to question 2a is "yes," has the applicant demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality? [To be answered by Committee members who vote "yes" in 2a.]

So, open for discussion. Yes, Dr. Giovino.

DR. GIOVINO: The biomarkers of exposure are certainly in the right direction, and certainly the emissions from the HPHCs are clearly reduced, some amazingly so, and I think that's a major technologic advance. I struggle -- I'm in the "leap of faith" zone when it comes to the biomarkers of potential harm, and I know Dr. Hecht said it's not very clear. I'm wondering if I may ask you to clarify what you mean?

DR. HECHT: Well, in contrast to the biomarkers of exposure, which they looked at, which all went down, which is

completely consistent with the constituent studies, the biomarkers of potential harm, the studies were not nearly as convincing, although they mostly went in the right direction towards less harm, but the changes were very small, in most cases not significant. So I think, you know, that is a problem. But in terms of exposure to harmful or potentially harmful chemicals, absolutely it's a yes.

DR. GIOVINO: Thank you.

DR. HUANG: Dr. Rees.

DR. REES: Can I also ask about the potential for dual use? Of course, the claim refers to complete switching, but I don't think we've seen evidence about the potential harms or risks associated with dual use, that is, the combination of exposure to constituents from IQOS, which does include a small number of constituents that are not normally present in conventional tobacco smoke, combined with exposure to conventional tobacco products. I think to have a complete understanding of the implications of switching to IQOS on disease outcomes should encompass the implications of dual use.

DR. HUANG: Okay. Other comments? Dr. Ossip on the phone?

DR. OSSIP: Yeah. This one, I think, is a more

challenging one to grapple with because for some measures and many measures, exposure was, in fact, reduced significantly. For some, there was greater exposure, and those aren't well characterized yet for the HeatSticks.

And, in general, as I'm looking back through the FDA summary, and that was my sense in reading through the materials as well, it's not clear that the constituents in the HeatSticks has been fully characterized.

We also have the finding that consuming 10 HeatSticks exposes users to levels of acetaldehyde and a host of other things, formaldehyde, other constituents that's comparable to smoking one to three cigarettes, so you know, it becomes use-sensitive in terms of the levels of exposures of these.

So, you know, the accurate statement, and again, I know we're not dealing with wording, is that it reduces exposure to a lot of things in combustible cigarettes, it increases exposure to some, and some of this is dose dependent, but that's not the statement that we're voting on. So I'd be interested in hearing others weigh in on that.

DR. HUANG: Thanks. Dr. Thrasher.

DR. THRASHER: I just want to ask a clarifying question of Mitch and others at FDA around this issue of whether we should

be considering dual use at all or whether we should just be considering switching completely as it says in this statement.

DR. HOLMAN: So let me provide two clarifications. I mean, one is just on Question 2a and b. You know, the expectation was that the discussion and the voting would sort of be done in thinking about both parts of the question because Question 2a is essentially do you believe that there's evidence, convincing evidence, that there's a reduced exposure if you completely switch? And then Question 2b is essentially, is it clinically meaningful, right?

And so what we are expecting, to answer your question more directly, is that as you get to Question 3 -- 3b specifically around dual use -- that part of that conversation would be not just explicitly answering the question of high/medium/low, but also part of that discussion would be what do you guys think that really means for the dual users? So that's what we were hoping as we framed these questions. Does that help?

DR. THRASHER: I think so. If I can try and simplify the response, then, hold off on thinking about dual use until the next question?

DR. HOLMAN: That's what we were hoping, yes.

DR. THRASHER: Okay. Thank you.

DR. HUANG: And can I go back to Dr. Hecht, in terms of the use -- the term "significantly," what is your feeling on that?

DR. HECHT: Yeah. I think, you know, if you look at the HPHC list and look at their data, it's significant. I mean, most of them are massively reduced. So I think it is significant.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: So the statement says harmful or potentially harmful chemicals, which is HPHCs, which is what we're looking at. To address the issue that Dr. Ossip raised, there are a lot of chemicals that have a lot -- that are a lot more concentrated. In fact, I don't think I've ever seen 27,900% increase in anything in my life or, you know, in my professional life or at least that percent, that high a percent increase, which was in one of the menthol HeatSticks. But if I understand correctly, none of those chemicals are on the HPHC list, and Steve, I'm going to ask, you know, should we be concerned about any of those that have really gone up? And -- well, I'll leave it at that.

DR. HECHT: Well, there were increases in a number of chemicals, and some of those are probably innocuous, but there

are others that I don't think we know that much about in terms of their full toxicology profile. But I mean, I interpreted this question to specifically relate to the FDA HPHC list, not to the ones -- I mean, none of the contents that went up are on the HPHC list. So that's how I interpreted this question.

DR. HUANG: And that's where -- pardon?

(Off microphone comment.)

DR. HUANG: Can FDA clarify that?

DR. APELBERG: Yeah, I just wanted to say I don't think you should interpret it to be restricted to the defined HPHC list for combusted cigarettes if there's information about other, you know, unique harmful chemicals that, for example, may not be in combusted cigarettes. I mean, I think that's all fair game.

DR. HUANG: Okay, because it is -- this is proposed language, labeling, and advertising language which the general public isn't going to know, which are the HPHCs, so --

MR. ZELLER: But there's also a reason why there's Question 5.

DR. HUANG: Okay.

MR. ZELLER: Question 5 also goes to the issue of consumers understanding the risks, so --

DR. HUANG: But we do have on here "and the appropriateness of the proposed modified risk information."

Dr. King.

DR. KING: Yeah. So my 2 cents or maybe 10 cents, I'll give you a little extra, this one is actually palatable for me, (a) at least. You know, I think that if you look at the actual science and the constituent profile, you know, just thinking about cigarette smoke in itself, you know, 7,000 chemicals, 70 carcinogens, and based on the data that we've seen here as well as for other aerosol products, particularly e-cigarettes, which I know we've been, you know, repeatedly told over the past 2 days that it's closer to a conventional cigarette, but in this instance, I think that it's, you know, very interesting to see the actual constituent profile. And so based on that, (a) to me is actually palatable, and I think that, you know, of course, there could be some finessing in semantics.

I think still there's some wiggle room, and it's some harmful and potentially harmful constituents. And, you know, the scientific studies thing, as I mentioned before, still bothered me because I think you can conduct a study to define, you know, preconceived beliefs quite easily, but you have to look at various factors.

You know, that being said, on (b), I'm a little less convinced, probably more so when you start looking about clinically meaningful outcomes; I think that goes beyond the data that were presented to us by the Applicant. But based on my read and the information presented, I think that (a) is reasonable, but I wouldn't be able -- I think (b) would be premature based on the data we were provided.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: Well, I'll give an 8-cent agreement with you. I think that (a) is easy for me to say yes; (b) I have more difficulty with in that it wasn't so much the clinical issue for me as the substantial. We've gone over multiple times over 20 years using mortality as an outcome, and I'm troubled with mortality being the outcome, but even using that outcome on a public health basis, it doesn't fit, for me, a major change in the health of the public.

DR. HUANG: Yes, Dr. Bierut.

DR. BIERUT: I look at the Applicant's Slide CC-31, which I think is, you know, the summary of the constituents, and I think it gives a good visualization of there's a lot of things in combustible cigarette smoke. There's still quite a bit in this product. Only three are unique to the product. And of

these, many constituents that are shared between this product and combustible; it's less than 10% are higher in combustible cigarettes. So just kind of looking at that scientific evidence of what we're showing, I think our worry is, is that it's not no risk, but this, I think, is very strong evidence.

DR. HUANG: Dr. Blount.

DR. BLOUNT: And just to add to that discussion, to keep in mind that exposure, it's not about the number of chemicals we're exposed to; it's about their toxicological and carcinogenic potency.

And when the presenters -- when the data was presented putting that into perspective about the harm thresholds, there was an objective comparison that found that for those few chemicals where there were higher levels resulting from use of the IQOS, those chemicals of higher exposure had -- the exposures did not surpass the toxicological thresholds of concern.

So just keep that in mind if the answer to Question (a) is one of on balance there are many different, well-known, characterized human carcinogens for which exposure decreased if one moved from the combusted product to the IQOS.

DR. HUANG: Dr. Wanke.

DR. WANKE: Just a quick question to Ben: Given what you had said, I think a lot of the discussion did kind of focus on carcinogens, and we know that a large proportion is cardiovascular, would you say, because I think of it as less dose dependent, and so a 90% reduction in the volumes, say, of chemical exposure doesn't translate to a 90% reduction in, say, heart attack risk. So would you say -- would you clarify it outside of carcinogens but more in other diseases?

DR. BLOUNT: Sure. And with other health endpoints such as cardiovascular endpoints or respiratory irritation, if you compare the impacts of the chemicals that were listed that I'm familiar with that were reduced by 90% or more, in comparing combusted product with the IQOS emission and then also in biomarker data, one would expect there to be -- there were reductions in cardiovascular active -- chemicals with negative cardiovascular outcomes and negative respiratory outcomes, such as acrolein, and the 50 plus 3 chemicals that were higher in IQOS emissions, I'm not aware of a substantial comparability, you know, in their risk for non-cancer outpoints -- endpoints as well.

DR. WANKE: So with the idea of a threshold, would you say it's lower than what you consider a threshold? Because you

used that term when you were talking about carcinogens.

DR. BLOUNT: And I'm speaking of the data that was presented. My expertise is an expertise as opposed to toxicology, so I can't address that.

DR. WANKE: If anybody else can speak to that, that would be great.

DR. McKINNEY: Yeah.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Oh, thank you. I thought you looked at me, so I felt I could talk.

DR. HUANG: Well, yes. If someone can speak to that particular issue, but --

DR. McKINNEY: I was actually going to comment on that because my expertise is toxicology, specifically inhalation toxicology. And one of the first things we do is we do depend on the chemistry, and we look at the literature, and we do a hazard assessment, really looking at the chemistry.

But if you noticed, there were other studies conducted, and that's where you depend on animal studies. There was a cardiovascular study conducted in animals, so these animals were exposed to those chemicals at much higher concentrations than what a human would be exposed to, and that's just the

typical -- that's the typical process. Of course, then, there's biomarkers that you look at as well. And it's the totality of the data that you look at to make an assessment.

I did have a quick question for Dr. Hecht, though, and it's related to biomarkers of exposure and the correlation or association, cessation and biomarkers going down and mortality and morbidity. Can you comment on that?

DR. HECHT: Well, there have been studies on biomarkers of exposure when people stop smoking, so there's a lot of data on that, and they all go in the expected direction at different rates. Some of them decrease very quickly within 1 or 2 days, others may take a couple weeks, but they all decrease significantly when people stop smoking.

Just going back to the Figure 2 on page 11, which is the reduction of 54 HPHCs, so I mean, if you think of the Cramer system, Cramer I, II, and III for the threshold of toxicological concern, most of these compounds in Figure 2 aren't even considered in the Cramer --

DR. HUANG: Where exactly is that?

DR. McKINNEY: He's pointing to the FDA briefing document.

DR. HECHT: Okay. Well --

UNIDENTIFIED SPEAKER: Wasn't this also a slide somewhere?

UNIDENTIFIED SPEAKER: Yes.

UNIDENTIFIED SPEAKER: Yes, it was.

DR. HECHT: So, anyhow, most of these compounds aren't even considered in the Cramer paradigm; they're basically off the chart because they're so active. So I'm not so concerned about the group of compounds that apparently increased, because they're related to a glycerol or menthol. When you look at this list of compounds, this is a horror show.

MR. ZELLER: This is Chemistry Slide 7. FDA Chemistry Slide 7.

(Pause.)

DR. HECHT: I was waiting for the slide. Anyhow, so you know, they're all down significantly. So, to me, that's very convincing.

DR. BIERUT: Steve, you used the word "horror show," so these are the horror show chemicals?

DR. HECHT: Yes.

DR. BIERUT: Okay.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: So there's obviously thresholds with some of these, I mean, and just to understand, it's possible that mercury, ammonia, or acrylamide might be above a threshold, it

might be active, but I don't really know that.

DR. HECHT: Very unlikely.

DR. GIOVINO: Variable?

DR. HECHT: Unlikely, very unlikely.

DR. GIOVINO: Unlikely. Okay.

DR. HUANG: All right, any other -- you know, again, for me, I also -- we do have in part of this in terms of the language, and I know we'll get to it in some of the later parts as we're discussing this. Again, it's a scenario of switching completely, and we will talk about the sort of implications of how people perceive this statement, but any other comments?

(No response.)

DR. HUANG: Are we ready to vote? Okay. So let me see here. We will now begin the voting process for Question 2a. Please press the button on your microphone that corresponds to your vote.

(Committee vote.)

DR. HUANG: Okay. And, Dr. Ossip, what is your vote?

DR. OSSIP: I, in a conflicted way, am going to land on no.

DR. HUANG: Okay. All right, everyone has voted; the vote is now complete and locked in. So the vote is 8 yes,

1 no. I'll go back to this side maybe.

Dr. Thrasher.

DR. THRASHER: Yeah. I mean, the data are compelling to me on exposure both in the human studies and nonhuman studies.

DR. HUANG: Dr. Weitzman.

DR. GIOVINO: I concur with Dr. Thrasher's statement.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I concur and just would like to add, you know, we don't know the full possibilities of harmful or potentially harmful chemicals, but based off of what we have before us, I voted yes.

DR. HUANG: And this is Phil Huang. I voted yes. I do have concerns about the appropriateness of it. I think the statement itself is justifiably yes, but I have problems about the implications that we can talk about later and how it's interpreted.

DR. GIOVINO: This is Dr. Giovino. I voted yes. I appreciated Dr. Hecht's and Blount's expertise on this. I do think the biomarker studies are compelling, the biomarkers of exposure.

DR. MERMELSTEIN: And this is Robin Mermelstein. I agree totally with Dr. -- what Dr. Giovino just said and appreciated

the expertise that we had in the room, and the data were convincing here.

DR. BIERUT: This is Laura Bierut. I concur with my colleagues' comments.

DR. O'CONNOR: This is Richard O'Connor. I concur. The data were very convincing.

DR. HUANG: All right, so now we are -- oh, Dr. Ossip. I'm sorry.

DR. OSSIP: Yeah. This is actually a difficult one for me, so I made my notes on each of the three possibilities, and I can reflect the compelling weight of the evidence that we saw along with some of the concerns that were expressed around the table, and my final vote just landed on kind of a direction of do no harm. Since I had doubt in some areas, I voted no.

DR. HUANG: All right, thank you.

And I think we are going to have a little more discussion, then, on 2b, so we're opening it up for discussion for the second part. Any comments on 2b?

Yes, Dr. Weitzman.

DR. WEITZMAN: Well, I'd love to hear some feedback from members of the Committee on what they think "substantial" means.

DR. HUANG: Dr. Bierut.

DR. BIERUT: What I'm going to say is do you live longer and have a better life with less disability?

DR. WEITZMAN: Thinking of that in terms of individuals rather than a population basis.

DR. BIERUT: Yes, I'm thinking at an individual level, not a population level, because I think that the other questions will deal with the population level. So I'm viewing this at -- with the idea of a smoker who transitions to this product.

DR. THRASHER: This is Jim Thrasher. I'm viewing it more at the population level and it really being something that's more meaningful in terms of the broader patterns of use in this particular context.

DR. HUANG: Other comments? And I would probably --

DR. WEITZMAN: And that's really helpful.

DR. HUANG: Yeah, I would probably be more inclined to be looking at the population level also.

Dr. Giovino.

DR. GIOVINO: I think I'd agree with that because it's morbidity and mortality, usually public health, epidemiologic terms. I do have to interpret this question as holding everything constant. It's very possible that, you know, other

things may happen that either contribute in a negative way, but I'm going to assume that this just means without compensation by, I don't know, other companies promoting other cigarettes in different ways or with the same company promoting cigarettes in different ways. You know, in other words, absent untoward side effects is how I'm interpreting this. I don't know if that makes sense to the Committee, but --

DR. APELBERG: Can I just --

DR. GIOVINO: There's --

DR. APELBERG: Yeah, just --

DR. GIOVINO: I struck a nerve.

DR. APELBERG: Well, no, just to make a clarification. We actually pulled part of this language out specifically from the statute, and in the statute, it's in the context of individual tobacco users. I mean, what we're really looking to understand is that if you -- if a smoker switches, gets the reductions in exposure that you anticipate them receiving, does that -- is that likely to translate to a measurable and substantial risk reduction for that individual, for individuals like them?

DR. HUANG: Dr. Rees.

DR. REES: Well, if we're going to -- if it has to be considered at an individual level, then I think we would have

to ask the question for whom, for younger smokers, for older smokers, and so on.

DR. HUANG: Dr. Fagan.

DR. FAGAN: I think Dr. Zeller --

MR. ZELLER: Just one additional clarifying point which we hope doesn't add to confusion. To the degree that -- and we won't put Dr. Hecht on the spot, but if he wants to weigh in on this, he can. To the degree that the Committee thinks that in the context of this question you want to consider additional biomarkers, meaning biomarkers of harm, as you grapple with this question, you can do that.

DR. HUANG: Okay, Dr. Fagan.

DR. FAGAN: I'm going to take a slightly different position than Dr. Giovino because when I look at the word "translate," I'm thinking of real-world environment and so -- and I'm thinking real-world environment for different groups of people.

And so when I'm looking at this question, I have to take that environment into consideration with regard to reduction in morbidity, in mortality, because this word "translate" has powerful meaning to me. So I just wanted to voice that thought.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: But, again, it's on the individual level, right, Dr. Fagan? So I'm missing the -- you know, the environmental context is not something I'm understanding. I must be misunderstanding what you're saying.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: So, I mean, I think about data for individuals who quit, and that's not quitting, so this is a very conditional statement. It's conditional on that they're getting the reduction of exposure, so you're already talking about people -- you're not talking about dual users necessarily but -- so if indeed they completely switch, if indeed you've gotten -- so it's all conditional on the reductions of exposure.

You know, there's another data that we have that does show that people show remarkable cardiovascular and other pulmonary improvements. So, on an individual level, I think it is potentially likely that, you know, individuals will experience changes, improvements in health.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Yeah, I'd like to ask that the Committee consider the terms "reasonably likely," but also to echo

Dr. Mermelstein, is biomarker changes with smoking cessation and the data that was presented in the biomarker changes with complete switching.

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah. So let's take cigarettes as an example, and people who are smoking, like, 10 cigarettes per day versus those who are smoking 20 cigarettes per day. And you take African-American populations, for example, who if they're smoking 10 cigarettes per day, their risk is very different from a Caucasian who is smoking 10 cigarettes per day.

So I'm looking at this statement that demonstrated that the reductions in exposure -- and people can have the same levels of exposure and we see different disease outcomes.

And so with the product that has been presented, I don't know what is to be true, and so I just wanted to use the kind of cigarette example as to my way of thinking around this whole thing.

DR. HUANG: Other comments? Dr. Wanke.

DR. WANKE: I'll just add that if we are considering the biomarkers of potential harm, I thought there was agreement or at least a suggestion that the biomarkers of exposure seemed compelling, but biomarkers of potential harm were not

compelling. And so if you are considering that as the evidence for the reasonably likely and measurable and substantial reductions, that the biomarkers of potential harm did not seem compelling.

DR. BIERUT: Can I ask about that because I thought that the -- I'll use the word again "horror show," which I thought were biomarkers of harm were greatly reduced.

DR. HECHT: So most of the biomarkers of exposure went down, and most of those are related to the "horror show" chemicals, so that was completely consistent.

I would go to the CC-64, which talks about how cigarette smoke causes cancer. They show carcinogens and genetic damage as the initiating event, and the carcinogens are the ones that we were talking about in the first part of this question, and those are -- human exposure to those are quantified by the biomarkers of exposure.

Then when you look at tumor progression and invasiveness and inflammation, so there's a lot of evidence in the literature that inflammation, tumor promotion, oxidative damage, it's all basically the same thing called by different names. That whole process is critical in enhancing the effect of the carcinogens and ultimately resulting in cancer. And we

didn't see much of an effect on the biomarkers of potential harm, for example, those that are related to inflammation. So I don't think, when you consider this mechanism that they presented, that other data really supports the reasonably likely.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I can't put my finger right now on the table, but I do remember seeing data about interleukins and white blood cells being significantly elevated. If I have that correct, then I think it somewhat contradicts what you just said.

DR. HUANG: Dr. McKinney.

DR. HECHT: I've forgotten where that was, but there was a whole list of biomarkers of potential harm, most of which did not change significantly.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Okay. I think that's an important point, important question. Perhaps we can have a slide. I'm asking for the Applicant to answer your question.

DR. THRASHER: Dr. Hecht, can I ask a follow-up question while they're getting the slides up? You know, one of the issues that we raised yesterday around these data were about

whether they have statistical power or if enough time has elapsed for these kinds of outcomes to really meaningfully reflect exposure. I don't know if I got a very clear answer, but I wonder what your opinion is on that.

DR. HECHT: Well, you know, it may be that with a larger study or in particular longer periods of time, you might see a significant change.

DR. THRASHER: But would you expect these biomarkers to change over such a short period of time?

DR. HECHT: The data in the literature, for some of them where there is data, is kind of mixed. For the biomarkers of oxidative damage and inflammation, there's some studies that show a decrease on smoking cessation that's fairly rapid, and there are others that don't show anything. So I don't know how to answer the question.

DR. PEITSCH: Mr. Chairman, if I may?

DR. HUANG: Sure, yes.

DR. PEITSCH: Okay, thank you very much, Mr. Chairman.

I would like to come back to the sequence of slides in my core presentation, especially starting with CC-67. So in this slide I have shown that the bronchoalveolar lavage fluids of smokers -- this is data from the literature -- actually has an

increase in macrophages and neutrophils. It has a statistically significant increase in the biomarkers of inflammation; especially, interleukin-1 beta was one of the drivers of the type of inflammation that is caused by nanoparticles that are carbon based and solid when they are inhaled. So this is the fundamental -- this is the difference between smokers and nonsmokers.

Now, interleukin-1 beta -- Slide 2 up, please -- has been proven in animal models, and we know this for over a decade, that interleukin-1 beta is actually a driver of tumor invasion and proliferation. We know this because the mouse, when the interleukin-1 beta gene is actually knocked out, these mice do not grow metastases, first of all. And in the same publication that was written by Voronov, we actually also see that these mice do not actually die from their cancer.

Now, that is a mouse study, we know this for over a decade, and it is just last October that a publication came out from a very large human study, the CANTOS study, where people were given a drug, this drug was canakinumab, which is a monoclonal antibody against interleukin-1 beta and therefore takes interleukin-1 beta out of the circulation. This drug has been proven and demonstrated to reduce both the incidence and

the mortality from lung cancer in a dose-dependent manner. And this is what this graph on the right shows, where the placebo control is the right, is the dark red upper graph, and then the three doses, 50, 150, and 300 µg of canakinumab show a reduction in the incidence.

Now, then, the question back, how does the animal model inform us of what is actually happening, and how does that tie and translate to the human situation, something -- an experiment we cannot do in humans. So if I may bring Slide 3 up, please.

So what we see is that in the ApoE mice in our longitudinal 8-month study, that interleukin-1 beta, interleukin-6, KC, which is the ortholog of interleukin-1 in humans but this is the mouse version of the same gene, okay, and MCP1 behave exactly as expected, in other words, activated by smoke exposure, not activated by 8 months of IQOS aerosol exposure and the reverse towards a longer cessation path upon switching to IQOS.

This data is not unique to the ApoE mouse. We've seen the same thing in the A/J mouse studies -- Slide 2 up, please -- where we basically see that, on the right in this large table, you can identify interleukin-1 beta, you can see interleukin-6,

you can see KC, interleukin-18, by the way, which is also transformed by NALP3 inflammasome, etc., all follow exactly the same mechanism as in humans.

Thank you very much.

DR. HUANG: Let me go back to Dr. Hecht's prior statement, that you were saying you did not think it was reasonably likely with respect to the biomarkers of potential harm.

DR. HECHT: Right. I don't think that data is particularly convincing, even though they all go in the right direction, but the changes are very small. In most cases, they're not significant. So maybe the studies were not carried out for long enough, maybe the conditions were wrong, maybe the studies weren't large enough, maybe with further research you would see a more convincing change. But just based on what we've been presented, I don't think the overall picture of the biomarkers of potential harm was very convincing.

DR. HUANG: Okay, thank you.

Other comments? Dr. Blount.

DR. BLOUNT: Just one comment about respiratory irritation: That is something where we didn't have, in the human studies, a biomarker specific to that, but something to keep in mind, looking at the emissions data and the exposure,

the biomarkers of exposure, where chemicals such as acrolein are highly irritating to the lung and a marked reduction in that exposure. The few chemicals that do increase in the IQOS emissions are not known respiratory toxicants, and so when factoring this in from a non-cancer standpoint, just one other issue to keep in mind.

DR. HUANG: Okay. Dr. McLoughlin.

DR. McLOUGHLIN: Thank you. When I read this question, and I've been a little stuck on the "reasonably likely" piece, in my mind it translates to how much confidence would I have that it is to translate to measurable and substantial reduction in morbidity and mortality, and I can't find that confidence to the level with the data shown.

DR. HUANG: Okay. Were there any other -- Dr. Bierut.

DR. BIERUT: Can I ask, which biomarkers of potential harm are you looking at? And so which group was that, because we had the exposure that were very significantly reduced.

DR. HECHT: Right. So there was a slide that had all the --

DR. GIOVINO: Fifty-seven.

DR. HUANG: CC-57.

DR. BIERUT: Aren't these really just biomarkers, again,

of -- so this was a short 90-day study, so the ones with the lipid metabolism, inflammation, airway impairment, those are the ones that you are concerned about?

DR. HECHT: Yes.

DR. BIERUT: Okay.

DR. HECHT: This is CC -- okay.

DR. HUANG: CC-57.

DR. HECHT: CC-57 in the book.

(Pause.)

DR. HECHT: So, yeah, they went down, but if I recall correctly, these were not significant, so, you know.

DR. HUANG: All right, any other comments?

(No response.)

DR. HUANG: Are we ready to vote? Okay. And, Dr. Ossip, since you voted no on 2a, you do not vote on 2b.

So, again, let me see, we'll begin the voting process for Question 2b. Please press the button on your microphone that corresponds to your vote.

(Committee vote.)

DR. HUANG: Has everyone voted? Two yes, one abstain, five no. Maybe we'll start at this end. No, that side.

DR. O'CONNOR: So this is Richard O'Connor. So I voted

yes in the conditional sense, in the sense that given the first part is true, given the complete switching and the observed reduction in biomarkers of exposure, is it reasonably likely that that would result in disease, and I thought that was -- the burden for that, for me, was met, though I have larger concerns about the reality of that that we can get into later.

DR. BIERUT: I voted yes because I -- again, I believe that there's this reduction in the harmful effects, I think there's reduction -- or there's reduction in the exposure to these harmful chemicals overall. There's the reduction to the multiple different types of particle sizes.

And I'll specifically comment about Slide CC-57, which showed no statistical significance with abstinence at 90 days, though that I think of as very -- you know, I know that abstinence causes this, and I think that this study of 90 days, short period of time, I didn't weigh that as heavily.

DR. MERMELSTEIN: This is Robin Mermelstein. I abstained. I followed the logic and I felt that -- I do believe in the reduction of exposure, and I felt that that would, indeed, lead to changes, certainly on an individual level. I think just some of the harm issues versus the exposure, I was just not as confident about, although I was very reluctant. I lean far

closer to the yes side here than the no.

DR. GIOVINO: This is Gary Giovino. I anchored on the words, "Has the applicant demonstrated," and I didn't think they did.

DR. HUANG: This is Phil Huang, and similarly, yeah, I did not think there was adequate demonstration of that.

DR. FAGAN: I voted no. I think reduction in exposure is not equivalent for all populations. In terms of leading to disease outcomes, there are different pathways to disease outcomes for different groups.

There was a recent paper that just came out from a team at NCI, Ryan et al., that showed some of that data, different pathways for different racial/ethnic groups related to lung cancer specifically, but I think it's important for us to take into consideration and also take into consideration that, you know, two of the three products that are being under consideration are menthol products, and I also took that in consideration in my judgment.

DR. WEITZMAN: This is Michael Weitzman. I voted no, although I had great difficulty with this. These were not measures of exposure. These were measures of biologic reaction, and virtually all of them were not statistically

significant, although they went in the right direction in most cases. So I didn't think that one could say that it was reasonably likely.

DR. THRASHER: This is Jim Thrasher. I also voted no. I guess I was focused on the substantial reduction in this case, and I assume that if the reduction was substantial, then it would show up statistically, and maybe it will with longer follow-up and greater power so that the Applicant can demonstrate this. And I'll say, not being an expert in this area, I certainly lean on the information that Dr. Hecht provided to the rest of the group.

DR. HUANG: Okay. We're going to now take a 30-minute break for lunch, okay? So, Committee members, please remember there must be no discussion of the meeting topic during lunch either amongst yourselves, with the press, or with any members of the audience. Thank you. We'll reconvene again in this room 30 minutes from now at 12:20.

(Whereupon, at 11:50 a.m., a lunch recess was taken.)

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

(12:20 p.m.)

DR. HUANG: So we are now up to Question 3. Question 3 is to discuss evidence regarding the likelihood that existing combusted cigarette smokers will initiate use of the IQOS system, completely switch to IQOS, and/or become long-term dual users of IQOS and combusted cigarettes.

So Question (a) is: What is the likelihood that U.S. smokers would completely switch to use of the IQOS system? And we have options: high, medium, and low.

(b) is: What is the likelihood that U.S. smokers would become long-term dual users of IQOS and combusted cigarettes? High/medium/low.

DR. GIOVINO: I have a question.

DR. HUANG: Okay, Dr. Giovino.

DR. GIOVINO: Just a question of clarification. Does completely switch mean 95 to 100 or 100%?

DR. APELBERG: I interpret it to be 100%.

DR. HUANG: Okay, any comments? Yes, Dr. Mermelstein.

DR. MERMELSTEIN: So, to me, this question is under what environmental context, because whether people can completely switch or not is a function of not just giving them the

product, but everything else that's going on in the environment. And you can create an environment where it's easy for people to switch, an environment where they're less compelled to switch. What we've heard so far is that people on their own, and we know this from e-cigs, are -- and other products -- they're not good at making behavior change. They need some support, they need some help, and they need an environment that supports that behavior change, and this is a behavior change.

So are there assumptions behind how we answer this, because you can create environments where it's a lot easier to switch than other environments. So it's hard to just answer this in the absence of understanding what environmental supports are around there.

DR. HUANG: Dr. Rees.

DR. REES: I very much agree, and I think now that we're talking about smokers, I think we need to understand the heterogeneity of the smoking population. And, you know, we have touched on gender and race and ethnicity, but we haven't touched on income strata, and we see, you know, one of the greatest disparities in the prevalence of smoking is among those with the lowest income level in the United States. If

we're to have impact among that population, we would hope that IQOS would be an acceptable alternative and that use of IQOS would translate into exclusive use or complete switching, but we haven't seen evidence on the interest in use of this product among those of the lowest income strata in the United States.

DR. HUANG: I mean, I would guess it's in the real-world setting. I mean, we're talking about the whole context for a lot of this discussion is the proposed labeling and advertising for the modified risk tobacco product, you know, being out there and the wording that we've been voting on is -- you know, includes the situations where there's been switching completely.

DR. REES: Well, we can assume that, but the data has not been presented to us. And so, you know, I think that leaves a question up, I think, that needs to be considered by the Committee.

DR. THRASHER: I mean, a related point is how most of the studies that we've reviewed have provisioned IQOS for free along with the HeatSticks, and so for those low-income smokers, that initial cost may be a significant barrier.

DR. HUANG: Yes, Dr. McLoughlin.

DR. McLOUGHLIN: Thank you. And just to add to what

you're saying, I work with a lot of vulnerable populations, I do a lot of work with folks with serious mental illness, and I have similar concerns. And, you know, the rates of tobacco use in folks with serious mental illness is really high.

DR. HUANG: Yes, Dr. Blount.

DR. BLOUNT: And does this question -- I assume it relates to where things are today with combusted products. Do we put out of our mind the possibility of a reduced nicotine cigarette in the future?

MR. ZELLER: Yes.

DR. HUANG: Other comments? Yes, Dr. Mermelstein.

DR. MERMELSTEIN: So, you know, this is a really tough question in the sense of, over time, there's also penetration, there's use familiarity. And so, you know, as some of the data showed, that interest and use increases over time, too. So this is a case where the probability of switching might increase over time, and it's hard to say.

DR. WEITZMAN: I mean, another confounder is this remarkable epidemic of e-cigarettes, and that may change the whole landscape over the next decade or so of nicotine delivery systems. Plus, I don't think we have any data. I don't know if the Applicants do, from other countries, about rates of

change, but I wouldn't know how to answer this question other than speculatively.

DR. HUANG: Dr. Thrasher, do you have a question?

DR. THRASHER: Yeah. I mean, I guess I was going to raise the issue of the e-cigarettes in this context, where I don't know if we have much information on substitutability of e-cigarettes for this product, how this product may be appealing in a way that would be different from the appeal of e-cigarettes, although I know that the marketing materials and the way in which the product is framed is to try and frame it as a tobacco product so that it may capture some of the people. But I didn't sense that we had any data to really be able to assess the extent to which it would be capturing a different segment of the smoker market.

DR. BIERUT: And I had a question about how to interpret this question. Do we mean if you use the IQOS system, what is the likelihood that you would completely switch, or in general in the whole smoking population, what is going to be the -- where we think the penetration is going to be? And I don't know if there's -- could the FDA clarify which you meant?

DR. HOLMAN: Yeah, I'll make two clarifications. It's the latter of what you just described that we had in mind.

DR. BIERUT: So in a general population?

DR. HOLMAN: Correct.

DR. BIERUT: Okay.

DR. HOLMAN: And then to clarify the question or comment earlier, we're asking you to make a decision today. It's hard to know what the marketplace is going to look like in 1, 2, 3, 4, 5 years.

But one of the things I just want to remind you guys is that if we were to issue a marketing order for a modified risk tobacco product, it is time limited. It has to be reevaluated or reassessed, so this is -- you know, if you were to make a recommendation that's not from here to eternity, you know, the likelihood is high, medium, or low. It's what you feel like that likelihood is today.

DR. WEITZMAN: Clarify on that?

DR. HUANG: Yeah, Dr. Weitzman.

DR. WEITZMAN: So you're asking us, if the application is approved, do we think that in a very finite period of time new smokers and those who currently smoke cigarettes are going to switch? Is that what this question is really trying to get at?

DR. APELBERG: Partially. I mean, what it's trying to get at is, based on the evidence that you've seen, like you said,

if an MRTP order were authorized which allowed claims to communicate this --

(Off microphone comment.)

DR. APELBERG: Yeah, what is the -- basically, the relative likelihood that you would see the kind of behavior, you know, that would be more beneficial versus less beneficial. I mean, essentially, that's what we're trying to get at here, the complete switching versus the dual use over some constrained period of time. It's not like some 6 months, 1 year, you know; it's really in general.

DR. HUANG: And, again, that's why the proposed language for the MRTP has been complete switching scenarios. And so you know, that's part of -- has been part of my concern about the language. I mean, in terms of the data that we've seen, we're talking about when you're defining at 100%, you know, maybe 6, 7, 8% of complete switching in all of the data that we've been presented.

Yeah, Dr. Mermelstein.

DR. MERMELSTEIN: So does this also assume, given a complete marketing package, because whether people switch, so given the marketing approach that we've had described to us under those assumptions that they launch that and what would be

the probability of success in that?

DR. APELBERG: That's correct. Based on the proposal from the Applicant on their marketing and advertising and labeling plans, what do you believe the likelihood is that -- you know, that there will be complete switching? You know, I think the other piece of this is just there is some experience outside of the United States and how extrapolatable you think that is to the United States in terms of complete switching as well, is what we're interested in hearing your thoughts on.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: I'm hard pressed to think of any change that rapid in behavior of something that's gone on for a long period of time in any area. I can't picture, in the next couple of years, 100% of people, whatever we mean by 100%, because it's all of sudden giving up a longstanding behavior and starting something differently.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Well, actually, this is -- this was much easier. This was almost a no-brainer behavior change, but when filter cigarettes came on, that innovation took off pretty quickly. And when low tar cigarettes, you know, supposed low tar cigarettes came on, that innovation took off pretty

quickly, but that was just a matter of purchasing a pack. As I'm thinking of it, that wasn't a matter of buying this big device and then learning how to use it and getting some coaching.

I mean, what happened in Japan, I think, is quite interesting. We never did get the data on 100% switching in Japan that I had asked for, but you know, there's something big happening in Japan, and there's a lot of people initiating in Japan obviously.

But, again, people ask, well, Japan is cultural. You know, a lot of that is cultural and, you know, one might hypothesize, in America we might see differences based on the strength of their smoke-free air law in the state or in their community, which may reflect both getting used to, you know, being considerate but also, you know, just maybe supporting it in the first place. What I do wonder and I never -- I wonder out loud, I guess. Will Philip Morris work to, you know, get laws that allow IQOS indoors? I mean, I think that's part of -- if we think about this question, I think that might be part of, you know, an important variable. I'm not saying I support that; I'm just objectively asking it.

DR. HUANG: I mean, I think what we're supposed to be

looking at is the evidence that we have been presented at this point.

DR. WEITZMAN: I was just going to say, as a person who studies hookahs, that many, many cities that have clean air acts allow hookahs to be used as long as they are tobacco free. So it's going to require a lot of work with lots of different governments.

DR. HUANG: And, I guess, at the community level, I think of -- you know, I think we have smoke-free indoor air and policies like that. I don't know that opening it up to allow that indoors, it would change anything or make it more likely that people would switch. I mean, just because it's just -- it would keep, I think, for our -- at the local level, the preference is to keep all of these places still with the policies, but it's just where they are outside they would, you know, have the opportunity to use other products.

DR. GIOVINO: I don't see them changing, but -- you know, in case they do, then you're right. Let's assume that that's not going to change for this extra slice. I'm sorry.

DR. HUANG: Yeah.

DR. APELBERG: Can I just make a request? I think, in this discussion, it would be useful for us at least to hear,

you know, some of your discussions about the Japanese experience, like Dr. Giovino talked about in particular in that postmarket consumer purchasing study.

And then I think also, you know, the pharmacological studies, the studies that looked at nicotine exposure and, you know, sort of if it will appeal to smokers, I think, you know, to the extent that you all have thoughts on that, that would be helpful.

DR. HUANG: Dr. Rees.

(Off microphone response.)

DR. HUANG: No, okay. Dr. McKinney.

DR. McKINNEY: If we do what Ben is suggesting and think about -- Dr. Apelberg, sorry, what he's suggesting and think about what happened in Japan, I think the question that Dr. Giovino asked about the 100% switching, there may be a slide that can be presented, some data that can be shared by the Applicant, I think.

DR. HUANG: Oh, okay. Do you have some -- because you presented some this morning on 100% switching, but it was U.S. smokers that switched completely, and we were up to -- it was what, at Week 4 to 7% then back down to 6% at Week 6.

DR. GILCHRIST: So Slide 1 up, please. So you can see in

the top row the 100% or complete switching to IQOS, and the row below that is exclusive use, which incorporates 95 to 100%. So in the case of Japan, you can see that 68% is 100% IQOS use and an additional 4% in the 95 to 100% bracket.

DR. HUANG: Yes, Dr. Giovino.

DR. GIOVINO: I was also -- and it may be too late for this. Thank you for showing that. I was also interested in, when you showed the monthly data, if the percent, you know, what happened with the trend in 100% over the months, because it was becoming more and more -- it seemed like it was disseminating.

DR. GILCHRIST: Yeah. Antonio.

MR. RAMAZZOTTI: What we showed was still days on 95 to 100, but you can extrapolate the same difference that you see here to apply also to that progression that we showed. So, in general, to summarize, what we see is that if you take the exclusive usage defined as we did, at 95 to 100, there is always a difference between four and six percentage points about those who really go to complete switching of 100%.

DR. HUANG: Dr. Ossip on the phone, I believe, has a question or a comment.

DR. OSSIP: No, that's okay. That's already been asked by

others. Thank you.

DR. HUANG: Okay. Yeah, Dr. Holman.

DR. HOLMAN: Could I just ask two clarifying questions? First, what is -- so you have the *n*'s up there. Who is the study population here? Was the survey done for the entire population of these countries, or was this your registry of consumers in each country that had some level of interest in IQOS? So I was wondering if you could clarify that.

And I was also just wondering if you briefly state -- so the survey results are from last August -- how long the product was on the market in each of these five countries at that time in August.

MR. RAMAZZOTTI: Thank you. So the population is IQOS purchasers who registered their device after buying it and agreed to be part of this panel. As I was saying yesterday, just to give you a size of the pond in which we recruited these people for Japan, 70% of the total IQOS purchasers registered the device, and that's from where we draw the random sample that then is of these people that are invited to be part of the panel. And we recruit new adult smokers who bought IQOS every month to keep the panel representative of our sales progression.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: Thank you, Antonio. And do you know what percent of Japanese smokers ever purchased, or at least as of the time of the survey, had purchased an IQOS device?

MR. RAMAZZOTTI: You mean out of the total population?

DR. GIOVINO: Of all, yes.

MR. RAMAZZOTTI: Adult smoking population?

DR. GIOVINO: What percent of all smokers.

MR. RAMAZZOTTI: So I'm going to give you an answer and a bit of a disclaimer quick. We have data showing that the penetration of our devices within the adult smoking population is about 30%, but quite a few people own more than one device, and so it's very difficult to make -- to give you a number which is precise.

DR. HUANG: Yeah, this data is very -- not comparable to what we're talking about. If this is IQOS purchasers who registered their device, I mean, they're already using it. This is not more of a population-level sort of percentage.

MR. RAMAZZOTTI: And if I may comment to your question, Mr. Chairman?

DR. HUANG: Sure.

MR. RAMAZZOTTI: That's why I gave the example of Japan.

In Japan, since 70% of all IQOS purchasers have registered their device and we source from that a sourcing factor, the recruitment for the panel, we believe that this panel is reasonably representative, although we cannot exclude that within the 30% that doesn't register the device there could be slightly different trends.

I have still to answer one question from Dr. Holman about how long the product has been in the markets in different countries. So, in Japan, we started initial launch in September 2015. Slightly later in Italy, but more or less at the same time. In South Korea, we launched in May of last year, 2017, and in Switzerland, also, if I remember correctly, we launched at the end of 2015. In Germany, also at the end of 2016. So the markets where the product has been longer present is Japan and Italy.

DR. HUANG: Okay, Dr. Thrasher.

DR. THRASHER: I guess I just want to clarify that one of the key distinctions between Japan and the U.S. is the presence of e-cigarettes on the market in the U.S., and they're only available by prescription, at least if they contain nicotine, in Japan. And so one of the key, kind of, competing products, competing potentially reduced harm products not on the market

in the Japan, correct?

MR. RAMAZZOTTI: That's correct and -- but the markets that you see in front of you on this slide have a different penetration and popularity of e-cigarettes. So in South Korea, there is quite a penetration of e-cigarettes and usage of e-cigarettes. So is in Italy and in Switzerland and in Germany. But you are correct; in Japan they are only available under prescription.

DR. HUANG: Yes, Dr. Wanke.

DR. WANKE: So I'm wondering how to reconcile this data with the data that was presented from the postmarket study results from Dr. Anic's presentation, Slide Number 13, where it said that the percent of current heat-not-burn users that concurrently use one other tobacco product was 91.8%. At least one other tobacco product, and they break it out by product type or cigarettes, including roll your own is 84.9%, and this is in Japan. So how do I reconcile that? Maybe a reminder of how this study population is different.

MR. RAMAZZOTTI: May I, Mr. Chairman?

MR. ZELLER: Dr. Wanke, are you asking the Applicant to respond? Or is it a question for the Committee?

DR. WANKE: I think it's -- I guess it was a question,

since this is an FDA presentation, I'm asking FDA --

MR. ZELLER: Yes, ma'am.

DR. WANKE: -- to help clarify.

DR. APELBERG: Yeah, I can jump in. This is based on our own analysis of data that were submitted by the Applicant, which was a cross-sectional survey. I think this is from one time point in 2016. So the survey was, I believe, among 2,000 -- 2016, but the number of people that were in this. The survey was among 2,000 individuals, and so this is just among the 71 individuals who reported use of heat-not-burn products. The one thing to keep in mind is, I mean, it's a pretty small number.

DR. WANKE: Right.

DR. APELBERG: But this is something we wanted to explore because we had received that data from the Applicant. I don't know; they might have more information about more recent data, but that's where that came from.

DR. WANKE: Thank you.

(Off microphone comment.)

MR. RAMAZZOTTI: For this discrepancy?

DR. HUANG: Sure, if you could --

MR. RAMAZZOTTI: Thank you.

DR. HUANG: -- respond to that.

MR. RAMAZZOTTI: I think what we are looking at is a study which had a very different purpose with a very different reference population and recruitment and methodology. More importantly, in all the data that we shared with you yesterday and today, you have seen us defining the IQOS of -- the IQOS usage according to different switching categories.

And what we have vividly seen in our data is that the full switching is time dependent, meaning it takes a few weeks of adaptation until an adult smoker can fully switch, and this is faster or slower depending on the adult smoker himself. So in the cross-sectional study, beyond the fact that this is a very small basis, 21, we cannot control and we didn't control in the same follow-up of IQOS users that we found in the general population sample. When did they buy the device? So we don't know if they owned the device for 1 day or for 1 week or for 3 weeks or for a month and it could continue. So, basically, a cross-sectional study for a product which is at launch is not able, in the first stages, to categorize the switching of such a product in the right way.

I expect that cross-sectional studies and the panel data that we showed a minute ago will converge over time when there

is a standardization of the penetration. But in the first phase of launches, cross-sectional studies are excellent at defining and measuring the incidence and prevalence but not switching to this product, which is time dependent and quantity of product dependent.

DR. HUANG: I guess I just see Slide CC-84 being the most relevant to us in the United States but -- Dr. Rees.

(Off microphone response.)

DR. HUANG: Dr. Fagan.

DR. FAGAN: Yeah, I have to agree with Phil. I mean, we've got two different denominators, which I think explains why we see these differences. For CC-84, the denominator is adult daily smokers; is that correct? Smokers are the denominator for CC-84. And then for the data shown by country, the denominator is those of the IQOS users, which might explain these huge differences we see in switching. So we're dealing with -- complete switching, I think, was said to be about 5.9% for the U.S., and we just saw the data for the other countries, but the denominator difference, to me, explains why we see what we see.

DR. HUANG: Yeah. And those other countries' data just are not comparable to this.

Yes, Dr. Rees.

DR. REES: So my point that I had in mind earlier, and again, I think, you know, I made the comment yesterday, the Japanese cigarettes are quite different to U.S. cigarettes, and I think it's conceivable that this shift or the transition from a conventional Japanese cigarette to the IQOS device is a lesser step.

It's easier to accomplish than perhaps changing from a U.S. cigarette to IQOS, given different chemosensory qualities in the product. I think that that contingent is supported by the data that were presented yesterday on abuse liability measures. The initial response among U.S. smokers to IQOS was that it is less preferable, that it is not as satisfying, that the enjoyment of the effects and psychological reward are not as would be expected with a conventional product, which, to me, suggests that switching is going to be a greater challenge for U.S. smokers than it might be for Japanese smokers.

DR. HUANG: Right. And, again, the U.S. data that were presented, and even what was presented this morning, it was like 6% when we're talking about 100% switching. I mean, I think this is sort of an easier question, but I am being told we need to call the question to move on, so can we -- is

everyone ready to vote on this? Again, for me, this one's an easier response in terms --

(Off microphone comment.)

DR. HUANG: Okay. So what is the likelihood that U.S. smokers would completely switch to use of the IQOS system? Okay, for high/medium/low, it's above your voting button. Is that right?

MS. COHEN: Okay. So for high/medium/low, you have the three choices on your voting microphone that's obvious, but if you want to -- if you choose not to vote or abstain, just don't push anything, and we'll ask you, after everybody else has entered their vote, to raise your hand if you abstained.

(Committee vote.)

DR. HUANG: All right, has everyone voted? And so Dr. Ossip, how do you vote?

DR. OSSIP: Low.

DR. HUANG: All right. Any abstentions?

(No response.)

DR. HUANG: Okay, let's see the results. Okay, so it's two middle, seven low. Total votes, nine.

All right, let's start with Dr. O'Connor.

DR. O'CONNOR: Yes, I went with the middle category. The

overall uptake appeared to be relatively low, but it appeared to be relatively high conversion, so the people who liked it tended to stick with it, and so that gave me some confidence that you get decent uptake and complete switching in the population that at least used it.

DR. BIERUT: Laura Bierut.

I think I weighed it somewhat differently because my understanding is that we were supposed to weigh it on the population of smokers' level, and so I agree that if you take it up, you're more likely to go on, but I'm not sure how good the take-up is going to be.

DR. MERMELSTEIN: This is Robin Mermelstein, and I put medium because the U.S. population is very heterogeneous in terms of smokers, and I think that there are going to be some subsets who will uptake this pretty quickly, and there may be an adult subset who you don't want them having a long-term history of combustible cigarettes, and they're a good population, and I think the marketing is targeted. And then I think there are also older cigarettes -- older smokers who have had a hard time quitting, where this presents another option for them.

So I think within some segments there will be good

motivation and good ability to get them to switch completely. And then I think the low SES smokers, which may comprise a large number, may be harder to reach. But I put medium because I think there are subsets, and it's another tool, at this point, to reach some of those subsets.

DR. GIOVINO: This is Gary Giovino. I voted low; although I'm appreciating the points about medium, but I'll stick with low. I don't know if it could change if it wanted to, but the -- I think, in the short term, it is low. I think it could clearly build over time. But for in a short year or two, I think it is low.

DR. HUANG: And this is Phil Huang. I voted low. I think the evidence that we actually saw that's most relevant to the U.S., nothing indicates anything higher with switching.

DR. FAGAN: I based my vote on, you know, the evidence that was before us that was presented in CC-84.

DR. WEITZMAN: Michael Weitzman.

I voted low based on the evidence and the fact that people are going to have put out a good deal of money to begin this, and we have a poverty rate that's 20% with much higher smoking rates amongst that 20%. It's a fair amount of money to start this thing.

DR. THRASHER: Yeah, Jim Thrasher.

I also put low, primarily based on the data from the U.S., which we're already a subset because they don't refer people to even participate in those studies; they had to express an interest in using the IQOS, and we never knew, kind of, how big or small that subset was. And I didn't really see much evidence in the U.S. studies that the complete switchers were going to grow over time. In fact, it looked like more and more people were becoming dual users over time, as far as I could tell. So that's why I said low.

DR. HUANG: Dr. Ossip.

DR. OSSIP: Based on the available evidence that we've seen in the materials we reviewed and over the past day and a half, the evidence that I saw influenced my vote for low.

DR. HUANG: Okay. Let's move on to then 3b. What is the likelihood that U.S. smokers would become long-term dual users of IQOS and combusted cigarettes?

So discussion? Dr. Weitzman. Oh, okay.

DR. WEITZMAN: Oh, no. I was getting ready to vote.

DR. HUANG: Oh, okay. No, I was going to see if there was any additional discussion.

Okay, Dr. Mermelstein.

DR. MERMELSTEIN: So, you know, it's hard to know what long term means because there's nothing that's been long term, you know, over years, to know what the data are with that and whether people revert one way or another. So do you have a sense of what you mean by long-term dual users and what that --

DR. HOLMAN: We don't have a particular definition. I think what we just wanted to make sure you would consider is the discussion about that it might take a little bit of time, you know, for people to transition, you know, and sort of like get to a kind of plateau on what their behavior is going to be. So I figured if we didn't put something like that on there, then you might just wonder if it's just okay, on Day 1 or within a week, what are people going to do. It was intended to try to give -- to allow for the discussion around that it might be some transitionary period.

I think it was also to get at, you know, what is the trend. I mean, are we going from complete switchers to dual users over some period of time, you know, whether it's 1, 2, 3 years, or is it stable and that, you know, at the end of Year 1, at some point later down the road, you sort of have the same percentage of complete switchers, who are dual users, or do complete -- you know, do complete switchers just eventually

go back to, you know, smoking combusted cigarettes at some rate?

DR. MERMELSTEIN: Clarifying?

DR. HUANG: Yeah, Dr. Mermelstein.

DR. MERMELSTEIN: Is this contingent on those who completely switch? I was reading this actually differently. Among those who may not completely switch, what's the probability that people will dual use and keep dual using? So how does this relate to them that completely switch?

DR. HOLMAN: So I think it's also people that might completely switch, and then over time -- again, not defining exactly what that time is, that they morph into dual users.

DR. MERMELSTEIN: So they relapse?

DR. HOLMAN: Yeah, they relapse.

UNIDENTIFIED SPEAKER: But you would also include people who would never become complete switchers in that category, right?

DR. HOLMAN: Right.

UNIDENTIFIED SPEAKER: Okay.

DR. HOLMAN: Yeah. I mean, I think we wanted you to think of these two sort of in parallel, right? I'm going to guess there's a third track here, which is no interest in trying the

product and, you know, aren't going to use it. But sort of thinking about how you would answer (a), you know, sort of what do you think about the magnitude of uptake in long-term dual use of the product, the likelihood?

DR. HUANG: Dr. Ossip on the phone has a comment.

DR. OSSIP: Yeah, so this is following up on the same line. So if you could just clarify, I guess I'm still a little confused about what's relative to which group here. Is it, again, the likelihood that U.S. smokers, as our denominator, will become long-term dual users of IQOS as opposed to doing anything else, or is it become dual users as opposed to becoming complete -- as opposed to completely switching? So in a population of smokers, what percent are likely to become dual users? Or assuming that some percent will become users of IQOS, what's that balance between are they more likely to become dual users or completely switch to IQOS? So are we looking at the U.S. population on here or amongst --

DR. HOLMAN: Yeah. So it should be the same denominators as 3a. So 3a we already said was the whole population of smokers. I mean, one is sort of understand it relative to one another, to those behaviors.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: Yes, is the Committee to also consider that with dual use there's a reduction in the number of cigarettes smoked?

DR. HOLMAN: I had mentioned this earlier, but I'll just repeat it and respond, I think, to your question, which we were also looking for some discussion here about what does it mean for the dual-use population. I mean, you know, whether you think it's low, medium, or high, do you think that, you know, some of the claims we talked about earlier for complete switching, that there would be some relative reduction in risk or tobacco-related disease as part of your conversation or discussion about what you think the likelihood of this dual-use group would be over some period of time?

DR. HUANG: And I guess I go back to, again, that CC-84, and over time it looks like there were fewer predominant users and actually more of -- there was a consistent contingent, more so than the exclusive users, of combined users, and then there was more that then they went back to cigarette use, of anything.

Dr. Weitzman.

DR. WEITZMAN: So I believe that amongst e-cigarette users, that a very significant percentage of them are dual

users. So I don't know, and I wanted feedback what other people think since I think of e-cigarettes as the first major vaping agent, whether or not one can extrapolate from that or make assumptions from that for this. You're shaking your head no. Why do you say that? I shouldn't ask her?

DR. HUANG: No, no, no, in our discussion.

Yes, Dr. Fagan.

DR. FAGAN: I have a similar concern because the device being presented is not an e-cigarette; we understand that. But we do know we're in an e-cigarette environment and that dual use is common and the dual use occurs in the context for various reasons. It could be related to their levels of dependence on the product, it could be related to can they smoke indoors or outdoors, you know, where is it convenient for them to use their cigarette versus an e-cigarette product, and IQOS is similar in that way because we don't know at this point what the laws will be related to where it can be used.

But one might imagine that, for a dual user, their levels of dependence may keep them in the dual-use stage, their likeability of the product may keep them in the dual-use phase, as well as what the particular laws are around them smoking and using their device as well.

And then another point I just want to make about this dual-use component is, again, two of the three products are menthol products, and I'm still unclear about the differences between the Menthol Smooth and Menthol Fresh. I saw the differences in level of nicotine in, you know, menthol, but that doesn't really give us a real good idea of what the differences between those two products are. But, you know, given that, and we're talking about this dual use and dependency, I don't really know how that plays out when it comes to two of the three products being menthol, and we know from previous scientific evidence that people who use mentholated cigarettes have greater difficulty quitting and quitting successfully. And so, for me, this question about dual use is critically important.

DR. HUANG: Dr. Ossip on the phone. And then I think, for our timing, we're going to have to call this vote quickly.

DR. OSSIP: Okay. So I just wanted to get back to CC-84, which I think seems to be the most relevant slide, and that gets back to that denominator question.

So if you look at, like, what's the likelihood that they will become users, when you go out to among U.S. smokers with this particular sample, the likelihood out at 6 weeks is that

they're not going to become either complete switchers or complete dual users because most of them are just cigarette smokers at that point. But if you look at among those who are using, you know, you come up with a very different conclusion. Are they predominantly complete switchers, or are they predominantly dual users? So that's why I just want to be very, very clear on what question we're answering.

DR. HUANG: Okay, Dr. Apelberg, did you want to say something?

DR. APELBERG: Yes. That point makes complete sense, but I think just going back to what I said before, we envision that these, both 3a and 3b, would sort of be parallel questions. So we'd like you to think of the denominator in the same way.

DR. HUANG: Okay. And then, so in that sort of sense, when I look at CC-84, I mean, there's certainly not any indication that more of them are becoming more completely -- complete switchers. They're either staying as dual users, or they're going back to regular cigarette use.

DR. OSSIP: Right.

DR. HUANG: So I mean, as I read that, I would almost read that -- the likelihood that they would become long-term dual users is pretty high, or they go back to cigarette use or

something.

But, I guess, are we ready to vote?

Oh, Dr. McKinney.

DR. McKINNEY: Yeah, just one comment. I know you're relying heavily, when it says discuss evidence, and you're looking at CC-84. If I recall, there was an actual use study that had some data that may be of interest as well, and I think it didn't -- the dual use -- the actual use study, the data was a little bit different from this.

DR. HUANG: Okay, any other thing to discuss? I think, let's go and vote. Okay. So we're going to begin to vote for Question 3b. Please press the button on your microphone that corresponds to your vote. Again, it's the high/medium/low, and if you wish to abstain, then let us know and don't push anything.

(Committee vote.)

DR. HUANG: Dr. Ossip, what is your vote?

DR. OSSIP: Medium.

DR. HUANG: Okay, the vote is 3 high, 5 middle, and 1 low. So maybe we'll start on Dr. Thrasher.

DR. THRASHER: Yeah. So I'm looking at the evidence that was presented. I voted medium, and I'm looking at the evidence

that was presented, and I mean, kind of anchoring my decision to my prior vote of low for exclusive use. I see more dual, and I also see kind of analogous support for dual use in the context of the U.S., around how it is that smokers are using e-cigarettes. And so that's how I landed there.

DR. WEITZMAN: So I voted high based upon the limited data that we have and e-cigarettes and just the generic whether it's your own addiction. And so until you reach the point where a critical mass of people weren't smoking conventional cigarettes, I could picture somebody walking into a house where somebody is smoking a conventional cigarette, and unless these two provide the exact same sense of satisfaction, that you would regress. So I could see dual.

DR. FAGAN: I voted high and for the previous reasons mentioned, and this particular interaction of menthol-menthol combination related to the menthol cigarette smokers switching to a menthol-laded IQOS product, and we know enough about addiction related to menthol smokers, and so I have some concerns about that.

DR. HUANG: And this is Phil Huang. I voted high also, I guess, based on the data that we saw in terms of actual versus exclusive use versus dual use. I see that there was probably a

high likelihood that there would still continue to be long-term -- a considerable population of long-term dual use.

DR. GIOVINO: Gary Giovino.

I voted medium because I think more people would use -- be dual users than complete switchers and because I also think there are some people in the population who won't adopt IQOS at all.

DR. MERMELSTEIN: And this is Robin Mermelstein, and I also voted medium, sort of more consistent with my prior vote of medium and also looking at that's, you know, a substantial number of the population are dual users.

DR. BIERUT: This is Laura Bierut. I think it may be on the way that I'm interpreting the math. If I think of low as 30% in the great state of Missouri, I am viewing this as 22% of all smokers are dual users, and so that's how I voted low. I do think that if you are a user, you're more likely to be a dual user than you are to be a single consistent. So if I considered it amongst users, I would have said medium.

DR. O'CONNOR: It's Richard O'Connor. I voted medium for similar reasons, in the sense that this is going to be sort of a bifurcated thing; you're either going to like it or not, and eventually, you'll transition back to cigarettes if you're not,

if you're not -- on IQOS.

DR. HUANG: Dr. Ossip.

DR. OSSIP: I voted medium. It was also the denominator issue for me, that it's two-stage. First, you have to become an IQOS user and then among -- so that's a much broader denominator. Among IQOS users, you're more likely to be a dual user, but first you have to start using IQOS, so that put me in the medium range.

DR. HUANG: Okay, thanks.

Okay, we'll move to Question 4, so this is: Discuss evidence regarding the likelihood that persons who do not use tobacco products will start using the IQOS system.

For (a): What is the likelihood that U.S. never smokers, particularly youth, will become established users of the IQOS system?

And then (b): What is the likelihood that former smokers will re-initiate tobacco use with the IQOS system?

Comments? Dr. Mermelstein.

DR. MERMELSTEIN: So, for me, a critical distinction here is whether youth become established users, not whether they try it, not whether they just experiment, but do they become an established user, which if you want to use the same old

definition of 100 cigarettes or that they're smoking regularly, so that's a critical distinction. That means do they become (a), have a source that either is supplying them with the product or they're buying it at a relative price point and how many times that they have to do this and over what period of time. So, again, it's not do they try it, but do they become established users? And some of the data that we saw doesn't -- isn't convincing that the experience of youths mimics that as well of cigarettes, so it may not be as rewarding to kids. We don't know that; kids' brains are a little different.

So, yeah, they are. So, you know, we don't really know, but again, if the threshold is established users, that's not just trying, but it's meaning you're making some continued use, you're getting a supply, and it's a larger threshold to get to.

DR. HUANG: Dr. Ossip on the phone has a comment.

DR. OSSIP: Yeah. I think this is one where we really -- we haven't seen really data on this because of the lack of studies with youths, and I was actually surprised, within the experience of this having been on the market since 2015 in a couple of countries, that the Applicants said they would do postmarketing surveillance and take a look at this, but they haven't, or at least it wasn't presented, in countries where

they've had the opportunity to do that. So we really don't -- we don't really have evidence to be able to look at what might happen with youths in the U.S., which then, you know, when you don't have that, you look at what else can you look at, and again, it's that question of how close is the cigarette experience to this. It's certainly the other novel tobacco product, and you know, it's hard not to make that comparison in the absence of any evidence for IQOS with youth.

DR. HUANG: Okay, Dr. Fagan.

DR. FAGAN: Yeah, this question is puzzling to me because when I first read it, I thought I was going to be reading a question about initiation, but it's exactly what Dr. Mermelstein says; this is about established users, and so I'm -- I don't understand why we're answering this question, but we are answering the question, so we just don't have enough information. You know, Philip Morris is saying they were told that the youth studies are inappropriate for them to do.

DR. HUANG: Is that correct?

DR. FAGAN: I mean --

DR. HUANG: Was that a policy?

DR. FAGAN: -- maybe FDA can clarify this.

DR. HUANG: Yeah.

DR. FAGAN: You know, because what we were told is that FDA said that the youth studies were inappropriate. So is that correct information?

(Off microphone response.)

DR. FAGAN: That is correct information. So it's really -- this question is just challenging for us to really entertain based -- I'll go ahead and yield to someone else, so --

DR. HUANG: Okay. Yeah, Dr. Weitzman.

DR. WEITZMAN: So it's true that there aren't specific data that speak to this, but you do have a rather steep decline in use of cigarettes amongst youth at the same time that you have a profoundly steep increase in e-cigarettes. So I would imagine that a lot of those kids are dual users, so it's 16% use e-cigarettes, 6% use cigarettes. I don't know what the actual percent is when you combine them, but let's just estimate that it's about 10%.

So I think that there's a fair chance that -- from a public health point of view, a substantial number of kids will initiate.

DR. HUANG: Dr. McKinney. Oh, I'm sorry. Dr. King was first, yeah.

DR. KING: So I'm going to preface my comments by saying

that I'm fully cognizant of the fact that we're talking about the modified risk application and not the premarket.

That being said, I think we'd be remiss if we do not account for youth use when the charge is to account for the effect on the population as a whole. And I think it's very convenient that the Applicant noted that they don't do any research on youth because my guess is that those data would be quite telling, as they have been. The public health community has collected data on youth for decades, and those help demonstrate a 900% increase in e-cigarette use over a very short period of time. So the data on, at least, population-based use of the products can be collected.

That being said, it's been on the market for many years in Japan, and I think that the youth use is something that we should be concerned about, and absent the data, which no data have been presented, we have to look to the closest comparator; in that case, I think it's e-cigarettes, even though we've been encouraged to compare to cigarettes. And I also disagree with the notion that we should only be concerned with the established use. Most youth tobacco users are not established users, so why are we making a paradigm for these products that we do not for cigarettes and other products?

And so, you know, the bottom line for me is that, you know, this notion that we're going to assess the population-based impact on a whole without actually seeing data among youth, to me, is disingenuous at best and public health malpractice at worst.

DR. HUANG: Dr. McKinney.

DR. McKINNEY: I would ask that the Committee be very cautious in applying data from one product category to another product category. This product is not an e-cigarette. And I think we've heard from the Applicant the differences in how they claim to market the product and etc., so we should be very cautious in applying data from e-cigarettes.

DR. HUANG: Dr. Mermelstein.

DR. MERMELSTEIN: You know, again, we're being asked about established users, not the tryers themselves, but data from -- that Dr. Weitzman talked about in terms of rates are not established e-cigarette users. Those are significantly, significantly lower of youth who progress and continue and become established e-cigarette users. So we can't be making comparisons that, you know, of just trying, an occasional use versus an established use. There is no really good comparison if we compare it to what percentage of youth who try to become

established cigarette smokers, and again, that's -- you know, that's not the same product; that's a range in there, too. And I agree that we don't really have -- I mean, this is all hypothetical here, and if that's -- it's a challenging question.

DR. HUANG: Dr. Giovino.

DR. GIOVINO: There are many differences. I mean, they don't -- you know, like a lot of youth I see on videos, they have a ball just blowing the aerosol and pretty talented in some ways but -- and they won't get that sort of feedback in whatever neurotransmitters that stimulates.

I guess we should expect compliance with the marketing restrictions of tobacco products, and clearly, it will -- purchase online will be more difficult, although I agree with Dr. King, it won't be impossible. But I think there are differences here. Just for a point of clarification, because they clearly did use the legal age to 25 as a category of young adults. I believe by youth here, you mean underage youth or not? Do you mean never users or under 18 or 19 in some states?

DR. HOLMAN: We mean adolescents.

DR. GIOVINO: Okay. All right, thank you.

DR. HUANG: And I have to say, I mean, I agree with

Dr. King's concerns. I mean, we are charged with looking at the population effects. I mean, to not -- I think it is sort of convenient to not have presented any data on this, and it's very important for us to make this decision, and I think there is comparable information for other products that are obviously not the same.

I mean, I'm concerned about seeing some of the marketing in the way that these are packaged. I mean, I think -- again, you know, I mean, they are comparable to other products that are having youth appeal, but there is a lack of data, and I think that's something that we should absolutely, you know, sort of not be happy that there's none.

Yes?

MR. ZELLER: I want to follow up on Dr. McKinney's point and on the issue of differences between this product and e-cigarettes. You know what the Applicant said about the differences. You each need to decide where you land on that. The claim of difference is basically the difference between a category of products coming onto the market and being available for youth access not on a premarket basis and initially in the absence of any regulation at all versus this pathway, and that's the distinction the Applicant tried to draw. You all

need to factor that in as you see fit along with everything else, the presence of information, the absence of information, but that's the point that the Applicant made.

DR. HUANG: Last question, and I think we need to call the vote.

So Dr. Thrasher.

DR. THRASHER: Yeah, I mean, I guess a couple of things. One is that -- I mean, my sentiment is that if we're not talking about adolescents and we're talking about nonusers, my sentiment would be that it's low. I think some of the evidence would suggest that and kind of what we understand about uptake of tobacco products would kind of reinforce that contention. So it's really about youth.

And so, I guess, when I'm voting, I'm wondering are we talking just about youth here? I mean, we just had the question about adolescents, but the way that the question is phrased, it says "particularly youth," it doesn't say "youth," so are we trying to consider all nonsmokers but with a greater weight towards adolescents?

DR. HOLMAN: I mean, we really meant all never smokers --

DR. THRASHER: All never smokers.

DR. HOLMAN: -- but knowing the data on when never smokers

become smokers, we included youth in the question. And so it could be adolescents, it could be --

DR. THRASHER: So I guess --

DR. HOLMAN: -- never smokers in their twenties.

DR. THRASHER: -- in some ways I would have a different response depending on what the population is, and so, say that --

DR. HOLMAN: So you should vote however you interpreted it, and I think, when you explain your vote, I think you could qualify it by how you viewed the question or weighted the different age populations.

DR. THRASHER: Okay.

DR. BIERUT: So I'm comfortable weighting the data that we have about combustible cigarettes, e-cigarettes; we have lots of data about youth in the United States under 18 and up to 25. I guess the question that I have is -- I'm going back to my math here -- is what is high, medium, and low? Because if I think of 100%, low is 30% and -- versus 10%, 20%, 30%, which is different. So do you have -- can you give me some guidance?

DR. HOLMAN: I would say use whatever metric you did on the previous question, right? That was a high/medium/low, and I think, based on the explanations provided to your votes, it

was clear that different members of the Committee had a different idea about what low, medium, and high meant, and I think that came out in the discussion of your votes, and so I'd say take the same approach here.

Thank you.

DR. HUANG: So if we're ready to vote, we will begin voting on Question 4a. If you will please press the button on your microphone that corresponds to your vote, high, medium, or low.

(Committee vote.)

DR. HUANG: Dr. Ossip, have you voted?

DR. OSSIP: Yeah, I said high.

DR. HUANG: Okay. And we have one abstention. All right.

(Off microphone comment.)

DR. HUANG: Oh, two abstentions. Okay, let's look at the results. There are 2 high, 1 medium, 4 low, and 2 abstentions.

Okay, maybe we'll start with Dr. Ossip first. If you want to talk about your vote?

DR. OSSIP: Yeah. I think in the absence of any data being presented to us when we're being asked to make a decision, short of abstaining, which was the other option, we have to use what data we do have in something that's as close

as comparable, and that's the e-cigarette experience as an alternate tobacco product.

I will say that I did adjust my denominator somewhat here from what I did in the prior question just because of the risk level of that population of adolescents starting. And so based on all of those considerations, I'd place the risk at high. Or the -- sorry, the likelihood of high.

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

DR. O'CONNOR: Yeah, so I voted low because, going back to my previous thinking about the relatively low proportion of people taking it up at all, that I thought it was relatively unlikely that older never smokers would take it up and that there might be slight -- I might rate adolescents slightly higher than that, but the prospect of them continuing to establish use of IQOS in the absence of use of other products, I categorized as low.

DR. BIERUT: I also categorized it as low with the idea that I think that those over 25 will have a very, very low rate of initiating. The group that I am concerned with is the under 25, and I balanced it based on what I know about combustible cigarettes and electronic cigarettes, and I think that it's going to be low, much lower than 30%, which is my general

denominator.

DR. MERMELSTEIN: I also voted low, and I liked the 30% category of low or not being a reasonable way of splitting 100%. So I also agree with Dr. Bierut that probably the biggest risk group are the young adults. I think that there will be a lot of boundaries in place for adolescents, the price, the marketing, the other approach, I think, you know, comparing them to e-cigs and cigarettes as well. Again, the threshold is established users. So I think, overall, considering it's not as easy a product, the access is not as great, and I have a feeling that the addiction potential is not as great.

DR. GIOVINO: So I voted low because I basically thought of tertiles and I considered established use. Not to say that there aren't some challenges with the product, especially because it looks a bit like -- you know, it resembles the iPhone technology, and there might be concerns there, but still, based on just answering this question, I thought the probability was low.

DR. HUANG: This is Phil Huang. I voted high. Similar to Dr. Ossip, in the absence of evidence, I was looking at some of the experience with e-cigarettes. I look at how it's packaged

and marketed, and I think it has -- would have very likely appeal to youth.

DR. FAGAN: I abstained. I think parsing this question out to youth and then the whole population of smokers, I think, is a challenge, and I just could not yield a vote on this one.

DR. WEITZMAN: And I voted medium, and I used tertiles, and I used tertiles from maximum use in the early 60s, and so I thought that a third of that seemed reasonable to me, given the e-cigarette epidemic. I get it that they're different, but they both are nicotine delivery systems, and they're both vaping products, and so I listed it as medium.

DR. THRASHER: Jim Thrasher. I abstained. If it had just been adult never smokers, I would have said low, and then I would have wanted to have kind of some indication that it was higher amongst adolescents, but because I wasn't able to do that in the absence of data to kind of firmly anchor my thinking, I abstained. If I had thought about the likelihood that 33% of never smokers would become IQOS users, then I would certainly have been in the low category.

DR. HUANG: And we did Dr. Ossip first, okay. Okay, we need to move to 4b, and so we will have limited discussion on this one, but what is the likelihood that former smokers will

re-initiate tobacco use with the IQOS system? Discussion? Ready to vote? Any discussion? Ready to vote?

(No response.)

DR. HUANG: No discussion?

DR. GIOVINO: So --

DR. HUANG: Dr. Giovino.

DR. GIOVINO: -- just by -- the question means by will re-initiate tobacco use, you don't mean go back to smoking cigarettes. Basically, you're saying, well, try the IQOS system; is that correct? You're not saying they'll try IQOS and then go back to combusted tobacco?

DR. APELBERG: Yeah, I mean --

DR. GIOVINO: I just want to make sure I understand.

DR. APELBERG: -- this is really about the -- right, the appeal to former smokers or former users, in general. I mean, they could go back to smoking, but it was really about coming back to tobacco through IQOS.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: So I have a question. What do we know -- what is the rate of recidivism or falling off the wagon for current -- people who were cigarette smokers and who managed to stop; does anybody know?

DR. HUANG: Dr. Giovino.

DR. GIOVINO: I'm sorry. There's a high percentage of smokers in the United States who try to quit every year, I think it's in the 50s, and about 7%, based on cross-sectional studies, are abstinent. Do I have those numbers?

(Off microphone comment.)

DR. HUANG: This is former smokers we're looking at.

DR. GIOVINO: Yeah. Yeah, yeah. So people who have quit. Now, this is recently, right?

DR. WEITZMAN: I don't know whether they're former smokers.

DR. GIOVINO: So there was some data in the 1990 Surgeon General's report that I put in that were based on -- well, based on the NHANES epidemiologic follow-up study, that even up to a third of smokers who have been off at least a few years, if memory serves, might go back, but clearly, the probability of relapse was way down after a year. I mean, it really levels off, and Prochaska considers, I think, a year of abstinence is in the clear. Correct me. But I think the real danger is in the first --

DR. WEITZMAN: Right.

DR. GIOVINO: -- 3 to 6 months.

DR. WEITZMAN: So we need to know what you mean by former smoker because I assume that it's not a month or two; it's somebody who felt like they really --

DR. GIOVINO: Well, former -- recent former smokers are a small percentage of former smokers, right? Recent former smokers, former smokers abstinent less than a year, are perhaps 2 or 3% of all former smokers.

DR. HOLMAN: So I think we were thinking about -- and I agree with everything that Dr. Giovino said, and I mean, we were thinking about, you know, potentially former smokers at the 1-year mark or later, you know, that have established themselves as abstaining from tobacco products as opposed to the ones, like you said, that have recently given up tobacco products and still have a very high likelihood of returning to tobacco products. Does that help?

DR. WEITZMAN: That helped me a lot.

DR. GIOVINO: Yeah, that clarifies.

DR. HUANG: Dr. Ossip on the phone has a comment.

DR. OSSIP: Yeah, so the slides that I'm looking at are CC-91 and CC-92. And I think this is relative to this question, I think these are the data that were presented to us. I just wanted to point that out and see if anyone -- this is

what I recall, but if anyone recalls any other data having been presented to us. And this is intent, so it's not actual conversion or relapse, but -- so it's, you know, with that caveat, it's based on intent, on stated intent, reported intent.

DR. HUANG: And I think this combines both people who have quit more recently, maybe within the last 3 months, as well as those who have quit for more than a year.

Okay. Can we go ahead and vote on 4b, then? We'll go ahead and begin the voting process for Question 4b. Please press the button on your microphone corresponding to your vote, high, medium, or low. And if you abstain, don't vote.

(Committee vote.)

DR. HUANG: Dr. Ossip, how did you vote?

DR. OSSIP: I said low.

DR. HUANG: Okay. Any abstentions?

(No response.)

DR. HUANG: All right, everyone's voted; the voting is now complete and locked in, if we could read the results. And we have 9 votes for low.

Okay, the last question: Discuss evidence regarding consumer comprehension and perceptions of the proposed modified

risk labeling and advertising.

(a) is: Has the applicant demonstrated that, after viewing the proposed modified risk labeling and advertising, consumers accurately understand the risks of IQOS use as conveyed in the modified risk information?

And (b): Does additional information need to be communicated other than what has been proposed by the applicant for consumers to understand the health risks of the IQOS system?

Is that an actual vote, or is that just comments? Or -- oh, am I looking at the wrong one? No.

(Off microphone comment.)

DR. HUANG: Oh, what additional information, if any, needs to be communicated other than what has been proposed by the applicant?

So it's just comment?

MS. COHEN: Yeah.

DR. HUANG: Yeah. All right, so 5a. So any comments, discussion?

Dr. Thrasher.

DR. THRASHER: I mean, I guess my perception of this part of the application is it's probably the most, one of the most

fraught pieces, particularly due to some of the design issues that were raised around assessing people's comprehension of the messages, and also kind of how it is that the study design was laid out for us to be able to really tell whether there's a difference between when people are exposed to the reduced risk and reduced exposure claims versus not.

And so the other key issue for me is that it's not clear at all whether people understand what completely switching means and also kind of whether there may be, sort of, the implication that partial switching means a reduction of harm that -- for which we don't have any data.

DR. HUANG: Okay. Dr. Mermelstein.

DR. MERMELSTEIN: Yeah, I agree. I was most concerned about the level of literacy needed for the information that was conveyed, so I'm not sure that that maps well onto smokers as consumers. So I just felt that this part of the data were not as well thought through.

DR. HUANG: Dr. O'Connor.

DR. O'CONNOR: Yeah, the thing that sticks with me is the real, sort of, lack of effect of the claim in moving risk perception relative to smoking and the apparent lack of association with intention to use, and that goes to the heart

of what the modified risk claim is supposed to do. And I can't disentangle how much of that is issues of literacy and truly understanding the content versus the format in which it's presented versus issues of do people even believe the underlying truth, and I think it's difficult in the study that was presented to really unpack all of that.

DR. HUANG: Other comments?

DR. HUANG: Yes, Dr. Weitzman.

DR. WEITZMAN: Yeah, it's not just literacy, but health literacy, so I don't know that the public is going to get a lot of what's said in that one sentence.

DR. HUANG: And I would go back to some of the comments made earlier in our first discussions with 1a, just that the way the statements are structured, yeah, it's requiring this switching completely scenario and then that it can reduce risks. I mean, we had our own debates of understanding what that meant, what the thresholds were, I think.

But the general sense is that these are safe, these are safe -- safer products, but I don't know that it would accurately convey that, the need for complete switching or other aspects of that. And, again, I was struck by the lack of impact of some of the assessment of the messaging also.

Are we ready to vote? Okay, Question 5a. We'll now begin the voting process for Question 5a: Has the applicant demonstrated, after viewing the proposed modified risk labeling and advertising, consumers accurately understand the risks of IQOS use as conveyed in the modified risk information?

This is going to be, then, a yes/no/abstain vote.

(Committee vote.)

DR. HUANG: Dr. Ossip, what was your vote?

DR. OSSIP: No.

DR. HUANG: Okay, if we can look at the results. And it was 9 no votes.

Okay, now we'll go -- the vote is complete. We'll go around the table again and ask everyone who voted to state their name, vote, and reason they voted as they did into the record.

This side. Dr. Thrasher.

DR. THRASHER: Yeah, I already expressed my views. I think the study design made it difficult for us to understand whether they were really achieving the objective of increasing comprehension of the message and particular concerns around the issue of whether people would understand what complete switching means and what would happen along with dual use or

incomplete switching, especially given the data that were presented around actual behavior.

DR. WEITZMAN: This is Michael Weitzman. I completely concur with Dr. Thrasher.

DR. HUANG: And we might quickly -- I don't know if we need to, I think maybe all of us -- anyone feel compelled to explain more? We were saying in the final few minutes we may want to spend more time on 5b. Would anyone like to express anything particularly about their vote, since it was unanimous?

Dr. Ossip?

DR. OSSIP: No, I'm in complete agreement with what's been said.

DR. HUANG: Okay. Then let's move on to discussion with 5b: Does additional information need to be communicated other than what has been proposed by the applicant for consumers to understand the health risks of the IQOS system?

Dr. Wanke.

DR. WANKE: For this question, one of the things I'd like to raise is the issue that the message may be interpreted by consumers as a government or federal generated statement. And that's why I think for that understanding, it would be important to have some way of having this not appear to be like

a health warning, that this is clear that this is the industry-generated packaging and labeling statement. You know, it's like advertising, in essence.

DR. APELBERG: Just to clarify, are you speaking specifically about the PMI Important Warnings or just broadly?

DR. WANKE: Both.

DR. APELBERG: Okay.

DR. WANKE: Both the reduced risk and, you know, the modified risk statements, but also especially is PMI Important Warnings. I'm concerned that they appear as health warnings that -- and especially if they're meant to substitute for the health warnings, which I'm really not clear about, and we haven't really discussed these PMI Important Warnings, and I have concerns about them.

DR. HUANG: Dr. Bierut.

DR. BIERUT: I think communication is difficult, and I think we need the Goldilocks position here of just right. And I think what we're trying to balance is the communication that these devices have less risk than combustible cigarettes, but that they have more risk than never smoking, and making sure we get into that Goldilocks spot, I think, is difficult.

DR. HUANG: And I'd like to just -- you know, earlier in

our discussions, I agreed with Dr. Giovino. I mean, I think the potential -- if you have someone who completely switches and uses these products, there is great potential, but we are also very concerned about the population effects. We need more information regarding initiation among youth and appeal to youth. And I mean, again, experience with the electronic cigarettes is very worrisome.

I mean, we're not in position here -- I mean, again, like the clarification, we're not deciding if the product comes into the market, but it's just if it gets this, you know, label of being safer. And so I think that there's, you know, a lot of opportunity with this, but I just don't think, right now, we have the evidence to justify those.

DR. GIOVINO: I thought the messages were too wordy and confusing. I don't hold out that information can be communicated well and more clearly, but I also think more effective emotional communications, which aren't technically information, should be explored.

I am a firm believer that people make decisions based on both sides of the brain, and sometimes the affective/emotional is more influential than the cognitive/rational, and we've been talking cognitive/rational the whole while here, and we need

clear cognitive/rational, in my opinion, and some enhanced affective/emotional.

DR. HUANG: Dr. McLoughlin.

DR. McLOUGHLIN: Thank you. I have one concern, so I just want to say it. When we talk about decreased risk, I get really worried related to consumers in a product like this because I fear that people don't understand the addictive -- the addictive, sorry, properties of nicotine and might think that somehow, because we're talking decreased risk, we're also talking decreased addiction related to nicotine.

DR. HUANG: Dr. Fagan.

DR. FAGAN: In addition to the just very high literacy levels, especially when we're thinking about populations who have been left behind, this is just too complex for them.

The other thing is that we keep talking about relative risk. But, you know -- and even in the e-cigarette world we talk about relative risk, but what is the risk? You know, many people ask, well, what is my risk; that's a different question from relative risk, and I think there needs to be messaging that says there is a risk, and then there's a separate message about relative risk, because people want to know all the time what is their risk of something and what is it the risk for.

And, you know, even with any kind of harm reduction product, we should be thinking about both types of messaging.

DR. HUANG: Dr. Weitzman.

DR. WEITZMAN: And I don't want to complicate things and it's late in the day, but I need to elaborate on what Dr. McLoughlin said. There is something wrong with us excluding nicotine from this discussion. There is an extensive literature that suggests that it is the gateway drug.

The leading cause of preventable death of people under the age of 50, at this point in the United States, is the opioid epidemic. There's lots of literature to show that you have priming of addiction to opioids if you previously have been exposed to nicotine or been addicted to nicotine, cocaine as well.

So I don't mean to change the argument at this point, but I do think that we're trivializing a big danger of the use of tobacco products, of nicotine-containing products. So I don't know how you fit that into a sentence along with all the other -- I'm trying to figure out what Goldilocks effect is. I don't remember Goldilocks.

DR. HUANG: Any other -- yes, Dr. McKinney.

DR. McKINNEY: Yeah, as I think about the July

announcement by Dr. Gottlieb and Mr. Zeller, I think nicotine and addiction is considered, and FDA does have a framework, and I think that non-combustibles are a component of that and reduced risk products, as they stated earlier, so I just want to make that point.

DR. HUANG: All right, I think we've got about 2 minutes left, and we want to devote the last 2 minutes to Mitch.

MR. ZELLER: On behalf of FDA and the Center for Tobacco Products, I want to thank everyone who participated in this meeting, starting with the members of the Committee -- again, thank you to the departing members of the Committee -- the CTP staff, for their presentations, and Philip Morris Products S.A. for not only their presentation yesterday but willingness to stand there and answer the questions, come back and answer more questions, and come back again and answer even more questions.

And also, too, the members of the audience who sat through 2 long days and to all the members of the public that sought time and went to the podium to share their views with the Committee, with the world, on all these issues. We are enormously grateful for everybody who participated. Our job now is to take back what we've all heard over the last 2 days, the votes that were taken today, every piece of information

that was put on the table over the course of the 2 days, and the information still to come in, whether it's through subsequent amendments to the application and additional filings and comments by the public, and we will take all of that into consideration as we think about the decision that we have to make.

And, remember, there are two applications here. Here we were only talking about the MRTP application for claims, but the company has said publicly that there is a PMTA application for marketing authorization.

We take the responsibility that we have under the standard and the statute, that you've heard discussed at length over the course of the 2 days for the claims part of this, very seriously. I think I heard a chuckle from the audience when I made the comment of, you know, welcome to the world of being a regulator.

As we take the standard, we take the mandatory considerations that Congress wrote into the law, that is the law. Our job, as the regulator, is to interpret and implement it, and the members of the Committee, the Sponsor, the folks that came to the podium, the staff that came to the microphone to answer questions, we're all in this together, working

through, on a premarket basis, with a population-level public health standard, whether or not, in this instance, the evidence warrants authorizing the particular claims that the Sponsor has sought.

And, again, we take the responsibility that we have to render the decision on that very, very seriously, taking into account everything that has been said by everyone.

And so, again, on behalf of FDA, I just want to thank everyone for their really great participation in the 2 days of meetings. Thank you very much.

(Whereupon, at 3:00 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

January 25, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Tobacco Products.

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TIMOTHY J. ATKINSON, JR.

Official Reporter

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