Tobacco Products Scientific Advisory Committee Meeting, October 7, 2025

Cristine Delnevo:
Good morning, everyone, and welcome to the October 7th, 2025, meeting of the Tobacco Products Scientific Advisory Committee or TPSAC. Thank you for joining us. I'm Cristine Delnevo and the chair of the Tobacco Products Scientific Advisory Committee. Next slide, please.

Today, the committee will discuss the renewal of an exposure modification order submitted by Philip Morris Products for five IQOS products listed. Discussion will focus on whether the statutory standards continue to be met. I will now start with a few opening statements.

For topics such as those being discussed at today's meeting, there is often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a productive, fair, and open forum for discussion on these issues. Any individual can express their views without interruption. As a reminder, individuals will only be allowed to speak into the record if recognized by the chair. To do so over Zoom, please use the raised hand function at the lower end of your screen. 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 the Advisory Committee members take care that their conversations about the topic at hand take place in an 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 the meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks.

And with that, I will turn the meeting over to Rachel Jang, the Designated Federal Officer, to make administrative announcements, conduct the roll call, and read the conflict of interest statement.

Rachel Jang:
Thank you, Dr. Delnevo. Next slide, please.

Good morning, everyone. I am Rachel Jang, and it is my honor to serve as the Designated Federal Officer for today's Tobacco Products Scientific Advisory Committee meeting. On behalf of the FDA, the Center for Tobacco Products, and the Committee, I welcome everyone to today's virtual meeting. Next slide, please.

At this time, I would like to acknowledge and thank the Office of Science and other individuals whose contributions have been critical in preparing for today's meeting. The FDA staff in the Office of Science have put great effort into this meeting, including Dr. Ben Apelberg, the Deputy Director in the Office of Science; Dr. Amber Koblitz, the Technical Project Lead for this IQOS application; Dr. Sagie Wagage, the toxicology reviewer; and Dr. Erin Ellis, the Modified Risk Tobacco Products Coordinator. You'll be hearing from some of them throughout the meeting.

I would also like to thank our advisors and consultant staff, Ms. Cristi Stark, the Associate

Deputy Director of the Office of Science; Ms. Jennifer Schmitz, Supervisor; and Ms. Lisa Johnson, the Conflict of Interest Specialist, for their administrative guidance and support in preparation of this meeting. Lastly, I would like to acknowledge our wonderful leadership for their hard work in making today's meeting happen, Dr. Bret Koplow, the Acting Director of CTP, and Ms. Michele Mital, the Deputy Director of CTP. Next slide, please.

Please direct any press or media questions for today's meeting to HHS' press room at 202-690-6343 or visit the webpage at the address displayed. This web address is also provided in the *Federal Register* Notice published on July 30th, 2025. The captioning and transcription services for today's meeting are provided by Ms. Lisa Davis and Mr. [Ms.] Edie Eaton from the National Capitol Contracting.

Before we proceed with the roll call, I would like to mention a few housekeeping items related to today's virtual meeting format. For anyone joining us on Zoom Room, please keep yourself on mute unless you're speaking. If you have your hand raised and are called upon to speak by the chairperson, please turn on your camera, unmute, state your name, and speak clearly so that your comments are accurately recorded for the captioning and transcription. Next slide, please.

We will now take a formal roll call for the committee members and temporary members. When it's your turn, please make sure your camera is on, and you're unmuted. Then state your first and last name, organization, expertise, and role. When finished, you may turn your camera off so we can proceed to the next person. Please see the member roster slide in which we will begin with the chairperson and the voting members.

Dr. Delnevo, please go ahead and introduce yourself.

Cristine Delnevo:
Good morning. Christine Delnevo. I am the chair of TPSAC, and I am a professor and the Director of the Rutgers Institute for Nicotine and Tobacco Studies. And my areas of expertise are in the population epidemiology of tobacco use, rapid surveillance, the tobacco marketplace, and regulatory science.

Rachel Jang:
Thank you. Dr. Jordt?

Sven-Eric Jordt:
Good morning. My name is Sven Jordt. I'm a professor in anesthesiology, pharmacology, and cancer biology at Duke University School of Medicine. My expertise is in the toxicology and behavioral effects of flavor chemicals and other constituents in new tobacco products.

Rachel Jang:
Thank you. Dr. Popova?

Lucy Popova:
Good morning. I am Lucy Popova. I'm a professor at the School of Public Health at Georgia State University. My expertise is in communication and marketing, as well as tobacco regulatory

science and behavior related to various tobacco products.

Rachel Jang:
Thank you. Dr. Rigotti?

Nancy Rigotti:
Hello, I'm Nancy Rigotti. I am a professor of medicine at Harvard Medical School, based at Mass General Hospital, where I direct the Tobacco Research and Treatment Center. I'm a general internist and focus on smoking behavior.

Rachel Jang:
All right. Dr. Scout?

NFN Scout (they/he):
Good morning. I'm Dr. Scout, the Executive Director of the National LGBTQIA Cancer Network. My areas of expertise would be disparity population impacts of tobacco, particularly the LGB and transgender populations.

Rachel Jang:
Dr. Upson?

Dona Upson:
Good morning. Dona Upson, professor of medicine at the University of New Mexico, staff physician at the New Mexico Raymond G. Murphy Medical Center. My area of expertise is treatment of tobacco dependence.

Rachel Jang:
Thank you. Next, we will introduce the non-voting members of the committee. First, we'll go to our industry representatives, starting with Dr. Bailey.

William "Andy" Bailey:
Yes, my name is Andy Bailey, tobacco extension specialist and professor, University of Kentucky. My expertise is in the area of tobacco production and agronomy, working with tobacco growers, and I represent tobacco growers on this committee. Thank you.

Rachel Jang:
Dr. Madl?

Amy Madl:
Hi, my name's Amy Madl. I'm President and Senior Principal Health Scientist with Valeo Sciences, scientific consulting company. I am representing small businesses, the industry representative, and my area of expertise is inhalation toxicology.

Rachel Jang:
Thank you. Now, we'll go to Mr. Murphy.

Patrick Murphy:
Patrick Murphy, Vice President, Scientific and Regulatory Affairs for RAI Services Company, a wholly owned subsidiary of Reynolds American, and today I'm representing manufacturers.

Rachel Jang:
Thank you. We will continue with the ex-officio member, Ms. Becenti.

Alberta Becenti:
Good morning. Alberta Becenti, Public Health Advisor with the Indian Health Service, and my expertise is working with American Indian and Alaska Native population as it relates to commercial tobacco use.

Rachel Jang:
Finally, we'll introduce the expert consultants who are joining us today as temporary non-voting members. We'll start with Dr. St. Helen.

Gideon St. Helen:
Hello, good morning. Gideon St. Helen, associate professor from the University of California San Francisco, and I focus on the clinical pharmacology of novel tobacco products and cannabis.

Rachel Jang:
Thank you. Dr. Stepanov?

Irina Stepanov:
Good morning. Irina Stepanov. I'm a professor in the School of Public Health at the University of Minnesota. My background is in tobacco product chemistry and toxicology and developing and applying biomarkers to understand exposures and effects.

Rachel Jang:
Thank you. Last but not least, Dr. Zelikoff.

Judith Zelikoff:
Hi, my name is Judith Zelikoff, and I'm a professor at New York University School of Medicine in the Department of Medicine, and my areas of research are inhalation toxicology in animal models, and toxicology in general, and environmental health.

Rachel Jang:
Thank you. Next slide, please.

Thank you for your attention as I now proceed with reading the FDA conflict of interest disclosure statement for public record.

As was mentioned by the chairperson earlier, the Center for Tobacco Products' TPSAC is meeting today to discuss the renewal of an exposure modification order submitted by Philip Morris Products for the products listed in the *Federal Register*'s Notice announcement published on July 30th, 2025. This matter is a particular matter involving specific parties.

All 14 participants in attendance today, with the exception of the industry representatives, all standing and temporary non-voting members of the TPSAC, are appointed as special government employees, or SGEs, or regular government employees, or RGEs, from other federal agencies, and are subject to federal conflict of interest laws and regulations.

All committee members and consultants have been screened for potential financial conflict of interest, both personal and imputed, including those of their spouse, minor children, and for the purpose of 18 U.S. Code Section 208, their employers. Interests reviewed include, but are not limited to, investments, consulting, expert witness testimony, contracts, grants, cooperative research and development agreements, teaching, speaking, writing, patents, royalties, and primary employment, current or under negotiation.

FDA has determined that all members of today's advisory committee meeting are in compliance with applicable ethics and conflict of interest requirements. Under 18 USC 208, FDA may grant waivers to SGEs or RGEs with financial conflicts of interest if the agency determines that the need for the individual's expertise outweighs the potential conflict, or if the interest is not substantial enough to affect the integrity of the employee's service. For today's meeting, no waivers have been issued.

Committee members and consultants are reminded that if discussions extend to products or firms not listed on today's agenda, and an FDA participant has a personal or imputed financial interest in such matters, that individual must recuse themselves. Any recusals will be noted for the record. One recusal is noted for today's meeting for Dr. Maria Gogova, an industry representative. Mr. Patrick Murphy, the alternate industry representative, is participating today in Dr. Gogova's place. Finally, FDA encourages all participants to disclose any financial relationship with firms under discussion.

This statement will be included in the official meeting transcript and made available for public review. This concludes the reading of the FDA conflict of interest statement. At this time, I would like to invite Dr. Bret Koplow for opening remarks.

Bret Koplow:
Thank you, Rachel, and good morning, and thanks to all in attendance this morning as we convene today's Tobacco Products Scientific Advisory Committee, or TPSAC, meeting. I'm Bret Koplow. I'm the Acting Director of the Center for Tobacco Products, and it's a pleasure to be here this morning for CTP's first-ever virtual TPSAC meeting.

The purpose of today's meeting is to discuss the MRTP renewal application submitted by Philip Morris Products for five of its IQOS products. The MRTP pathway here at CTP helps the Center achieve its public health goals by informing consumers of the relative harm of specific tobacco products, thereby helping people who use combustible products who would like to move down the continuum of risk. This TPSAC meeting is an important aspect of CTP's evaluation of these MRTP applications, and indeed, the Tobacco Control Act requires that CTP refer all MRTP applications to TPSAC.

We appreciate everyone coming together today and continuing to implement this component of what Congress intended for the Center. I'd particularly like to thank the members of the public who are participating in today's meeting, either during the open public hearing or by providing written comments. Public participation in the regulatory process is an important part of the work FDA does, so thank you to those who submitted comments and who will be speaking today.

The purpose of this committee is to provide valuable advice, information, and recommendations to the agency. CTP has put together some thoughtful and targeted questions to focus the committee's discussion today. And we have many staff here from the Office of Science who will be paying close attention to the discussions, which will be used to inform our evaluation.

Once again, many thanks to the committee members, the three additional guest consultants joining us today, the applicant, and—because we know a lot of effort goes into these applications—and the many CTP staff members who have worked for months to ensure a successful meeting. We look forward to a productive scientific discussion. And I'll turn it over now to Dr. Delnevo. Thank you.

Cristine Delnevo:
Thank you, Dr. Koplow. And with that, we're going to start with our first presentation from the applicant. I'd like to introduce Ms. Keagan Lenihan, who is the Vice President and Chief External Affairs Officer for Philip Morris U.S.

Ms. Lenihan, please proceed with your presentation and introduce the next presenter when you are finished.

Keagan Lenihan:
Thank you, Madam Chair.

Good morning, everyone, and thank you. Thank you to the Food and Drug Administration and members of the Tobacco Products Scientific Advisory Committee for the opportunity to discuss our MRTP renewal today. While we are sorry not to be with you in person, we appreciate the FDA and the committee members moving ahead with this TPSAC meeting today. My name is Keagan Lenihan, Vice President and Chief External Affairs Officer for PMI U.S.

Twenty years in public health and health care policy, mostly in government settings, have led me here today. I'm very excited to be a part of Philip Morris' vision of a smoke-free future and the public health benefit that vision will bring to American adults who smoke. At PMI, we believe science and innovation are keys to making our vision—that vision, a reality.

To be clear, we do not sell combusted cigarettes in the United States. Combusted cigarettes are the most harmful form of tobacco use, and they are responsible for the vast majority of tobacco-related disease and death in the U.S. We unequivocally agree that complete cessation is the best choice for adults who smoke and that no one under the age of 21 should use any tobacco product. But the reality is that there are approximately 30 million adults who smoke in the U.S. And while many of them want to quit, more than 90 percent will continue smoking each year. We must provide these adults with better alternatives to continued smoking.

IQOS was first introduced internationally over 10 years ago. Today, IQOS is available in 83 countries around the world, and it's making positive changes in global health. Our latest estimates show that approximately 23 million adults have fully switched to IQOS and stopped smoking cigarettes. CTP's mission is to make tobacco-related disease and death a part of America's past. Smoke-free products like IQOS play a critical role in helping achieve this mission and providing adults who smoke with a real opportunity to change.

We are here today to discuss the renewal of the reduced exposure claim for IQOS. The post-market evidence shows that FDA's conclusion for IQOS continues to be true. Switching completely from cigarettes to IQOS significantly reduces exposure to harmful and potentially harmful chemicals, also known as HPHCs. Consumers understand the authorized reduced exposure claim. IQOS users completely switch from or reduce their cigarette use. And lastly, IQOS use among youth is very low.

The post-market evidence continues to support FDA's prior conclusions. There has been no change in the MRGO status of IQOS. The authorization of IQOS as modified risk tobacco product should be renewed.

The MRTP orders authorize the marketing of IQOS products with specific reduced exposure communications to adults that smoke, which states, "The IQOS system heats tobacco but does not burn it. This significantly reduces the production of HPHCs. Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to HPHCs." These communications are critical to help move adults who smoke completely away from combustible cigarettes and down the continuum of risk.

This MRTP renewal encompassed two authorized IQOS devices and three authorized HEETS consumables, which compromise—comprise the IQOS system. The IQOS 2.4 device was updated and replaced with the IQOS 3.0 device, which features multiple design changes to improve consumer experience. These ergonomic and aesthetic differences do not impact the composition of the aerosols produced by the device.

We submitted MRTP applications for the IQOS 2.4 products in November of 2016. The FDA granted these MRTP authorizations in July of 2020. We submitted a supplemental MRTP for IQOS 3.0 products in March of 2021. And FDA granted these MRTP authorizations in March of 2022. Across both the PMTA and MRTP review process, we have submitted a total of 10 applications, presented at two Product Scientific Advisory Committee meetings, including today's, and submitted 6 years' additional post-market evidence to FDA in comprehensive annual reports.

As a part of the conditions outlined in our order letters, we have also routinely submitted required notifications for any changes to marketing materials. Throughout the 6-year surveillance period, the APPH or MRTP status of these products has not changed.

Under the initial agreement granting Altria exclusive rights to commercialize IQOS in the U.S., FDA-authorized IQOS products were marketed in select U.S. locations starting in October of

2019. Due to a patent dispute before the International Trade Commission, IQOS products were removed from the U.S. market in November of 2021. It's important to note that the dispute did not involve any matters under FDA's authority, PMTA, or MRTP authorizations. The patent dispute was subsequently resolved and marketing of IQOS products solely by PMI U.S. resumed in select U.S. locations beginning in Austin, Texas, in March of this year.

Following extensive and rigorous review, FDA's modified risk granted order was based on these four key conclusions. First, IQOS, as actually used by consumers, has the potential to significantly reduce tobacco product users' exposure to HPHCs. Second, testing of actual consumer perception shows that consumers understand the relative risk of IQOS compared to cigarettes and the need to switch completely. Third, IQOS, when marketed with reduced exposure claim, promotes complete switching and reduction in cigarette consumption. And fourth, youth uptake of IQOS is low.

Based on the PMTAs, FDA concluded that marketing of IQOS is APPH for the population as a whole, taking into account adult users, nonusers, and youth. Based on the MRTPAs, FDA found that IQOS, as actually used by consumers, will significantly reduce exposures to HPHCs and that communicating the reduced exposure claim is expected to benefit the population as a whole. While U.S. commercialization has been limited, the results of our post-market surveillance studies, or PMSS, continue to support and reinforce FDA's authorizations.

Today, we will summarize the scientific evidence and post-market surveillance studies which continue to demonstrate that the MRTP authorizations should be renewed. We will show that over 99 percent of IQOS users have a history of smoking cigarettes and that over half of the IQOS users completely switched from cigarettes to IQOS. We will also demonstrate how responsible marketing practices support the renewal of these authorizations.

This leads us to the agenda for the remainder of our presentation. Dr. Patrick Picavet, Chief Medical Officer, will begin our overview of the scientific assessment of IQOS products. He will also discuss the health risks to individual users. Pierpaolo Magnani, Global Head of Regulatory Insights, will discuss consumer understanding and perceptions and tobacco use behaviors and the impact to the population as a whole. JB Simko, Vice President and Chief U.S. Underage Prevention Officer, will discuss our responsible marketing practices for the IQOS products and the MRTP claim. I will return to conclude our presentation and help moderate our responses to your questions. Thank you.

Dr. Picavet?

Patrick Picavet:
Thank you, Ms. Lenihan, and good morning. The purpose of my presentation today is to discuss what we learned on the health risks for legal-age individual users since our original MRTP authorization and how the data we have gathered since then supports the reduced exposure claims.

When FDA authorized IQOS as an MRTP with a reduced exposure claim, the decision was primarily predicated on considerably lower levels of HPHCs, substantial reductions in

biomarkers of exposure, and a reasonable likelihood that a substantial reduction in HPHCs would translate to lower risk of tobacco-related disease. Based on the results of the PMSS and voluntary studies, we will demonstrate how the evidence reinforces and strengthens the original MRTP conclusions and the authorized reduced exposure claims.

Specifically, I will discuss results framed around the following three pillars. We will start with the significant HPHC reductions in IQOS aerosol that were presented as part of the original MRTP application. Next, we will focus on the computational toxicology assessment results and the calculation of the excess lifetime cancer risk for IQOS, which showed that IQOS has the potential to reduce the excess lifetime cancer risk by around 80 percent. These estimates are conservative and likely underestimate the actual reduction potential.

Finally, we will demonstrate that in the studies presented here, that there is up to 91 percent reduction in biomarkers of exposure and significant favorable differences in biomarkers of potential harm when switching to IQOS versus continued smoking. Taken together, the collective HPHC biomarker of exposure and biomarker of potential harm data further demonstrates that IQOS is reasonably likely to show a reduction in tobacco-related disease and mortality in subsequent studies.

Regarding HPHCs, in the 2020 MRTP TPL review, FDA concluded that the yields of potential carcinogens, respiratory toxicants, and reproductive and developmental toxicants were considerably lower in IQOS aerosols compared with combusted cigarette smoke. This conclusion was based on aerosol chemistry data that was submitted as part of the original IQOS MRTP application. This data included also the results of a non-targeted differential screening, NTDS, with the aim of identifying and characterizing the IQOS aerosol and comparing it with 3R4F reference cigarette smoke for all constituents present above a concentration of more than 100 nanograms per stick.

The NTDS showed the following results. First, the 3R4F reference cigarette smoke yielded 3,580 unique constituents that were not present in IQOS aerosol. The NTDS demonstrated that the 3R4F reference cigarette smoke and IQOS aerosol contain common constituents. 670 of these common constituents were present at lower or equivalent levels in IQOS aerosol compared to 3R4F reference cigarette smoke. Lastly, 80 constituents were either present at higher levels in IQOS aerosol compared to 3R4F reference cigarette smoke or unique to IQOS aerosol.

It should be expected that there are unique compounds detected in IQOS compared to 3R4F, considering that IQOS and 3R4F are based on different tobacco plants. The data provided up to this point was part of our previous MRTP application. As part of our PMSS program, FDA requested us to further investigate the toxicological profile of these 80 constituents and their potential metabolites. Let me show you how we approached this and what the results were.

We performed a multi-year research program using computational toxicology to predict the genotoxicity and carcinogenicity potential of those 80 parent constituents and their relevant metabolites based on their functional properties and chemical structure. The study protocol was reviewed and accepted by FDA.

The study itself was conducted in three phases. Phase 1 was to determine the genotoxicity and carcinogenicity potential of the 80 parent constituents. Phase 2 was to determine the potential metabolites of these 80 constituents, which would be relevant to humans. And Phase 3 was to determine the genotoxicity and/or carcinogenicity potential of these relevant metabolites.

For the 80 parent constituents, we first determined which constituents are of no concern and which have potential concern. The majority, 44 out of 80, had no structural alerts for either genotoxicity or carcinogenicity. Then, we assessed the characteristics and prediction confidence of the remaining 36 constituents with potential structural concern. Prediction confidence measures the extent that the computational method is predictive of experimental results, for example, animal studies.

This assessment showed that the predictive confidence was high for only five constituents regarding genotoxicity and for only six regarding carcinogenicity, with one of those constituents predicted as potentially both. Therefore, only 10 constituents out of the 80 parent constituents investigated were found to have cancer-related toxicity potential with a high level of certainty.

When we look at the potential metabolites of the 80 parent constituents, the vast majority, 93 percent, were not biologically relevant. In addition, 30 metabolites had no structural alerts for genotoxicity or carcinogenicity. Of the remaining 87 metabolites with potential structures of concern, prediction confidence was high for only eight metabolites regarding genotoxicity and one metabolite regarding carcinogenicity, with one metabolite predicted as potentially both. Therefore, there were eight metabolites in the model that were found to have cancer-related toxicity potential with high level of certainty.

The computational toxicology screening demonstrates that the vast majority of constituents present in higher quantities, or that are unique to IQOS aerosol and their metabolites, pose no toxicological concern. Considered in conjunction with the well-characterized reduction of HPHCs in IQOS aerosol compared to cigarette smoke, the overall toxicant exposure profile of IQOS is significantly reduced relative to cigarettes.

This is further supported by our previously submitted in vitro and in vivo toxicology studies, which showed a significant reduction in toxicity due to IQOS aerosol compared to cigarette smoke exposure, and a significantly decreased genotoxicity and carcinogenicity potential for IQOS aerosol relative to cigarette smoke.

Until now, we have discussed the outcome of aerosol chemistry and computational toxicology data. To help put the NTDS data into context, we calculated the excess lifetime cancer risk, or ELCR, which was not part of our PMSS requirements. For this analysis, we followed the methodology outlined in the FDA memorandum on calculating ELCRs for ENDS PMTAs.

The results show that the ELCR of IQOS aerosol is estimated around 80 percent lower than that of cigarette smoke. Taken together, the new computational cancer screening data and ELCR calculation, further supports the conclusion reached by FDA in our prior authorization, that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely.

Finally, let's discuss human biomarker studies. Our pre-market biomarker studies showed a significant reduction of HPHC exposures in smokers who completely switched to IQOS. The FDA confirmed this during review of our original MRTP application stating that, “Findings from the clinical studies suggest a significant reduction in biomarkers of exposure to 15 HPHCs when smokers switched completely to IQOS. The reduced biomarkers of exposure reflect the range of chemical and toxicity classes.”

While FDA did not require additional biomarker studies as part of our post-market studies, we took an additional step to further assess exposure reduction in additional clinical studies. Since our original submission, we completed two additional human studies and one post-hoc analysis to further characterize the exposure reduction potential of IQOS products.

These studies include a 6-month extension of our exposure response study that was submitted as part of our original MRTP application, a 12-month ambulatory smoking cessation study, and a cross-study post-hoc analysis between the two studies. The data from the smoking cessation study adds important insights on how reduction in exposure from using IQOS versus cigarettes would compare to the exposure reduction achievable when quitting smoking.

So, let's look at the results from the cross-study post-hoc analysis. Using the data from both the exposure response and smoking cessation studies, we assessed changes in biomarkers of exposure over time associated with two conditions of use, predominant IQOS use and exclusive IQOS use. Predominant IQOS use is defined as equal or more than 70 percent IQOS use on more than 50 percent of the days in the analysis period, based on self-reporting. Exclusive IQOS use was biochemically verified.

As you can see, predominant IQOS use, the light blue bars, and exclusive IQOS use, the dark blue bars, were compared to continued smoking over time, represented here by the zero line on the top of the graph. At the 6 months time point, results show that predominant IQOS use led to statistically significant reduction in the measured biomarkers of exposure compared to continued smoking while exclusive IQOS use had even greater reductions in all measured biomarkers of exposure.

To provide further context, we compared these reductions observed in the group switching to IQOS to those achieved in the group of smokers who quit, the green bars on the graph. To clarify, quitting is defined as abstaining from using any tobacco and nicotine consumer product for the duration of the study. As shown by comparing the dark blue bars to the green bars, exclusive IQOS use showed significant reduction across all biomarkers of exposure, which were similar in magnitude to those observed among smokers who quit all tobacco and nicotine.

This data demonstrates a clear and measurable association between the reductions in biomarker of exposure and the rate at which users successfully substitute IQOS for combustible cigarettes, highlighting the need for effective consumer education to encourage complete switching to IQOS for maximized individual health benefit. This data also shows that exposure reductions from switching to IQOS exclusive use come close to those achieved when quitting smoking.

In our original MRTP application, we also submitted results on biomarkers of potential harm stemming from our 6 months exposure response study in about 1,000 healthy smokers. The study results showed that all biomarkers of potential harm shifted in the direction that would be observed when people quit smoking, with five out of eight biomarkers of potential harm tested being statistically significant.

To investigate how biomarkers of potential harm evolve in a real-world setting when IQOS users are compared with current and former smokers, we designed a risk marker cross-sectional study. In brief, we screened 1,300 participants, of which, in total, 974 current smokers, current IQOS users, and former smokers were enrolled.

Current and former smokers were matched with current IQOS users by region, age, sex, and self-reported product use, which resulted in 888 participants or 296 triplets being included in the analysis. Current smokers were included in the study if they had used equal to or higher than 10 cigarettes per day and had smoked 10 cigarettes per day for at least 10 years. IQOS users and former smokers had similar smoking history and were required to have either switched to IQOS or stopped smoking for, at minimum, 2 years prior to the study.

Using the data from the risk marker, cross-sectional study, we assessed changes in biomarkers of potential harm for respiratory function, lipid metabolism, cardiovascular function, inflammation, oxygen transport, genotoxicity, oxidative stress, endothelial function, and blood clotting in a real-world setting. IQOS users had switched, on average, for 4.5 years, and former smokers had stopped smoking, on average, for 8 years.

The results show that switching to IQOS, the dark blue bars, were associated with favorable and significant differences in all biomarkers of potential harm, including those directly related to cardiovascular and respiratory function, in comparison to current smokers, represented by the zero line on the two graphs. Importantly, IQOS users had similar results compared to former smokers, the green bars.

And while biomarker of potential harm may not be direct predictors of disease risk, all are related to biological pathways linked to smoking-related disease, and some of them, for example, FEV1, AIx, and HDL-C, are used as risk factors or diagnostic criteria for smoking-related diseases. The fact that all biomarkers of potential harm showed similar results for IQOS users and former smokers in a real-world setting gives strong confidence that it is reasonably likely future studies will demonstrate a reduction in morbidity and mortality in those who completely switch to IQOS versus continued smoking.

The collective evidence presented today further supports FDA's prior conclusion that the totality of evidence presented suggests that the measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely. This determination predominantly stems from the substantial reduction in HPHCs relative to combusted cigarette smoke.

This concludes my presentation, and I'll hand it over to my colleague, Mr. Magnani, who will discuss our post-market evidence on consumer understanding, perceptions, and use behavior. Thank you.

Pierpaolo Magnani:
Thank you, Dr. Picavet, and good morning. Today, I will cover two important areas. The first area is the consumer understanding of IQOS reduced exposure claim, as well as the risk perception of IQOS. The second area is IQOS use behaviors and its impact to the population as a whole, taking into consideration tobacco users and nonusers.

FDA authorized the marketing of IQOS in the U.S., concluding that the scientific evidence submitted with the applications demonstrated that IQOS is expected to benefit the health of the population as a whole. The modified risk granted order also set out clear marketing requirements that require us to conduct rigorous post-market surveillance and studies. Based on those requisites, we submitted our plan, and upon the FDA's review and approval, started to implement the studies.

As we will see in the next two sections, the results of the studies continue to demonstrate that, first, consumers correctly understand the authorized reduced exposure claim as shown by data from our IQOS cross-sectional post-market adult consumer study, PACS in short. Second, IQOS has a positive impact on tobacco use behavior as observed in both the PAC studies, as well as in the IQOS owners panel longitudinal study. Specifically, the overwhelming majority of IQOS users have a history of cigarette smoking. Many of them switched completely to IQOS or smoked fewer cigarettes, and the reduced exposure claim helps promote such behaviors.

Third, there is very low use of IQOS among youth as evidenced from the Underage Tobacco Use Survey, or UTUS, and confirmed by the NYTS. Therefore, in line with FDA previous conclusions, the totality of evidence continues to demonstrate that IQOS is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

Let's begin with the consumer understanding of IQOS to reduce exposure claim, as well as the risk perception of IQOS. FDA concluded that consumers demonstrated understanding of the authorized reduced exposure claim. The TPL review stated that consumer understanding is in line with the relative risk of the products that are reasonably likely, and consumers did not interpret the claim to mean that IQOS use was risk free.

We confirmed this is in one of the studies implemented as part of the post-market studies requirements, the cross-sectional post-market adult consumer study, or PACS. This study was a repeated cross-sectional post-market study among adult IQOS users. It provided important and robust data on consumer understanding of the IQOS reduced exposure claim, and the risk perception of IQOS compared to combustible cigarettes.

The study ran from September through November of 2021 and collected data from 688 established IQOS users. The study was altered in November 2021 because of the International Trade Commission ruling mentioned earlier. On October 13, 2021, information was sent to IQOS users stating that IQOS would no longer be available for sales in the U.S. as of November 28, 2021. Therefore, the study results shown today focus on the current IQOS users who completed the study prior to receiving the information letter in October 2021, resulting in an arrayed sample

size of 463 participants.

The first important aspect when assessing the understanding of the claim is to measure the extent that IQOS users understood that using IQOS reduces the exposure to HPHC compared to continuing smoking cigarettes. This graph illustrates how IQOS users perceive the exposure to HPHCs after switching completely from cigarettes to IQOS. It shows the percentage of users who understood their exposure as decreased, remained the same, increased, or there was no exposure.

In this chart, the dark blue section shows that a high proportion, 81 percent, of IQOS users understood that exposure to HPHCs is reduced when switching completely from cigarettes to IQOS. In other words, 81 percent had a correct understanding.

The second important aspect when assessing the understanding of the claim is to measure the extent that IQOS users understood what smokers are supposed to do to reduce their exposure to HPHCs. This pie chart presents the level of understanding of IQOS users about what smokers must do to reduce their exposure to HPHCs. The dark blue section here shows that a high proportion, 85 percent, of IQOS users understood that they should stop smoking completely and only use IQOS. In other words, 85 percent had the correct understanding.

The same PAC study also provided data regarding the perceived health risk associated with using IQOS compared to combustible cigarettes. We used a psychometrically validated ABOUT-Perceived Risk instrument, with a score ranging from 0, no risk, to 100, very high risk, to assess the perceived health risk of IQOS and cigarettes.

Data shows that IQOS users perceive the health risk of smoking combustible cigarettes, the gray bar on the left, to be higher than the risk associated with using IQOS, the dark blue bar on the right. Importantly, consumers did not interpret the reduced exposure claim to mean that the product is risk free. Consumers' understanding of the health risks associated with using IQOS aligns with the relative risks of the product that are reasonably likely, as outlined by the FDA.

I will now turn to the second topic, IQOS use behaviors and its impact to the population, taking into consideration both tobacco users and nonusers. As concluded in the FDA's thorough reviews of our MRTP applications, "Marketing of IQOS with a reduced exposure claim could appeal to current smokers who are most likely to benefit from their use, and this supports a likely benefit to population health."

FDA's conclusions align with our mission to market smoke-free alternatives, such as IQOS, to adults who smoke. Our post-market evidence confirms FDA's previous conclusion that current smokers are the most likely population to use IQOS and that these users are likely benefiting from the products and the claim.

The PAC study described previously also provides data about the participant's history of tobacco product use before trying IQOS. The data shows that all IQOS users had a tobacco-use history prior to trying IQOS. More specifically, 99.3 percent of them had a history of cigarette smoking. while the remaining 0.7 percent used other tobacco products before trying IQOS. This data

supports that the population most likely to use IQOS is current adults who smoke cigarettes and shows little to no initiation of IQOS among never tobacco users.

In addition to the history of tobacco product use before IQOS, the study also measured whether IQOS helped to stop smoking cigarettes, as well as the impact of IQOS on cigarette consumption. At the time of the survey, 50.6 percent of IQOS users were no longer smoking cigarettes as shown in the light blue section of this pie chart [inaudible] were former smokers. The proportion of former smokers was higher than the proportion of IQOS users who were using both IQOS and cigarettes, 48.8 percent, as shown in the dark blue section here.

Next, the role that the claim might have had in helping this transition. Here, we are looking at the smoking status of adult IQOS users according to the understanding of the reduced exposure to HPHCs. On the left-hand side of the slide, we are showing IQOS users who incorrectly understood the reduced exposure to HPHCs. Meaning that they understood that by switching completely to IQOS, their exposure remains the same, increases, or there was no exposure. 61.9 percent of them continue to smoke cigarettes, the dark blue bar, while 34.9 percent were not smoking cigarettes, the light blue bar.

Conversely, on the right side of the slide, we are presenting IQOS users who correctly understood that switching completely to IQOS reduces their exposure to HPHCs. 45.9 percent of them continued to smoke cigarettes, the dark blue bar, while 53.8 percent were not smoking cigarettes at the time of the survey, the light blue bar.

To summarize, the percentage of IQOS users who were former smokers, shown by the two light blue bars, was lower when there was an incorrect understanding compared to when there was a correct understanding. This data suggests that a correct understanding of reduced exposure to HPHCs might be linked with higher likelihood of becoming a former smoker.

At the time of the survey and as previously mentioned, there was a portion of IQOS users who were smoking cigarettes. This chart presents what was reported by IQOS users who were smoking cigarettes in terms of changes in cigarette consumption per day compared to before trying IQOS. The dark blue section of this pie chart shows that a large proportion of IQOS users, 83 percent, reported smoking fewer cigarettes compared to before first trying IQOS.

Now, still looking at IQOS users who are smoking cigarettes, we can observe a second positive outcome of having correctly understood the reduced exposure to HPHCs. Among those who had an incorrect understanding of the reduced exposure to HPHCs, shown on the left-hand side of the chart, 59 percent of them smoked fewer cigarettes per day compared to their baseline consumption, as indicated by the dark blue bar. Conversely, among those who correctly understood the reduced exposure benefit of IQOS, shown on the right-hand side of the chart by the dark blue bar, 89.1 percent of them decreased their cigarettes-per-day consumption compared to baseline.

To summarize, the percentage of IQOS users who smoked combustible cigarettes and reduced their cigarettes-per-day consumption, shown by the two dark blue bars, was lower when there was an incorrect understanding compared to when there was a correct understanding.

So far, I have presented data demonstrating that the vast majority of IQOS users have a history of cigarette smoking before starting to use IQOS. The data also demonstrates that IQOS use was associated with stopping cigarette smoking for many adults who smoke and that many IQOS users who are using both IQOS and cigarettes were reducing their cigarettes consumption. Finally, that also shows that the correct understanding of the claim may have a positive effect on both cigarette smoking status and cigarette consumption.

We can now turn to an examination of use trajectories over time. In line with FDA's recommendation to collect longitudinal data and in addition to cross-sectional studies, we conducted a longitudinal post-market study among IQOS users in markets where IQOS was commercialized, called the IQOS Longitudinal Owners Panel. Unlike the PAC studies, which collected data at one point in time, this longitudinal study followed participants starting May 2020, with a growing number of IQOS users in the survey over time.

Similar to what was mentioned earlier, on October 2021, an informational letter was sent to IQOS users stating that IQOS would no longer be available for sale in the U.S. as of November. Therefore, the study results shown today focus on the IQOS users who were in the study prior to October, resulting in the analyzed sample size of 443 participants in August 2021.

Data from the IQOS Longitudinal Owners Panel shows that over time, the majority of IQOS users completely switched from combustible cigarettes to IQOS, shown here in the dark blue bars. The proportion of IQOS users who completely switched to IQOS from cigarettes remained slightly above 50 percent throughout 2021.

Finally, let's discuss the risk of youth uptake. We are committed to preventing youth initiation and youth use of nicotine-containing products. Therefore, we have continued to carefully monitor this specific population across time and following FDA requirements on our post-market surveillance program. In its TPL review, FDA stated, "Current use patterns available for the authorized products within the U.S. have not raised concerns regarding product use in youth and young adults." We provide post-market evidence that youth use of IQOS remains very low.

To monitor youth in the U.S., we developed an analysis plan as one component of the post-marketing surveillance studies program approved by FDA. We analyzed data from a preexisting underage tobacco use survey called the Underage Tobacco Use Survey, or UTUS. This study is a repeated, ongoing, nationally representative, cross-sectional survey of individuals between 13 and 20 years of age living in the U.S. The study targets a sample of 5,000 participants annually. The study measures awareness and use of different categories of tobacco products, including e-tobacco products, with some specific questions on IQOS as set out by the FDA as part of the modified risk granted orders.

This chart presents the past 30-day use prevalence estimates of e-cigarettes, cigarettes, and HTP use between 2020 and 2024 among U.S. youth and young adults. Data shows that the past 30-day use of HCPs between 2020 and 2024, displayed by the purple line at the bottom of the chart, is very low, with less than 1 percent among U.S. youth and young adults. The very low use of IQOS was also observed during the time when IQOS was commercialized in 2020 and 2021.

The National Youth Tobacco Survey, often referred to as NYTS, similar to the UTUS estimates, shows a very low past 30-day use of HTPs. Based on the NYTS data, past 30-day use of HTPs among U.S. youth has remained low since 2020, including during the time when IQOS was commercialized in 2020 and 2021.

To conclude, first, the evidence presented by my colleague, Dr. Picavet, confirms previous FDA findings that IQOS is effective in reducing HPHCs exposure compared to combustible cigarettes. Computational toxicology results show that the majority of screened constituents pose no carcinogenic concern, which translates to an estimate of around 80 percent reduction in excess lifetime cancer risk.

Relatedly, when evaluated, exclusive IQOS use at 6 months, in the studies presented today, there were up to 91 percent reductions across all measured biomarkers of exposure, which were similar in magnitude to what was observed for cessation. Switching to IQOS was also associated with favorable and significant differences in all measured biomarkers of potential harm, including those directly related to cardiovascular and respiratory function, in comparison to current adults who smoke.

Second, the evidence from post-market studies continues to show that consumers understand the reduced exposure to HPHCs when switching completely from cigarettes to IQOS. Third, data also shows that the population most likely to use IQOS are adults who smoke and that many IQOS users no longer smoke cigarettes or have reduced their cigarette consumption. Fourth and finally, the data also shows that youth use of IQOS is very low.

The totality of evidence presented today continues to demonstrate that IQOS is expected to benefit the health of the population as a whole, taking into account both users and nonusers of tobacco products.

Let me now pass it over to my colleague, Mr. Simko, who will present our responsible marketing practices and controls as they pertain to IQOS in the U.S. Thank you.

JB Simko:
Thank you, Mr. Magnani. Good morning. The focus of my presentation today is on the nearly 30 million people in the U.S. who smoke cigarettes. The best choice is to quit tobacco and nicotine altogether, but the fact is, most don't. Adults who continue smoking deserve accurate information and access to FDA-authorized products like IQOS. And the reduced exposure claim is an important component in our approach to help them move away from combustible cigarettes.

Here are the specific topics that we'll cover in my short presentation. I'll first explain who our intended audience is and our marketing approach to encourage switching to IQOS. Next, we'll turn to the steps we take to minimize underage access. Last, I will discuss how the reduced exposure claim is used to inform and encourage adults who smoke to try IQOS and make the switch.

We believe IQOS could be the product of choice for many American men and women who

smoke. We specifically designed the IQOS system to appeal to adult smokers, but the technology is new and unfamiliar. For this reason, there are three key components to our approach for commercializing IQOS.

First, we need to build awareness about heated tobacco products as a category and IQOS as an alternative to smoking. Second, we need to create opportunities for adult consumers to try and buy the product. Third, we need to support IQOS consumers after purchase, so they can switch completely to IQOS or significantly reduce consumption of combustible cigarettes.

The reduced exposure claim as a comparative claim versus combustible cigarettes plays an important role throughout this process. While adults who continue smoking deserve access to information about IQOS, underage access prevention is also critically important and embedded throughout our business. Let me share with you some of our core policy positions intended to prevent underage access.

On this slide, you'll see some of our core positions for marketing our products. We direct our marketing to adults 21-plus who smoke. We conduct online age verification to control access to our branded websites. Our advertising only features individuals age 35 and over. We use age verification systems to direct our digital advertising, email, and direct mail only to those 21-plus. We also do not pay social media influencers to endorse our products.

As part of the FDA's post-market requirements, we submit marketing, labeling, and advertising materials through an annual report. We also report advertising impressions and media tracking by age segment each year. These practices demonstrate our commitment and actions to guard against underage use of our products and also the ongoing FDA oversight.

These practices also dictate our approach for age verification at the point of sale which are represented by the highlighted boxes on this slide. As you can see, there are multiple steps for age verification throughout the process for both face-to-face and e-commerce sales. Focusing on e-commerce, each visitor is age verified before accessing the site. At the entry page, each visitor is notified that age verification will take place. The individual is then asked to enter specific information, including a phone number and date of birth.

They then receive a text to confirm that the phone number provided is the person seeking access to the site. And once the code is confirmed, the personal information provided is cross-checked by an independent age and identity verification service to confirm the person is 21 or older. The individual will then have access to our e-commerce site. If a purchase is made, there will also be age verification done upon delivery, in line with applicable requirements for delivery of age-restricted products.

Let's turn to the reduced exposure claim, and I'll show you how this is used to communicate with adult consumers. I spoke previously about the importance of creating awareness, product trial and purchase, and conversion. These are the specific channels we use to communicate the reduced exposure claim to adult consumers. Advancements in technology enable us to have a very high level of confidence that we are communicating with adults 21-plus in these channels. And through our annual reporting, the FDA is aware of our marketing activities in each channel.

Let me show you some specific examples of where the reduced exposure claim is used. These are examples of marketing materials. The first box on the left is an example of a print or digital ad. We use this to help build awareness about IQOS. It's primarily focused on the science and the heating technology and includes the reduced exposure message.

The second box shows an in-store brochure. We provide product information, and the reduced exposure claim to encourage product trial and purchase. The third box shows device packaging. We use the reduced exposure claim on a side panel, along with instructions and aftercare support materials inside, which are intended to encourage complete conversion to the IQOS system.

As I said at the outset, adults 21-plus who continue to smoke deserve accurate information and access to alternative products like IQOS. And the reduced exposure claim is an important driver to encourage complete switching. I'll now turn it back to Ms. Lenihan to close our presentation. Thank you.

Keagan Lenihan:
Thank you, Mr. Simko.

The comprehensive review of post-market evidence continues to support FDA's previous conclusions regarding IQOS use and health risks, consumer understanding, consumer perception, consumer use behavior, and the potential impact on population health. No new information has emerged which contradicts or materially changes the scientific foundation on which FDA's conclusions were based. The available post-market evidence further reinforces FDA's original decision to authorize these products as modified risks with reduced exposure claim.

The available data continues to support that completely switching from combustible cigarettes to IQOS products can significantly reduce exposure to HPHCs. And the available evidence continues to show that communicating this information to adults who smoke is helping to achieve PMI’s and the agency's desired outcome for both individual adults who smoke and the population as a whole.

The opportunity for harm reduction in adults who smoke remains great. Potential risk of use by youth and adults who don't smoke remains low. Scientific evidence and data continue to demonstrate the harm reduction potential of IQOS with the reduced exposure claim and supports the conclusion that IQOS modified risk granted orders should be renewed.

It's important that we put ourselves in the shoes of American adults who smoke. They are bombarded with confusing, contradicting, and often misleading information about better alternatives to continued smoking. The needs and wants of adults who smoke are often ignored or outright dismissed.

Through the MRTP pathway, adults who smoke can receive clear, accurate communication about scientifically substantiated alternatives, providing them an opportunity to make informed decisions. The results are real. Initially, IQOS was marketed in one city in Japan and Italy, more than 10 years ago. Today, IQOS is making positive changes for adults who smoke in 83

countries.

Our most recent estimates demonstrate that approximately 23 million adults have left smoking behind and fully switched to IQOS. And already in the U.S., IQOS consumers are sharing their stories with us, expressing their sincere thanks for the impact switching to IQOS has had on their lives. Today, together, we can continue to meaningfully advance CTP's important mission to give adults who smoke more chances to move away from cigarettes.

In closing, I want to thank the committee, the FDA, members of the public, and our team for the collaborative effort to achieve these important MRTP authorizations, and we look forward to continuing the discussion. We are now happy to answer any questions you may have. Thank you.

Cristine Delnevo:
Thank you. We're going to proceed with some clarifying questions, and I'm going to start. I have a few. The first is actually not a question, but to be clear, PMI does sell combusted tobacco products in the United States. You don't sell cigarettes, but you do sell cigars in the United States; is that correct?

Keagan Lenihan:
We do not sell cigarettes, correct.

Cristine Delnevo:
You do sell cigars, though. Your point about no combustible tobacco products is limited to cigarettes.

Keagan Lenihan:
To be clear, yes, we do not sell combusted cigarettes in the U.S.

Cristine Delnevo:
Right. So, my first question has to do with the additional smoking cessation study, and I appreciate that that data was presented. And I just want—this is more clarifying for me. So, that was not a required study as part of the post-market surveillance requirements from FDA, right?

Keagan Lenihan:
That is correct; it was not required.

Cristine Delnevo:
Right. When was that study done, and did FDA review and approve that protocol?

Keagan Lenihan:
I'm going to ask Dr. Picavet to come talk about that study, to the best of his recollection. Thank you.

Patrick Picavet:
Thank you. I have to check, honestly, on exactly when it was done, so I'm happy to come back to you on this.

Maybe let me explain briefly why we did that study. At the time when we designed the exposure response study that was submitted as part of our original MRTP application, we actually were thinking, you know, should we include in a 6- to, you know, 12-month study, a former smoker arm, basically randomizing people, you know, to quitting smoking.

And I think we decided very quickly that this is probably not a good approach, simply from compliance point of view, and it's also a different study population. So, in the ERS, in the exposure response study, it was really, you know, people that did not want to quit, you know, and in the smoking cessation study, we enrolled smokers that were actually willing to quit. You know, so these studies were done in close proximity to each other.

Cristine Delnevo:
And I may have missed it, was that a U.S.-based study?

Patrick Picavet:
No, this was not a—it is—let me just briefly have a look at this. No, well, actually, it is true. The study was done in the U.S., in Europe, and in Japan. It was, in total, 43 sites. You know, as I said before, it was smokers willing to quit. And to give maybe a bit more information, we had a male-female split, roughly, 50-50, and the average mean age was roughly 44 years, and it was all healthy smokers.

Cristine Delnevo:
Thank you. And one more question and then I'm going to open it up to the committee for clarifying questions. So, there was a lot of referring to the totality of evidence, and so, a lot of the data I'm trying to follow was collected in 2020, 2021. And there's been no new consumer perception research that has been done?

Keagan Lenihan:
No. I mean, as you know, as I mentioned earlier in the presentation, removing the product from the market limited the opportunity to engage with the U.S. population since the product wasn't commercialized in the U.S. after we removed it from the ITC case.

Cristine Delnevo:
Thank you. Dr. Popova.

Lucy Popova:
Okay. It switches mute and unmute if I do it. I have a couple of marketing questions. I appreciate going over the responsible marketing practices that PMI has. How do music festivals fit with this vision? Currently, right around October 3rd, 5th, Austin City Limits Music Festival is happening, and IQOS is advertising on social media that they're there, featuring free drinks, IQOS trials, IQOS swag, and so on.

Keagan Lenihan:
Yes, thank you for the question. You know, IQOS is a new product. Heat Not Burn is not familiar to the U.S. population, so it's important that we meet smokers where they are to have an

opportunity to educate them on what the product is and what it's not.

Our closed, age-gated events, we educate and sell products only to adult consumers. These events are age restricted and invite only. We report all of these events to the FDA. We're competing with combustible cigarettes and trying to create awareness for this category by creating interest in the new product.

Lucy Popova:
All right. And the other question is, in the first store that has been reopened after the IQOS return to the U.S. market in Austin, we have not seen any reduced exposure claims used in the store itself. Could you comment why?

Keagan Lenihan:
So, actually, the reduced exposure claim is on the device box itself, so it is listed there. Like I said, it's a new product. It's a new category. There's a lot of explanation that goes into discussing what this product is and what it's not with the coaches there onsite. So, I do think this is a—it's something that if anyone were to read the box, the reduced exposure claim is there, and we'll continue to advance how we talk about that with consumers.

Lucy Popova:
Okay, thank you.

Cristine Delnevo:
Dr. Upson.

Dona Upson:
Thank you. Do you know how many people stop using IQOS after a certain amount of time, 6 months, or a year, or do you have any data from the cessation trial that you had?

Keagan Lenihan:
I'm going to ask Mr. Magnani to come up a little bit and talk about user experience and the switching rates.

Pierpaolo Magnani:
So, the data that we showed during the presentation, taken from the cross-sectional studies, showed that, actually, more than 50 percent—and we can put slide 2 up, please—more than 50 percent of the IQOS users, they stopped using IQOS. So, they became former smokers. So, we know that changing the behavior is difficult, particularly for smokers, and complete switching to a new product takes time, and it takes time to build the awareness, the trial, and then the use of the product. But we see that former smokers are there because of the use of IQOS in a modern [unintelligible] study participants' impacts.

Dona Upson:
If I can follow up, do you have any evidence that people who use IQOS stop using IQOS?

Keagan Lenihan:

Yes, go ahead.

Pierpaolo Magnani:
Yes, we do have evidence, not from the U.S. study, because of the short time that we were present in the markets. But from international data, yes, we do see that people that they switch to IQOS, then they're able also to stop using IQOS. And we can say that, from what we observed in Japan and Italy, there is almost an equal proportion that they stop using cigarettes, as well as they stop using IQOS.

Dona Upson:
Do they stop using—do you know if they switch back to cigarettes when they stopped using IQOS, or do they stop using all forms of tobacco?

Pierpaolo Magnani:
They don't switch back to cigarettes. They stop using IQOS, meaning that they stop using IQOS, and they stop using tobacco products.

Dona Upson:
And do you know what happened to the people who were using IQOS, and—sorry—in 2021 when it was taken off the market? What did they do?

Pierpaolo Magnani:
There was a study that was done after the IQOS was withdrawn from the market, and it was showing that a vast majority were actually going back to cigarettes, or they were looking for an alternative product, but vast majority were going back to cigarettes.

Dona Upson:
Thank you.

Cristine Delnevo:
Dr. Rigotti.

Nancy Rigotti:
Hello. My question is, when I look at the packaging materials and I read the statement about reduced risk; it strikes me that it's a fairly high reading level statement. And while I don't have any trouble understanding it, I wonder whether the company has done any assessments of how understandable the message is as it's being presented, especially since we know that many cigarette users are relatively low in educational attainment.

Keagan Lenihan:
Yeah, just to confirm, it's a reduced exposure claim, not reduced risk.

Nancy Rigotti:
Sorry.

Keagan Lenihan:

It's okay. I think it's a good point, and I think we have additional conversations that we'd like to have with the agency around what an appropriate claim or warning level would look like in these types of situations so that adult consumers actually understand the benefit or risk associated with any product.

I think there's a lot of opportunity for education to adult smokers on a wide variety of products, not just IQOS, around where they sit on the continuum of risk, what MRTP claims mean, what they don't mean. I think FDA—we would welcome the opportunity to work with FDA on that level of awareness for the adult smoker.

Nancy Rigotti:
Thank you.

Cristine Delnevo:
Dr. Bailey.

William "Andy" Bailey:
Yes, thank you. Andy Bailey, University of Kentucky. I've got a couple of questions, technical questions, about the HeatStick itself on behalf of tobacco growers. The first one is, what's the amount of tobacco in a HeatStick compared to a conventional cigarette? I know it's lower, but how much lower the amount of tobacco in a HeatStick versus a cigarette?

Keagan Lenihan:
I'm going to ask Dr. Picavet to come up and give you that answer.

William "Andy" Bailey:
Thank you.

Patrick Picavet:
I think the amount of tobacco in the HeatStick is about 0.5 milligram if I recall it correctly. I would have to check back how this would compare to a normal cigarette.

William "Andy" Bailey:
Okay.

Patrick Picavet:
About a third. That's what I get from my colleagues.

William "Andy" Bailey:
One-third, okay. And my second question is, you mentioned tobacco blends that were used in the HeatStick are somewhat different from conventional cigarettes. What types of tobacco are used in the blend for the HeatStick?

Keagan Lenihan:
I'm sorry, could you repeat that question one more time?

William "Andy" Bailey:
Yes. There was mention of the blend, the tobacco blend used in the HeatStick being different from the blends used for conventional cigarettes, and I was interested in what type or types of tobacco were used in the blend for the HeatStick.

Keagan Lenihan:
I'm going to ask J.B. Simko to come talk about that.

JB Simko:
Thank you. We can provide, you know, the—all the information related to the blend is provided to the FDA. It's less burley, but it's still a blend of international tobaccos, including some U.S. tobacco. And then the real difference is the way it's processed. It's a processed tobacco and intended to be heated. And so, there are other things we do in the manufacturing process of it that are very different than—it's a crimped tobacco, essentially, as opposed to a loose leaf or cut tobacco.

William "Andy" Bailey:
Okay. Thank you. I also wondered, on the sources of tobacco, you said there is some U.S. tobacco in there. Any idea what percentage of that tobacco in the blend is grown here in the United States?

JB Simko:
I don't know the specific, but we do source from the U.S. and internationally, obviously, as well.

William "Andy" Bailey:
Okay. All right, thank you.

Cristine Delnevo:
Dr. Jordt?

Sven-Eric Jordt:
Thank you. So, one population of smokers here wasn't mentioned, and this is pregnant smokers. What will be your marketing and information provided to pregnant smokers about IQOS?

Keagan Lenihan:
Yes, I'm going to ask JB to come up real quick to talk about that.

JB Simko:
Thank you. The message would be the same as it would be for, you know, the nicotine-related warning. We would not advise pregnant women to use tobacco products. Cessation is obviously the best choice, and so that's the message that we would give them.

Sven-Eric Jordt:
Thank you. By cessation, you mean complete cessation.

JB Simko:

Complete cessation, yes.

Sven-Eric Jordt:
No use of nicotine at all.

JB Simko:
Correct. And then if—you know, beyond that, obviously they—we provide them information. They're going to make their own decisions. I think even with nicotine replacement therapy, it would suggest that you consult with your doctor, but we would continue to repeat that, you know, who nicotine is not appropriate for, those who are at risk, and that includes pregnant women.

Sven-Eric Jordt:
Including pregnant women coming into your stores.

JB Simko:
Yes.

Sven-Eric Jordt:
But they—if they still insist, they would still be sold IQOS. If they—

Sven-Eric Jordt:
I don't know—I mean, I don't believe, you know—I don't know specifically what the current training is in terms of the actual sale. Normally, we would not sell to that person, but obviously, you know, it's an adult making a decision. It's—you don't know—we aren't asking specifically, are you pregnant, as part of that process. So, it would have to be something that's quite obvious. If they asked, we would give the recommendation that the consumption of nicotine is not advised for people who are pregnant.

Sven-Eric Jordt:
Thank you.

Cristine Delnevo:
Dr. St. Helen.

Gideon St. Helen:
Thank you very much. I appreciate the work to try to identify or at least describe the toxicology of the 80 chemicals that are present at higher levels in IQOS compared to tobacco. My question is regarding the consumer understanding, and as you just heard, there appears to be lower tobacco in HEETS, and then users will get lower nicotine compared to combustible cigarettes. How does this lower nicotine, the perception of lower nicotine that the individuals will get from the HEETS or from the IQOS affect their perception of exposure to the HPHCs?

Keagan Lenihan:
Let's start by—I mean, obviously, IQOS, we're very clear that this is not risk free. This product is not risk free. It does contain nicotine, and nicotine is addictive. I'm going to pass it over to Mr.

Magnani to talk a little bit about why this is a better choice than smoking.

Gideon St. Helen:
And what I'm asking is, how does the—so the users—the people who use IQOS would get lower nicotine from the IQOS. How does that perception of the lower nicotine that they get affect the perception of their exposure to HPHCs?

Pierpaolo Magnani:
So, first, they're not going to get lower nicotine because of the lower weight of tobacco present in HEETS compared to combustible cigarettes. So, they're going to get pretty much similar amounts of nicotine. And if I go back to the understanding of the HPHCs reductions, I think we saw during the presentation that these understanding is very high. So, more than 80 percent of the PAC study participants—and we can put slide up 1—they understood that by switching completely from cigarettes to IQOS, there is a reduction in HPHCs. Now, with respect to the nicotine, I'm not the expert, but Dr. Picavet, if needed, can provide more clarification.

Patrick Picavet:
Thank you for the question. So, from our clinical work, basically, I think, we could see in all the studies that we have done that nicotine exposure after ad libitum IQOS use is quite equal, you know, basically to what you would see in a cigarette smoker compared to baseline. I can give you just an example from our ERS extension study, so slide 1 up, please.

So, here, you can see the different groups, IQOS or people who actually combined IQOS and cigarettes to a certain extent. You remember we had this discussion on predominant users of cigarettes only, and you can see, you know, essentially that the nicotine exposure, you know, is quite similar. So, people simply adapt basically to, you know, to the new product and achieve, actually, the baseline nicotine levels that they had at the start of the study when they were still smoking cigarettes.

Gideon St. Helen:
So, this is from repeated use, but not from using one of the HEETS.

Patrick Picavet:
This is correct, and I think you referred to our pharmacokinetic studies, which is true in those. We actually have seen, in the U.S., I would remember it correctly, roughly 60 percent lower exposure. In the U.K., it was roughly 40 percent, and in Japan, it was a bit on equal terms. I think the way how you have to look at this is basically that transitioning to a new product and actually understanding how to use the product takes a bit of time.

To give you a concrete example, if you are a cigarette smoker, and you want to get more volume out of the cigarette, you inhale heavier at the end of the day, right? As you put more oxygen, you know, actually in the combustion process, so you get actually more smoke.

When you would do this with an IQOS product, it would actually have the reverse effect because you're drawing air through the system. It cools the blade. It lowers the temperature. And from that, the delivery actually becomes slower. So, single use, in a lot of cases, you know, shows that

people actually have to adapt, so which is why we're looking mainly on the multiple-use studies to actually understand how nicotine exposure really looks like.

Cristine Delnevo:
Dr. Zelikoff.

Judith Zelikoff:
Okay. Thank you. Thank you for the informative discussion. I have a couple of questions. Following up on the nicotine question, you said "found in a smoker." Do you mean it's equivalent to one cigarette? Do you mean that it's equivalent to a pack-a-day smoker? How do you relate—how can you relate the two?

Keagan Lenihan:
I'm going to ask Dr. Pat Picavet to come up and explain.

Patrick Picavet:
Thank you. Thank you for the question. So, look, I think when I just refer back to the exposure response study crafted that I showed you before, so here at baseline, people were using, roughly, somewhere between 18.5 and 19.5 cigarettes per day at baseline, as they were smokers. And so, at the end of the day, well, it gives you a feel of, you know, it's roughly a pack, basically, that they had used, at baseline.

So, when we switched them over to IQOS, what we actually see is that from a product-use perspective that they're not increasing, actually, their product use as such per item over time, but they're simply adjusting by using the product differently to the same nicotine level at baseline. So, it's not like, you know, you have had 18 cigarettes at baseline, and then you used 40 IQOS HeatSticks during the study. That's actually not what we are saying, you know, on average, of course.

Judith Zelikoff:
Okay. My next question is, if I understand correctly, the data that you have was accumulated while it was—while the product—while IQOS was marketable or marketed. So, is that 1 year?

Keagan Lenihan:
So, there was pre-market data as well as data while the product was on the market. And then certainly, we continue to collect international data as the product is available in 83 countries around the world.

Judith Zelikoff:
So, then I'm a bit confused because I thought it was stated that no studies were actually done after the shutdown of the product?

Keagan Lenihan:
I would say specifically to the U.S., but I'll have Mr. Magnani to come up, talk a little bit about some of the additional studies.

Pierpaolo Magnani:
I think that's exactly correct. So, no further studies in terms of consumer studies were done since the product was withdrawn from the market. And of course, we will start the study in accordance with the FDA, if the MRTP will renew it, and we will follow-up with the PMSS program in the future in the U.S.

Judith Zelikoff:
So, then my question for that is, that was a very short period of time, in general, for considering safety and perceptions. Do you feel that the data that you collected in that 1-year period or one-and-a-half-year period will be reflective of the data that you will collect once it's on the market for a longer period of time?

Keagan Lenihan:
I think if we're talking about comparable to cigarette smoking, yes, I think we're quite comfortable with the data. I think, you know, this was assessed by the FDA as part of our PMTA. FDA found this product to be appropriate for the protection of public health. While we're here to talk about the MRTP authorization and the reduced exposure claim, I do think that we're very confident as the product continues to gain momentum, internationally, and conversion rates away from cigarette smoking, it's a positive sign.

Judith Zelikoff:
Okay. Thank you.

Keagan Lenihan:
You're welcome.

Cristine Delnevo:
Dr. Stepanov.

Irina Stepanov:
Yeah. Thank you for a very informative presentation. I wanted to clarify something. So, I do appreciate that the lack of burning process would lead to much lower number of chemicals present in IQOS. However, looking at your data, you identified in the range of 3,500 chemicals in smoke, in reference cigarettes, which account for about half of all chemicals reported to be present in cigarette smoke. So, is it safe to assume that by using your method, you are missing about half of chemicals that might be present in IQOS aerosol as well, including some potentially carcinogenic or toxic chemicals?

Keagan Lenihan:
No, that's not the case, but I'll ask Dr. Picavet to come up and talk a little bit about the biomarks of exposure and then the studies.

Patrick Picavet:
Thank you. So, if I understand your question correctly, it is actually focused on our non-targeted differential screening.

Irina Stepanov:
Yes.

Patrick Picavet:
Thank you for confirming. So, I think what you have to keep in mind is that we used the 3R4F reference cigarette which is an unflavored, specific blend. Okay? You know, when you think about the—I think it's—today it's plus 8,000 chemicals that are listed in Rochman et al. This is something that goes across all various blends that are actually out there.

So, by definition, you will, depending on which potential cigarette blend you would actually look at, you would get different numbers. Okay? Which is also part of the reason, I think, why you see in—when you compare it to IQOS, why you see, for example, that there is some unique or some higher chemicals in IQOS than actually in 3R4F.

So, that said and to address the second part of your question, it is understood that the non-targeted differential screening is a semi-quantitative method, you know. So, the cutoff point is roughly 100 nanograms, basically, in terms of concentration. So, there is a possibility that there are compounds that under this that you cannot detect. But then, of course, you know, the reality also is that this compound you would not detect either in cigarette smoke or in IQOS. So, from a relative assessment point of view the statements that we made today, I think, still stay true.

Irina Stepanov:
Yeah, thank you for clarification. And just to make sure I understand, so you said the cutoff is about 100 nanograms, but most potent carcinogens do not require really high doses. So, it's not necessarily a direct-dose response effect with toxicity. Do you agree with that?

Patrick Picavet:
Yes, this is clearly understood. So, let me be a bit more specific then. So, when we look at the aerosol mass with this cutoff, we have identified basically, 98.9 percent of the total aerosol mass. Okay? When we look at the 80 parent compounds that were identified and we think about the 40 of them that we included in the ELCR calculation, the yield of those is roughly around 79—it's around 80 micrograms, basically. Okay?

When you compare this to the yield of carcinogens that you have in a 3R4F, which is roughly 3 milligrams, you can basically see there is tenfold-plus difference, no matter how you calculate it, between what you would find in an IQOS aerosol versus in a 3R4F. And as I said before, of course, if you would use a different cigarette with a different blend, you would very likely get different results.

Irina Stepanov:
Thank you. Again, just not to be repetitive, but it would be nice to see comparison to actual commercial cigarettes that are being smoked. But I have a couple of other, really brief clarifying questions. So, your figure 22, or it was slide CC48, so there is an obvious trend toward increase in dual use, meaning, you know, concurrent smoking in users of IQOS, over time, in two of your studies. Did you look into the potential drivers? So, what drives this increase in dual use and also, if there is anything about the demographics of people who end up being dual users?

Keagan Lenihan:
Yeah, I mean, I think, to Mr. Simko's earlier point, we have one kind of population that we're focused on, and that's the adult smokers. So, demographics isn't something that we spend a lot of time on. I think it's important to note that changing behavior is difficult. Switching from combustible cigarettes, especially for an adult that's been using this for potentially decades, takes time.

It's a new product. It's different for each adult smoker. Dual use is often a transitional state, but we do recognize that there is some dual use. But at the same time, moving away from combustible cigarettes, even if not completely, is still a benefit to public health and individual health. I'm going to ask Mr. Magnani to come up to talk a little bit about the switching.

Pierpaolo Magnani:
Thank you. I think you are referring to slide 1. Up, please. So, you're referring to these slides? Please, can you confirm that was—

Irina Stepanov:
No. I think it might have been one of the prior slides that shows increase—apologies, I didn't write it down correctly. It might have been 46, either 46 or 43. It is figure 22 in your submission.

Pierpaolo Magnani:
[Inaudible]. Anyway, we recognize dual use is one of the behavior. It's—we acknowledge. It's also, as Ms. Lenihan was explaining, one of the behaviors that might happen at the very beginning of the journey, moving away from cigarettes to IQOS. So, it's very often a transient status that then can turn into switching completely to IQOS, though some of the—of course, some of the IQOS users, they remain dual.

But that's also the importance of communicating the claim. Because communicating the claims can help convincing them to move away from cigarettes. And we saw that in international markets when we conducted a study—longitudinal studies, and we saw that the more participants were perceiving that there was a benefit in terms of reduction of production of harmful and potentially harmful compounds, the higher was the level of exclusive use in those international markets.

And just to close, again, referring back to the presentation, we saw also, and we can put slide 1 up, please, we saw that even in the U.S., with the limited time that we had the product in the market, when there was a correct understanding, there was also a higher reduction in terms of cigarettes per day compared when there was an incorrect understanding. So, even in dual users, there is a positive effect that is bring by the fact that they are aware, and they know about the claim, reduced exposure claim.

Cristine Delnevo:
I'm going to actually call on Dr. Scout for a final clarifying question, and then we're going to need to move along to keep the agenda going. Dr. Scout, do you have a—

NFN Scout (they/he):
I do, yes. Yeah. I actually have three questions. I would like to ask all three.

The first one is, there's a pretty marked contrast between the studies you're presenting and the independent studies that we got in the testimony that was submitted. And we do know that places like Cochrane have already found that there is an attempt by the tobacco industry to flood the arena with research and that much of that could potentially be biased.

As just one example, you report complete conversion over to IQOS and off of combustible cigarettes at a rate of about 70 percent, and there's one of the studies that shows consistently, again and again, it's about 33 percent from Japan. So, my first question is, if you could comment on the systemic difference in the level of findings between independent studies and your own, and if you can find any reason for that.

The second question, we are at a particularly interesting juncture where after the tobacco industry was the number one corporate donor to the current administration, at the recommendation, according to the Washington Post, by your own lobbyists as an effort to pursue deregulation of any tobacco products.

And after this administration has been put into place now, we have seen the Office of Smoking and Health be fired at CDC. Only one staffer is left there. As well, CTP, who we are dealing with here today, has had their Office of Management and their Office of Regulation fully fired. My question is simply a yes or no question. Is the tobacco industry going to continue to use political influence to undermine the regulatory process?

And then the third question, expanding on what Dr. Popova had talked about related to the music festivals, I was saddened to see one of my favorite electronic house DJs have a concert sponsored by IQOS. And as someone who has now been an expert advisor, subject matter expert on media outreach to both the FDA and the CDC, as well as other organizations for probably over a decade now, I am really at a loss to figure out why sponsoring an electronic house music concert—and just to be clear, I looked up this DJ's concerts and looked at a bunch of the pictures of the participants, and it is absolutely a portrait of the youngest adults, if they are all adults, in our population. Only 5.4 percent of that population even smokes in the first place.

So, I would like someone to explain to me why you think that that's a good marketing strategy, specifically to target current smokers who are looking to reduce their risk.

Keagan Lenihan:
Thank you. I'll try to address the questions. I'm going to start with the ITC study and just suggest that, obviously, studies are run differently. I think—Mr. Magnani will talk a little bit more about our specific study and the conversion rate that we feel is appropriate. All of this information, all of these study designs were all shared with FDA. All of them had review of this when making their decision about the PMTA and the MRTP.

I will say, even at a 33 percent conversion rate, that's much higher than any other product that's in the market today. So, I think we'd be very happy to see 33 to 70 percent. It's higher than NRT.

It's higher than any other product that's out there today. So, I think we're very happy with IQOS and the conversion rate that we have.

I think when it comes to this administration and deregulation, while that's not a topic of discussion under the MRTP reduced exposure claim today, PMI has invested a lot of time, energy, and money into the regulatory process at CTP. We have multiple products authorized with PMTA, and the majority of the MRTP products exist through PMI.

It's something we're committed to, making sure that adult smokers have good options for otherwise continued smoking, and that we have claims that we can tell adult smokers to move them down the continuum of risk and away from combustible cigarettes. We continue to be committed to that process.

And then lastly, when it comes to the events, I think I spoke to it earlier, all of these are age-gated events. They're age-gated at the door. They're age-gated—once again, if you wish to talk about a product, we're committed to ensuring youth-access prevention, not only to protect youth from our products, but also to ensure that we still have the opportunity to sell these products for adults that smoke. And with that, I'm going to just backtrack to Mr. Magnani really quick, if he wants to add anything on the ITC study.

Cristine Delnevo:
We actually need to wrap up right now and go to break.

Keagan Lenihan:
Okay.

Cristine Delnevo:
So, we're going to be taking a 10-minute break, and we will be coming back at 11:02.

Keagan Lenihan:
Thank you.

Cristine Delnevo:
Thank you.

[break]

Cristine Delnevo:
We're going to resume, and I'd like to introduce Amber Koblitz from the FDA, who is going to be starting us off with the FDA presentation. Amber?

Amber Koblitz:
Thank you so much, Dr. Delnevo. Good morning, everyone. My name is Dr. Amber Koblitz, and I'm the chief of Social Science Branch 1 in CTP's Office of Science. I'm the technical project lead of this application review, which means I'm a bit like the captain of the review team.

Today, I'm going to present an overview of Philip Morris Product S.A. or PMPSA's renewal modified risk tobacco product applications, or MRTPAs, currently under review. This presentation provides an overview of the MRTPA pathway and then focuses on the evidence that FDA intends to discuss with the committee.

PMPSA submitted additional information with the renewal MRTPAs that FDA is considering as a part of the totality of the scientific evidence. The presentation includes a subset of the new evidence submitted as part of these renewal MRTPAs and refers to the original MRTPAs as needed for context. Some of this information will be an overview of things the applicant already discussed this morning. The next slide is going to present a disclaimer about this presentation. Next, please. Next, please.

Today, we are going to talk about the history of PMPSA's exposure modification orders, including a brief overview of the Federal Food, Drug, and Cosmetic Act's Exposure Modification Order Standard. Then I will move into a summary of the current renewal MRTPAs under review. This summary will include details about the renewal request, post-market surveillance and studies, or PMSS, required by PMPSA's exposure modification orders, and the marketing landscape after PMPSA's exposure modification orders.

Then I will walk through the lines of evidence submitted by PMPSA in support of their renewal applications. After that, I will turn the presentation over to Dr. Sagie Wagage, our toxicology reviewer, to give us an overview of toxicology data submitted as part of these applications, as well as to provide an overview of studies published since the modified risk granted orders. Lastly, I will provide a final summary and leave time for clarifying questions. Next, please.

When determining whether to issue an order under 911(g)(2) of the Tobacco Control Act, FDA must assess, among other things, whether such an order would be appropriate to promote the public health, whether the scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Whether the product is actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal, and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users.

And whether the advertising and labeling of the modified risk tobacco products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all the tobacco diseases and health-related conditions associated with the use of tobacco products. In the original MRTPA review for IQOS, FDA determined that PMPSA had met these standards. Next, please.

FDA's evaluation of an MRTPA order authorized under 911(g)(2) can be thought of in terms of a few key overarching questions. Each of these involves the evaluation of many specific questions drawing from multiple scientific disciplines. In evaluating an MRTPA, FDA must consider the

product with the proposed exposure modification information.

The questions include: Are the proposed modified exposure claims scientifically accurate? Are measurable and substantial reductions in morbidity and mortality among individual tobacco users reasonably likely in subsequent studies? How do consumers perceive and understand the modified exposure claims, and what are the potential benefits and harms to the health of the population as a whole? Next, please.

To orient everyone to the discussion, these are the IQOS tobacco heating systems and components. The IQOS 2.4 and 3.0 system holder and charger are both included in the applications under review, as well as Marlboro Amber, Blue Menthol, and Green Menthol HeatSticks, also known as HEETS. Before we get into the history of these products at FDA, we note that throughout this presentation, we refer to these products collectively as IQOS and HeatSticks. Next, please.

There have been multiple important milestones in the history of the exposure modification orders for IQOS. On July 7th, 2020, FDA issued PMPSA MRGOs under Section 911(g)(2) of the FD&C Act, for the IQOS 2.4 system holder and charger, and the three HeatStick varieties listed on the slide. These MRGOs were for 4 years.

On March 11th, 2022, after review, FDA issued an MRGO for the IQOS 3.0 system holder and charger. On July 5th, 2023, PMPSA submitted renewal MRTPAs. On May 9th, 2024, FDA filed the renewal MRTPAs and began scientific review. After initial review, FDA sent PMPSA a request for additional information in November 2024, which they responded to in December of 2024. Next, please.

The modified exposure claim in the MRGOs has several parts. Available evidence to date: The IQOS system heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals. The image here is an example of the claim on a magazine advertisement for IQOS from 2021. Next slide, please.

Under Section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct post-market surveillance and studies in order to determine the impact of the order issuance on consumer perception, behavior, and health and to enable FDA to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by FDA.

The specific PMSS requirements for PMPSA included the following: Monitoring adult use of IQOS in terms of uptake, dual use, and complete switching, and monitoring youth and young adult awareness and use of IQOS. The requirements also included an assessment of consumers' perceptions of the products and understanding of the claim. PMPSA was required to conduct surveillance of IQOS sales and distribution in the U.S., adverse experiences, and new research study findings on IQOS and consumer perception, behavior, and health.

There was a requirement for computational toxicology studies assessing chemicals in HeatStick aerosols to predict potential adverse effects in users before toxicity may be evident. And they were required to submit post-market computational modeling of the impact of IQOS on population health, including information on acute and long-term health effects of using IQOS relative to combusted cigarette smoking in order to assess the short- and long-term population health impacts of the marketing.

The applicant was required to submit PMSS protocols for approval. The applicant did so, and FDA reviewed and approved the PMSS protocols before the studies began. The applicant submitted reports outlining their progress on PMSS activities each year as part of their annual reports. Next slide, please.

As the applicant was beginning to market their products in limited U.S. markets, they were issued a cease-and-desist order because of a trade dispute that prohibited the sale of IQOS products in the U.S. PMPSA stopped marketing and selling IQOS products in November 2021. This limited the sales and marketing of IQOS to approximately 17 months of the MRGO period.

The overlapping timeline of the MRGOs and the subsequent cease and desist order is complicated, so here we've mapped it out. The dark blue events and line outline the MRGO authorization period, spanning from July 7th, 2020, to July 7th, 2024. The orange event and line represent when IQOS was removed from the market on November 28th, 2021. The light blue events and line represent the renewal MRTPAs and related events. This timeline demonstrates the complexity around these MRGOs and that the cease-and-desist order impacted PMPSA's efforts to market their MRTPAs and their ability to complete their PMSS. Next slide, please.

Because PMPSA removed IQOS from the market in November 2021, many of their PMSS were affected, which required adjustments to the protocols. Here, the dark blue boxes indicate where no adjustments were made. The light blue boxes indicate limited data collection, and the orange boxes represent studies which were not able to be completed. The surveillance of awareness and use patterns were impacted heavily, with one study not completed, and three that had limited data collection.

In orange on the left, the cohort study, which was to follow IQOS users prospectively, was unable to move forward. In addition, the cross-sectional Post-Market Adult Consumer Study, or PACS, and the U.S. IQOS Owners Panel had limited data collection. And although the Adult Tobacco Consumer Tracker, or ATCT study, made no adjustments, and the Underage Tobacco Use Survey, or UTUS study, made only minor adjustments, their reporting of cross-sectional data that continued after the removal of IQOS from the market, rightfully reported almost no use.

The cross-sectional and the cohort packs were also intended to address the surveillance of perceptions and understanding, leading to limited data available to assess these constructs in the renewal. PMPSA were able to complete their three-phase computational toxicology study. Lastly, the renewal did include a population health impact model, but it was modified and limited, as inputs for the model specific to IQOS were unavailable. Next slide, please.

I'm now going to cover the evidence that was submitted in the renewal by the applicant. Next

slide, please. We will walk through the lines of evidence submitted by the applicant in support of their renewal applications, including consumer understanding and perceptions, patterns of IQOS use, and the health risks relative to combusted cigarettes. Next slide, please.

When assessing consumer understanding and perceptions in the original MRTPA, FDA concluded that the evidence provided supported a finding that adult consumers understood that IQOS use is not without risks, likely presents moderate risks of a range of tobacco-related diseases and conditions, and is more harmful than quitting smoking and using nicotine replacement therapy instead. FDA also concluded that the evidence demonstrated that consumers perceived the product as less harmful than combusted cigarettes, which was in line with the relative health risks of the product that were reasonably likely.

For the renewal, the applicant submitted results from one wave of the adult IQOS cross-sectional PACs, and their analysis used a subsample of data collected from September to October of 2021, when IQOS was available on the market and until participants were notified that IQOS would be removed from the market. The median age of participants was 44, and most participants were male, non-Hispanic White, with a household income of $60,000 or more, at least some college education, and were employed. Over 90 percent of participants, either formally or currently, used cigarettes.

The survey included items that assessed adult-established IQOS users' understanding of IQOS-related modified risk information. Among current established IQOS users, 80.9 percent responded that switching completely would lead to less exposure to harmful and potentially harmful constituents, HPHCs, and 85.4 percent further responded that people who smoke cigarettes would need to stop smoking cigarettes completely and only use IQOS to receive the conveyed benefits.

In summary, despite study limitations due to restrictions on product sales, the results of the applicant's data collection continue to support the conclusions from the original MRTPA with respect to consumer understanding and perceptions. Next slide, please.

When assessing patterns of use data in the original MRTPA, in both U.S.-based and international studies, dual use with combusted cigarettes was the predominant pattern of IQOS use. For example, results from a U.S. 6-week actual use study showed that 7.5 percent of participants exclusively used IQOS, and 22 percent dual-used combusted cigarettes and IQOS. FDA noted at the time that these studies were conducted over a relatively short time frame, and it was unclear whether dual use would be a sustained behavior over time or a state of transition before completely switching.

In the renewal, to look at the impact of IQOS on users of tobacco products, the applicant reported information from the first wave of the IQOS cross-sectional packs. In general, the user demographics demonstrate that most IQOS users, 98.2 percent, were ever established users of tobacco products other than IQOS. In the cross-sectional packs, dual use of IQOS with cigarettes at 29.2 percent and polyuse of IQOS with cigarettes and other tobacco products of 19.6 percent in total accounted for almost half of the sample.

Lastly, 31.2 percent of IQOS users reported having completely switched from cigarettes to IQOS after trying IQOS, and 83.1 percent reported that after trying IQOS, they have now cut down on the number of cigarettes they smoked per day. Next slide, please.

In the original MRTPA, PMPSA submitted two published international studies that provided estimates of the prevalence of IQOS use among youth, which suggested that youth use of IQOS was low. In the renewal, to look at initiation of IQOS for nonusers, the applicant reported information from annual samples of the ATCT and the UTUS. These are both repeated cross-sectional surveys of tobacco-use behavior in the U.S. that use probability-based samples weighted to be nationally representative. The ATCT is a monthly survey of adults age 21 and over, and the UTUS is a quarterly survey of youth and young adults between the ages of 13 and 20.

The 2021 to 2022 ATCT sample conducted while IQOS was still on the market identified only three current IQOS users from a sample of a little over 28,800. Similarly, the UTUS identified very few youth IQOS users. In the 2021 to 2022 sample conducted when IQOS was available in the U.S., only 0.4 percent of underage individuals reported ever use of IQOS, and only 0.1 percent reported past 30-day use. When looking at just the regions of the U.S. where IQOS was available, 1 percent of youth reported ever using IQOS and 0.2 percent reported past 30-day use. Next slide, please.

In summary, IQOS is used predominantly by those who were ever established cigarette users, and IQOS users commonly use both IQOS and cigarettes. In the data submitted from the cross-sectional PACs, 31.2 percent of IQOS users retrospectively reported completely switching from cigarettes to IQOS. Data from the general population indicate there is little uptake of IQOS by nonusers, both adults and youth. This is based on nationally representative surveys conducted while IQOS was initially available on the market and more recently. Next, please.

We now turn to the relative health risks of IQOS. The conclusions we made in the original MRTPAs related to biomarker and other clinical health data were that there was a substantial reduction in exposure to HPHCs when people who used cigarettes switched completely to IQOS. Longer-term studies were needed to demonstrate whether this exposure translates to an effect on human health outcomes.

For the renewal application, PMPSA submitted one new U.S. clinical study, a set of post-hoc analyses combining study samples, and two international studies. The U.S. clinical study was a 6-month extension to a 6-month randomized, controlled, multi-center study of IQOS in the U.S. These data demonstrated continued reductions of select biomarkers of exposure, or BOEs, related to HPHCs at 12 months.

Two post-hoc analyses were conducted comparing the results of the clinical study, just summarized, to a separately conducted smoking cessation study comparing predominant IQOS users to those who smoked cigarettes and to those that had quit smoking. Results generally demonstrated that select BOEs and biomarkers of potential harm, or BOPHs, were reduced in the IQOS group compared to the cigarette group, but these reductions were not as large for those for the cigarette-abstaining group compared to the cigarette group. Measures of lung function were

generally not different between the IQOS group and the cigarette group. Next slide, please.

In the next section of the presentation, Dr. Wagage, our toxicology reviewer, will give an overview of several topics related to the nonclinical evidence for IQOS, including the applicant's submitted toxicological risk assessment and published studies. Over 70 studies published since the MRGOs examined the toxicological effects of IQOS and heated tobacco product, or HTP, exposure using various methodologies.

The outcomes of many of these studies were consistent with the conclusions from the original MRTPAs, but a few of these studies raised concerns. Dr. Wagage will discuss the studies that raise concerns, in addition to the wider body of nonclinical evidence. For more detail on the totality of the evidence submitted, please see the backgrounder posted online.

This afternoon, the discussion questions for TPSAC largely focus on this nonclinical evidence submitted by PMPSA and the published literature on the potential health risks of IQOS. FDA is asking the committee to use their scientific expertise to discuss these complex studies and topics, and we will take the committee's recommendations into consideration to make a decision in the context of the entire application.

I'm now going to turn the presentation over to Dr. Wagage. When she is done, I'll provide a summary and some time for clarifying questions. Next slide, please.

Sagie Wagage:
Good morning. My name is Dr. Sagie Wagage. I'm a toxicologist in the Division of Nonclinical Science in the Office of Science at CTP, and I will be discussing nonclinical data related to potential health risks of IQOS use. Next, please.

I'll begin by summarizing toxicology findings from the original MRTPA. I'll then discuss information related to chemicals in IQOS aerosols, as well as cancer and noncancer toxicities associated with IQOS aerosols. Next, please.

For the original MRTPA, the applicant provided data from genotoxicity and cancer studies. Genotoxicity assays test whether chemicals cause DNA damage, which can lead to increased cancer risk. The applicant studies indicated that IQOS aerosols were genotoxic in mouse lymphoma assays.

Based on currently validated methods, such as OECD guidelines and ICH S2(R1), in vitro genotoxicity assays do not provide comparable—comparative information regarding genotoxic potency. Rather, under current methods, in vitro genetic toxicology studies provide binary positive or negative results. Therefore, this study, as conducted, cannot indicate whether IQOS aerosols are less genotoxic than cigarette smoke.

The applicant also provided data from a rodent cancer study for the original MRTPA. This study was inconclusive due to limitations in the mouse model that was used. Additionally, the applicant provided findings from mouse and rat studies that evaluated noncancer toxic effects of IQOS aerosol exposure.

Overall, the data from the applicant's nonclinical studies suggested that IQOS aerosols had lower toxic potential than cigarette smoke under the conditions used in the assays and for the endpoints that were measured. However, the applicant studies had significant limitations that prevented stronger conclusions about the relative health risk of using IQOS as compared to conventional cigarettes. Next, please.

The applicant also provided information on constituents or chemicals that are found in IQOS aerosols for the original MRTPA. In IQOS aerosols, most harmful and potentially harmful constituents, or HPHCs, on FDA's established list are either below the limits of detection or quantification, or lower than the levels in cigarette smoke. Some of these HPHCs are also found at levels below limits of detection or quantification in cigarette smoke.

The applicant also identified 80 chemicals that are found at higher levels in IQOS aerosols than cigarette smoke in a non-targeted differential screening study. This study was semi-quantitative, and the absolute quantities for most of these 80 chemicals are unclear. The toxic potential of some of these 80 chemicals is also not well characterized. Next, please.

Accordingly, the MRGO required the applicant to complete a post-market computational toxicology study to further evaluate the 80 chemicals that are found at higher levels in IQOS. Computational toxicology models use pattern recognition algorithms to analyze relationships between chemical structures and associated biological activities based on libraries of experimental chemical data. These models learn relationships between chemical structures and potential toxicities to predict the potential toxic effects of chemicals of interest.

Part of the applicant's post-market computational toxicology study evaluated the potential genotoxicity and carcinogenicity of the 80 chemicals found to be higher in IQOS aerosols. This study found that out of these 80 chemicals, 36 were potentially genotoxic or carcinogenic. This number is higher than the number of potentially genotoxic or carcinogenic chemicals that were identified for the original MRTPA.

For the original application, the applicant reported that four of the 80 chemicals were possible or probable human carcinogens and that 19 other chemicals generated computational toxicology structural alerts. Therefore, these new post-market computational toxicology findings suggest that the cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA. Next, please.

For the renewal application, the applicant also calculated excess lifetime cancer risks, or ELCRs, for IQOS aerosols and reference cigarette smoke. ELCR calculations estimate cancer risk based on the levels of potential carcinogens that users may be exposed to and the potency of these carcinogens. ELCR calculations assume that the cancer risk of exposure to multiple carcinogens is additive and that the carcinogens in aerosols do not have synergistic or inhibitory effects.

The applicant's calculations found that IQOS had a lower ELCR than cigarettes. However, the applicant's calculations had certain limitations. For example, the applicant's ELCR calculations were partly based on semi-quantitative chemical quantities from the non-targeted differential

screening.

As I mentioned earlier, ELCR calculations are partly based on the levels of potential carcinogens that users may be exposed to. Without having clear, absolute amounts for some of the chemicals in aerosols, it's not possible to reliably estimate the potential levels of these chemicals that users may be exposed to. Because of the limitations, it is unclear whether the applicant's ELCRs adequately reflect the cancer risk of IQOS aerosols. Next, please.

To summarize this part of the presentation, experimental data indicate that IQOS aerosols can have genotoxic effect. However, these data do not provide conclusive information on whether IQOS aerosols have a lower cancer risk than cigarettes. The applicant's post-market computational toxicology study suggested that the cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA.

IQOS aerosols contain lower levels of carcinogens on the established HPHC list than cigarette smoke. For example, when compared to cigarettes, IQOS aerosols have a 97 to 98 percent reduction in NNK, which is a highly potent carcinogen. However, levels of other potential carcinogens and genotoxicants are higher in IQOS aerosols than in cigarette smoke. The absolute quantities of most of the chemicals that are found at higher levels in IQOS are unclear, so the amounts of these chemicals that users may be exposed to are unclear. Next, please. Next slide, please.

In addition to increasing the risk of cancer, tobacco products have noncancer toxic effects. The next part of the presentation will discuss findings related to the noncancer toxicity of IQOS aerosols. These findings are from peer-reviewed literature studies that were published since the MRGO. Next, please.

Thirty-six studies in a literature review performed by toxicology reviewers evaluated in vitro or ex vivo effects of IQOS. Eighteen of these studies evaluated effects in respiratory cells. Five studies evaluated parameters related to cardiovascular toxicity, such as effects in endothelial cells.

Most of these studies found that IQOS exposures had less severe effects than cigarette exposures. However, most of these studies had certain limitations. For example, many studies tested the effects of aerosol extracts, which are not expected to contain all of the chemicals present in whole aerosols. Additionally, factors such as metabolism and the portal of entry affect the toxicity caused by chemicals. Therefore, it is difficult to compare toxicant doses in cell culture media to toxicant doses in animals or humans. Next, please.

The next part of this presentation will focus on findings from in vivo animal studies, beginning with respiratory toxicity. Next, please. The toxicology literature review identified studies published after the issuance of the MRGO that evaluated respiratory toxicity in mice that were exposed to cigarette smoke or IQOS aerosols for 90 days or less. These studies were funded through different sources, including government and the tobacco industry.

Two of these studies found that mice exposed to cigarette smoke for 7 days had increased levels

of cell death and reactive oxygen species in the lungs. These effects were not seen in mice exposed to IQOS aerosols. Reactive oxygen species cause oxidative stress which may contribute to the development of emphysema.

Four studies evaluated lung histology in mice exposed to IQOS aerosols for 7 days or 4 weeks. Histology involves the study of tissues and cells under a microscope and can reveal tissue and organ damage associated with disease. In general, these studies found that cigarette smoke exposure led to more severe histological signs of inflammation or lung injury than IQOS aerosol exposure. Next, please.

Four new subacute studies also evaluated protein levels in bronchoalveolar lavage fluid or BAL fluid. BAL fluid is obtained by instilling liquid in the lung airways and then collecting this instilled liquid. BAL fluid contains proteins and cells that are found in air spaces in the lung. BAL fluid from healthy lungs contains relatively low levels of protein because blood proteins are kept in the circulation by intact blood vessels. But higher protein levels in BAL fluid indicate increased permeability of blood vessels in the lung, which is associated with lung injury.

In general, the new studies found that exposing mice to IQOS aerosols led to increased protein levels in BAL fluid. Examples of these results are shown here. One study, shown in the graph at the top right of the slide, found that the levels of a specific protein, albumin, increased in the BAL fluid of mice exposed to cigarette smoke or IQOS aerosols compared to control mice that were exposed to air. It was unclear whether there were significant differences between mice exposed to cigarette smoke and IQOS aerosols.

Another study, shown in the graph at the bottom right of the slide, found that mice exposed to cigarette smoke or IQOS aerosols for 8 weeks had increased BAL protein levels compared to air-exposed mice. However, compared to mice exposed to cigarette smoke, mice exposed to IQOS aerosols in this study had significantly lower protein levels in BAL fluid.

In general, the studies found that IQOS aerosol exposure led to increased BAL protein levels compared to air-exposed mice. Findings regarding the relative effects of IQOS aerosol or cigarette smoke exposure on BAL protein levels indicated that in two studies, IQOS exposure appeared to produce similar or greater effects, while in two other studies, cigarettes generated a higher response. Next, please.

Two new studies published after the issuance of the MRGO evaluated BAL cytokine levels in mice exposed to cigarette smoke or IQOS aerosols. Cytokines are a type of protein that has effects on the immune system. Some cytokines can stimulate the immune system and have proinflammatory effects, which may contribute to the development of emphysema.

The authors exposed mice to cigarette smoke or IQOS aerosols for 2 or 8 weeks and evaluated BAL cytokine levels. As listed in the top row of the table, there were no significant differences in the levels of several cytokines in mice exposed to cigarette smoke when compared to mice exposed to IQOS aerosols. Other cytokines were found at significantly higher levels in BAL fluid from mice exposed to cigarette smoke but not IQOS aerosols. Next, please.

Studies published after the issuance of the MRGO also evaluated immune cell infiltration in the lung tissue from mice exposed to cigarette smoke or IQOS aerosols. Increased immune infiltration into the lungs is an indication of inflammation which may contribute to the development of emphysema.

One study, shown in the graph on the left, found that after 8-week exposures, levels of lung immune infiltration significantly increased in mice exposed to cigarette smoke or IQOS aerosols compared to air-exposed mice. The levels of infiltration were not significantly different between mice exposed to cigarette smoke and IQOS aerosols.

Another study, shown in the graph on the right, found that BALB/c mice exposed to IQOS aerosols or cigarette smoke had increased lung immune infiltration compared to air-exposed mice. This study designated IQOS as an ENDS. Compared to mice exposed to cigarette smoke, IQOS aerosol exposure led to significantly reduced levels of immune infiltration. In general, the new studies found that IQOS aerosol exposure led to increased lung immune infiltration compared to air-exposed mice.

Findings from these studies did not indicate a clear difference between exposures to IQOS or cigarettes. In two studies, IQOS aerosols led to similar levels of immune infiltration as cigarette smoke. In one other study, cigarette smoke exposure induced higher levels of lung immune infiltration than IQOS aerosol exposure. Next, please.

As I discussed, several relatively short-term studies evaluated effects of exposure to cigarette smoke or IQOS aerosols on lung inflammation. Lung inflammation can contribute to the development of emphysema, which leads to the question of whether these exposures cause emphysema in experimental models. The toxicology literature review included a total of three studies that evaluated emphysema in mice exposed to cigarette smoke or IQOS aerosols.

One of these studies was published by authors affiliated with Philip Morris Products S.A. This study evaluated A/J mice that had been exposed to cigarette smoke or IQOS aerosols for up to 18 months. In this study, mice exposed to cigarette smoke had increased levels of inflammatory cytokines in BAL fluid. Exposure to IQOS aerosols did not lead to significant increases in the levels of these cytokines. Mice exposed to cigarette smoke also developed histological signs of emphysema. This effect was not seen in mice exposed to IQOS aerosol.

The study has certain limitations. For example, A/J mice developed spontaneous lung tumors at a high rate, which may confound the comparative evaluation of effects related to respiratory toxicity following exposure to IQOS aerosols or cigarette smoke. Additionally, data provided by the applicant indicated that IQOS aerosols contain higher levels of total particulate matter than cigarette smoke when normalized in nicotine.

However, at matching nicotine concentrations, the exposure atmospheres for IQOS aerosols in this study contained lower levels of total particulate matter than the exposure atmospheres for cigarette smoke. This discrepancy raises the question of whether the IQOS aerosol exposures in this study fully reflected the constituent levels found in IQOS aerosols. Next, please.

In the other two emphysema studies that were included in the toxicology literature review, male C57 black 6 mice were exposed to cigarette smoke or IQOS aerosols for 6 months. One of the features of emphysema is an enlargement of air spaces. The authors evaluated mean linear intercepts which indicate the mean free distance in air spaces. Increased mean linear intercepts are associated with emphysema.

In both of these studies, exposure to cigarette smoke or IQOS aerosols led to a significant increase in mean linear intercepts when compared to air-exposed mice. Next, please. Both of the studies in C57 black 6 mice also evaluated changes in lung function that are associated with emphysema. For example, emphysema is associated with a reduction in lung elastic recoil.

The 2022 study, shown in the graph on the bottom left, found that cigarette smoke exposure led to a significant decrease in lung elastance, which is associated with emphysema. In contrast, there was no significant difference in long elastance between mice exposed to IQOS aerosols compared to air-exposed controls. Similar results were seen for the other lung function parameters that were measured in this study.

The 2023 study found that exposure to cigarette smoke or IQOS aerosols led to changes in lung function that are consistent with emphysema. For example, as shown in the center graph, there was a significant decrease in tissue elastance in mice exposed to cigarette smoke or IQOS aerosols when compared to air-exposed mice. There was no significant difference in tissue elastance between mice exposed to cigarette smoke compared to mice exposed to IQOS aerosol.

This study also evaluated the ratio of forced expiratory volume to forced vital capacity, which is a parameter that is used to clinically diagnose emphysema. As shown in the graph on the right, compared to air-exposed mice, this ratio was significantly reduced in mice exposed to IQOS aerosols or cigarette smoke, which is consistent with emphysema. This ratio was not significantly different between mice exposed to IQOS aerosols and mice exposed to cigarette smoke. Next, please.

These two emphysema studies have certain limitations. For example, there were limitations in the histology methods that were used for both papers. Relatively small numbers of images were used for histological analysis, and the studies did not indicate whether the images were analyzed by board-certified pathologists. However, these two independent studies had similar histology findings.

As an additional limitation, the 2023 study did not evaluate biomarkers of exposure in exposed mice. Biomarkers of exposure provide information to compare exposure levels between mice exposed to IQOS aerosols and cigarette smoke. However, mice in the study were exposed to aerosols generated from five HeatSticks or five cigarettes, which may have resulted in comparable exposures.

Although these studies have certain limitations, each of these two studies independently found that exposure to cigarette smoke or IQOS aerosols led to similar lung changes associated with emphysema. Next, please.

The findings related to the respiratory toxicity of IQOS lead to the questions of whether chemicals that can cause respiratory toxicity are present in IQOS aerosols and how the levels of these chemicals compare between IQOS and reference cigarettes. Based on an HPHC study provided by the applicant for the original MRTPA, 18 respiratory toxicants on FDA's established list are found at lower levels in IQOS aerosols than cigarette smoke.

Compared to one cigarette, a HeatStick has 60 to over 99 percent lower levels of these respiratory toxicants. For example, when compared to cigarette smoke, IQOS aerosols have a 93 to 95 percent reduction in the levels of acrolein, which is a highly potent respiratory toxicant. Compared to cigarettes, IQOS aerosols have higher levels of other potential respiratory toxicants. Some examples are shown here.

For example, IQOS aerosols contain higher levels of butylated hydroxytoluene compared to cigarette smoke. In rodents, injection of butylated hydroxytoluene causes cell death and inflammation in the lungs. The absolute quantities for most of the chemicals that are found at higher levels in IQOS aerosols than cigarette smoke are unclear. So, the levels of these chemicals that users may be exposed to are also unclear. Next, please.

The last part of this presentation will focus on new findings related to cardiovascular toxicity. Next, please. The toxicology literature review included two studies in animals that evaluated cardiovascular toxicity. One study found that rats exposed to cigarette smoke or IQOS aerosols had impaired flow-mediated dilation, which is related to vascular endothelial function. In another study from the same research group, rats were exposed to cigarette smoke, IQOS aerosols, or other aerosols for 8 weeks.

The authors measured systolic blood pressure in exposed rats. As indicated in the graph, systolic blood pressure did not change over time in rats that were exposed to air, shown in blue. In contrast, systolic blood pressure increased over time in rats exposed to cigarette smoke, shown in red. Systolic blood pressure also increased in rats exposed to IQOS aerosols, shown in brown. Next, please.

This study also evaluated cardiac fibrosis in exposed rats. Cardiac fibrosis is a scarring of heart muscle, which can affect heart function. As shown in the graph on the left, compared to rats exposed to air, rats exposed to cigarette smoke or IQOS aerosols had increased fibrosis in the right atrium of the heart. These exposures also led to increased fibrosis in the left atrium and left ventricle of the heart. These changes were associated with reduced ejection fractions.

Ejection fractions provide an indication of how well the heart pumps out blood. As indicated in the graph on the right, ejection fractions did not significantly change over time in rats exposed to air, shown in blue. In contrast, ejection fractions significantly decreased in rats exposed to cigarette smoke, shown in red. Ejection fractions also decreased in rats exposed to IQOS aerosols, shown in brown.

Taken together, this study found that exposure to cigarette smoke or IQOS aerosols led to hypertension, cardiac fibrosis, and impaired cardiac function. One limitation in this study is that it did not include data on biomarkers of exposure in exposed rats. As I mentioned, biomarkers of

exposure provide information to compare exposure levels between animals exposed to IQOS aerosols and cigarette smoke. This study also had relatively short daily exposure durations to IQOS aerosols and cigarette smoke. Next, please.

The new findings lead to the questions of whether chemicals that may cause cardiovascular toxicity are present in IQOS aerosols and how the levels of these chemicals compare between IQOS and reference cigarettes. Based on an HPHC study provided by the applicant for the original MRTPA, seven cardiovascular toxicants on FDA's established list are found at lower levels in IQOS aerosols than cigarette smoke. Compared to one cigarette, a HeatStick has 89 to 99 percent lower levels of these chemicals.

IQOS aerosols also contain higher levels of other potential cardiovascular toxicants that are not on FDA's established list. As I mentioned, the absolute quantities for most of the chemicals that are found at higher levels in IQOS aerosol than cigarette smoke are unclear. So, the levels of these chemicals that users may be exposed to are unclear. Next, please.

In addition to the studies that I discussed, the toxicology literature review included other findings. One study evaluated developmental toxicity in male mice that were prenatally exposed to IQOS aerosols or cigarette smoke. At 5 weeks of age, mice that had been prenatally exposed to IQOS aerosols had increased damage to seminiferous tubules which are the site of sperm production.

Prenatal exposure to IQOS aerosols also led to reduced levels of daily sperm production. These effects were not seen in mice that were exposed to cigarette smoke prenatally. The observed effects of IQOS aerosol exposure were transient in this study, and by 15 weeks of age, no differences were seen between any of the experimental groups.

Seven additional studies evaluated effects of exposure to IQOS aerosols in animals. These studies identified effects of IQOS on the liver, lungs, and brain. However, because these studies did not include cigarette smoke exposures, it was unclear how the effects of IQOS would compare to the effects of cigarettes.

Lastly, two animal studies evaluated effects of IQOS and cigarettes on the immune system. For most of the endpoints that were evaluated in these studies, IQOS aerosol exposure had less severe effects than cigarette smoke exposure. Next, please.

In summary, the applicant's post-market computational toxicology study suggested that cancer risks associated with IQOS aerosols may be higher than initially indicated by information available for the original MRTPA. The absolute quantities of most of the chemicals that are found at higher levels in IQOS aerosols than in cigarette smoke are unclear. This prevents the calculation of an ELCR that reflects the overall cancer risk associated with IQOS.

Studies published after the issuance of the MRGO include new data on potential noncancer toxic effects of IQOS aerosol exposures. Lastly, when compared to cigarettes, IQOS aerosols contain lower levels of most HPHCs on FDA's established list. IQOS aerosols also contain higher levels than cigarettes of other potential toxicants that are not on FDA's established list.

Dr. Koblitz will now conclude the presentation. Next, please.

Amber Koblitz:
All right. Thank you so much, Dr. Wagage.

All right. So, just to bring us full circle and put a loop on this, I'm going to talk about overall conclusions about relative health risk. So, overall, the clinical and toxicological evidence submitted by PMPSA continues to support the modified exposure claim from the MRGOs that scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

The clinical evidence suggests that switching completely from combusted cigarettes to IQOS reduces BOEs to a variety of HPHCs. And the toxicological evidence continues to support that IQOS aerosol contains a significantly lower level of a wide variety of HPHCs on the HPHC list relative to cigarette smoke. The overall long-term relative health risks of IQOS compared to cigarettes are still largely unknown.

The new computational toxicology study submitted in the renewal application identifies 36 potentially genotoxic and carcinogenic compounds found at higher levels in IQOS aerosol than in reference cigarette smoke, which is more than was identified in the original MRTPA, increasing uncertainty about the toxicological risks of IQOS.

Additionally, several studies that were published after the MRGOs raised questions about the toxic effects of the complete IQOS aerosol mixture in rodent models. The studies generally found that exposure to IQOS aerosols had similar or more severe effects than exposure to cigarette smoke on emphysema, cardiovascular toxicity, and one aspect of reproductive and developmental toxicity.

Dr. Wagage outlined why these studies are of concern within the larger body of evidence published since the MRGOs that investigated the implications of the long-term health risks of IQOS use relative to cigarette smoking. Next slide, please.

Thank you very much for your time. I'd be happy to address any brief clarifying questions. We will have time for more questions and in-depth discussion this afternoon.

Cristine Delnevo:
Thank you, Dr. Koblitz. I do have one simple question, and I think it's just a clarifying—I think you presented earlier that half of the IQOS participants in the study, the survey, at baseline, were former smokers, and the term was used "ever established"? Is that correct, that they were not using cigarettes at the time? Or was it that they quit during the period of time?

Amber Koblitz:
So, I think—and people can jump in and help me if they—but I believe—so, the majority, almost, I think, 98.2 percent of users in that survey were originally current established cigarette

smokers. And then, I believe, this is a retroactive, retrospective recall, and so, about 50 percent of those dual-used or polyused, then, within their retrospective recall. But they did start, almost all of them were cigarette smokers, and that was—

Cristine Delnevo:
At baseline?

Amber Koblitz:
—at baseline.

Cristine Delnevo:
Okay. Thank you.

Amber Koblitz:
Yes, absolutely.

Cristine Delnevo:
Dr. Upson.

Dona Upson:
Thank you, Madam Chair, and thank you for the presentation. I know in the background material that we had, there was some discussion of dual use, and I didn't see that in the presentation. Could you please discuss what was found on the potential or real health risks of dual use? Thank you.

Amber Koblitz:
Yes. Just briefly, the BOEs and the BOPH outcomes that we looked at did basically say that if there's dual use, the effects of reduction are gone. And so, the health impact, we don't know exactly what that's going to look like, but we're not seeing a lot of difference between those BOEs and BOPHs as far as dual use of the products—of cigarettes and IQOS. Is that the—what you're wanting?

Dona Upson:
Yes. And I think also on the background material, there was an indication that there is actual increased risk with dual use than with even cigarette use by itself.

Amber Koblitz:
There's the potential for that, yeah.

Dona Upson:
Thank you.

Amber Koblitz:
Absolutely.

Cristine Delnevo:

Dr. Jordt?

Sven-Eric Jordt:
Yes. Thanks for taking my question. Could you explain how you chose the publications that went into the analysis of the preclinical data? I see at least one publication by Kastratovic that was funded by the Foundation for a Smoke-Free World. This is 100 percent PMI, the applicant-funded publication. Are there more publications like that in the record we are asked to review? And how do you mitigate conflict of interest?

Amber Koblitz:
That's a great question. Yes. So, specifically, the toxicology literature review was a broad literature review that pulled everything related to IQOS, post the MRGOs, and there are both industry-funded and independently funded studies within that literature review. We do have that information coded, but we do take them all as independent. And that's—I mean, I think, Dr. Wagage did a great job of trying to present some of those limitations and taking into account that there's limitations with each study. And so, we didn't—we don't just discount something because of its source, but we do look at everything, and all the limitations involved.

Eric Jordt:
Yeah, just to mention that, for example, the European Respiratory Society and the American Thoracic Society, they exclude members that are funded by the Foundation for a Smoke-Free World due to undue influence in the—of the tobacco industry. And I'm very concerned about such studies making it into this review without explicitly being flagged. Thank you.

Amber Koblitz:
Thank you.

Cristine Delnevo:
Dr. Zelikoff.

Judith Zelikoff:
It says my picture is disabled. Okay.

Amber Koblitz:
Well, I can still hear you.

Judith Zelikoff:
Okay. Here I am. Okay, thank you. So, I had some questions, and actually, Dr. Jordt took one of them, about selection of the studies that you presented. And so, it was, for the most part, answered. However, I did wonder about—you didn't show us, you know, all of them, obviously. How did you come to select the ones you did show us?

Amber Koblitz:
Yeah, absolutely. It's a great question.

We are highlighting the ones that are not in line with what we've seen previously. So, I've

considered them a little bit as, like, they're raising flags. They're little spots of concern, and within the totality of the evidence, they're just a few brief spots. But I want—as the technical project lead, and as I'm thinking about this, I really want to know what that means to you guys and the committee. Like, are these brief spots of concern things that, you know, we should talk about more? And so, that's—we really highlighted those things that are bringing questions up for us that we want your expertise on.

Judith Zelikoff:
Okay, I have one other question.

Amber Koblitz:
Yeah.

Judith Zelikoff:
And that is, it was rather hard, from the data that you presented, to come up to real conclusions, because as toxicologists, as we all know, you know, dose is important, exposure duration is important, route of exposure is important, et cetera, et cetera, and can complicate the data. When you're doing—when the studies were doing comparisons, I wondered if the comparison dose was either an equimolar concentration or an equitoxic concentration, and how you can really compare them. Can you clarify or add something to that?

Amber Koblitz:
I absolutely cannot, but I can talk to Dr. Wagage and see if we can get you an answer to that. And it might be something we can turn back to, maybe, in the discussion this afternoon, that we get you, if that's okay.

Judith Zelikoff:
That's fine. Thank you.

Amber Koblitz:
Absolutely.

Cristine Delnevo:
I think that makes a lot of sense, Dr. Koblitz.

Cristine Delnevo:
Dr. Zelikoff, do you have another question?

Judith Zelikoff:
I'm sorry. Thank you, no.

Cristine Delnevo:
Okay. Thank you. Dr. Madl?

Amy Madl:
Hi. Amy Madl, representative for small businesses. So, my question is—actually, was partly

asked by Dr. Zelikoff, but I have a bit of an add-on to that, and it might be something that we talk about further in the afternoon. But it was raised, about the potential limitations of some of these toxicology studies, inhalation studies, with respect to lack of characterization of the aerosol and then also, lack of dosing determinations with respect to, like, for example, cotinine levels across the different comparison groups. So—which can be a pretty significant limitation if you don't actually know what is dosed to the animals, especially when you're looking at relative hazard, relative potency of IQOS in comparison to combustible cigarettes.

So, my question is, how did that get factored into FDA's assessment of the overall weight of evidence of the toxicology when evaluating the relative hazard potency, for example, of IQOS compared to combustible cigarettes?

Amber Koblitz:
Probably one I'm going to have to ask Dr. Wagage about and get you an answer to this afternoon, but I'm writing down the question. I think that's a good one.

Amy Madl:
Thanks.

Amber Koblitz:
Yeah, absolutely.

Cristine Delnevo:
Thank you. And with that, we are actually going to now break for lunch. We will be returning—I'd like folks to return at 12:50, because we do have an open public hearing that will start promptly at 1:00 p.m.

Amber Koblitz:
Thank you so much.

Cristine Delnevo:
Thank you.

[break]

Cristine Delnevo:
Welcome back, everyone. Welcome to the open public hearing session. Please note that the—

Gideon McMullin:
You still got 30 seconds ‘till we begin.

Cristine Delnevo:
Oh, sorry.

Gideon McMullin:
You're good. You can go live now.

Cristine Delnevo:
Thank you. Welcome, everyone, back to the meeting. Welcome to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker at the beginning of your written or oral statements, to advise the committee of any financial relationships that you may have with the sponsor, its products, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have 14 open public hearing speakers today. So that we may move through the agenda as scheduled, please remember that you've been allotted 4 minutes only for your presentation. The timer will start after the yellow flash. I would like to now invite our first speaker. Next slide, please. Open public hearing speaker number one, please turn on your camera and unmute to speak.

Rachel Jang:
Speaker number one is not here. If we can move on to speaker number two, please.

Cristine Delnevo:
Will do. Speaker number two, please.

Jeffrey Smith:
Good afternoon. My name is Jeff Smith. I am a senior research fellow at the R Street Institute. And we are very excited to be included in a conversation around the IQOS product today. R Street is a nonprofit, nonpartisan public policy organization focused on advancing free markets and limited, effective government in various areas, including harm reduction. Our work is based on the belief that health policy rooted in harm reduction can significantly reduce the adverse outcomes of harmful behaviors and alleviate the burdens of health care costs.

Decades of research show that abstinence-only methods are ineffective at the population level for risky behaviors, and policies that criminalize behaviors, like smoking, lead to unintended negative consequences. Providing testimony today in support for the renewal of the MRTPA is a key component to continuing the advancement of tobacco harm reduction. As advocates for public health and evidence-based tobacco regulation, we believe that renewing this MRTP aligns with the principles of tobacco harm reduction and the continuum of risk framework, which is essential for reducing tobacco-related disease in the United States.

The IQOS system, a heat-not-burned tobacco product developed by Philip Morris, represents a scientifically supported alternative for adult smokers who are unable or unwilling to quit nicotine

use entirely. By heating tobacco rather than combusting it, IQOS significantly reduces exposure to harmful and potentially harmful chemicals compared to traditional combustible cigarettes, thereby offering a pathway to mitigate the health risks associated with smoking.

Tobacco use remains one of the leading preventable causes of death in the United States, with combustible cigarettes accounting for the vast majority of tobacco-related morbidity and mortality. According to the U.S. Surgeon General, cigarette smoking causes over 480,000 deaths annually, primarily due to the exposure of toxins produced by combustion, such as tar, carbon monoxide, and numerous carcinogens.

In this context, the concept of tobacco harm reduction, that is providing less harmful alternatives to smokers, has emerged as a pragmatic public health strategy. Harm reduction recognizes that while complete abstinence from nicotine is ideal, most smokers face significant barriers to quitting. Instead of insisting on an all-or-nothing approach, harm reduction encourages transitioning users to products lower on the continuum of risk, where combusted tobacco products like cigarettes occupy the highest risks, and non-combusted alternatives, including HTPs like IQOS, offer substantially reduced harm.

The continuum of risk is a well-established framework. And I do not see my timer, so I apologize. The continuum of risk is a well-established framework in tobacco control, endorsed by scientific consensus and regulatory bodies. It suggests that tobacco and nicotine products exist on the spectrum of harm, with a level of risk determined primarily by delivery method and the presence of combustion.

Combusted products such as cigarettes are at the most harmful because burning tobacco at high temperatures generates thousands of toxic chemicals, including over 70 known carcinogens. In contrast, non-combusted products like smokeless tobacco or medicinal nicotine are at the lower end. HTPs, which heat tobacco to around 350 degrees Celsius without burning it, fall in between producing—fall in between, producing an aerosol with significantly fewer and lower levels of harmful constituents.

This framework is not merely theoretical. It's grounded in extensive research demonstrating that switching to lower-risk products can reduce individual and population-level health risks. For instance, the National Academies of Sciences, Engineering, and Medicine have acknowledged that e-cigarettes, another non-combusted product, likely expose users to fewer toxicants [spelled phonetically] than combustible cigarettes, supporting the harm reduction potential of such alternatives. Extending this logic to heated products like IQOS is consistent with promoting public health by encouraging smokers to migrate down the continuum toward reduced-risk products.

The scientific evidence provided by PMI today and in their application underscores its position on the lower end of the risk of continuum compared to cigarettes. Studies have shown that IQOS produces vapor aerosols containing nearly 90 percent fewer toxic substances than cigarette smoke, including reduced levels of volatile organic compounds and other harmful chemicals. For example, nicotine levels in IQOS aerosol, comparable to those in cigarettes, ensuring satisfaction from smokers but concentrations of HPHCs are dramatically lower. This reduction—

Cristine Delnevo:
Can you wrap up your comments? Your time is up.

Jeffrey Smith:
I'm sorry.

Cristine Delnevo:
That's all right.

Jeffrey Smith:
Well, in general, I support your application and thank you for the time.

Cristine Delnevo:
Thank you. Speaker number three.

Julie Gunlock:
Hi. My name is Julie Gunlock. I'm a senior policy analyst with the Independent Women's Forum. I appreciate the opportunity to present here today. I don't know of any financial support, but I suspect they do support our gala, which we have every year. But I don't do the fundraising, so I don't really know.

Independent Women's Forum is the leading national women's organization that celebrates women's accomplishments and fights to expand women's options and opportunities. During my virtual presentation, I will discuss why innovative—innovation in smoking cessation products is particularly important to women.

As members of the committee know, each year, millions of American women try to stop smoking. In order to do so, women need accurate information on nicotine replacement therapies and choices in the marketplace so they can choose a product that best helps them achieve that goal. Sadly, this isn't happening.

In fact, according to one recent survey, two-thirds of doctors reported that they are unsure if nicotine causes cancer. Another recent survey of more than 1,500 medical professionals showed that despite decades of research as part of tobacco control efforts, misconceptions about nicotine are pervasive among health care professionals. This is particularly damaging for women who have a far more difficult time quitting traditional combustible cigarettes than men.

To understand why, researchers have looked at the biological differences between men and women. Researchers at Uppsala University in Sweden discovered that nicotine can impede the production of an enzyme that regulates estrogen production, which can impact women's emotional health and sense of motivation. Research has also found that women deal with the fear of weight gain and changes in mood, that women's menstruation cycles increase neural activity related to cravings, which often hamper a woman's attempt to quit smoking.

As we all know, and while this might not be a fashionable statement today, it is a biological fact

that men do not have a menstrual cycle. As such, men do not have to deal with the added monthly cravings and mood issues that come with menstruation. Other studies have shown women have a much more severe symptoms of withdrawal than men, and that women are more likely than men to begin smoking again when faced with stress and anxiety.

Another study found that when men smoke, the number of nicotine receptors in the brain increases. But this wasn't true for women who, while smoking, had the same number of nicotine receptors as nonsmokers. This matters because women need treatment options that help replace other cravings, like taste, the smell of traditional cigarettes, and the hand-to-mouth habits associated with smoking.

Of course, we realize that the FDA doesn't want to punish women for their immutable characteristics, yet that's precisely what's going to happen if the FDA doesn't renew its approval of IQOS. Products like IQOS have a far higher success rate in helping people permanently quit cigarettes, which is why this innovative technology has already been embraced in the U.K. Limiting female smokers to cessation products that biologically cannot provide them with the help they need to quit traditional cigarettes is a recipe for making women unhealthy.

Independent Women's Forum supports HHS Secretary Robert F. Kennedy Jr.'s efforts to make America healthy again. And we believe giving women access to products like IQOS is the way to achieve that. The FDA should continue to authorize IQOS, as well as reforming the TCA process to facilitate more products that come to market. Thank you.

Cristine Delnevo:
Thank you. Speaker four?

Lindsey Stroud:
Yes. Hello? We're good? Okay. So, okay. Thank you again for your time today. My name is Lindsey Stroud. I'm the Founder and President of Tobacco Harm Reduction 101. Pertaining to the financials, I did go on a trip once with the Philip Morris, like, international. But as to date, no, the tobacco companies have not given us any funding. And based off of the testimony I'm about to present, I don't really see that in the future. But—so we'll just get into it.

Today, we're talking about the MRTP order for IQOS. Yes, THR 101 definitely supports that renewal. But we do believe that it does need reforms. The language for them to be able to convey that this is a safer product is determined by the FDA. And unfortunately, the FDA doesn't really meet consumer demand. And so, I'm going to talk about that.

I'm kind of here to talk about how the Tobacco Control Act needs to be reformed. It's inefficient, and it's slow to react to consumer demand. In 2023, we had 38-plus million American adults who were smoking, and about 20 million who were vaping. To date, as of today, the FDA has authorized only 81 products under the Premarket Tobacco Application, or the PMTA process. compared to 15,000 traditional tobacco products that have either been introduced or they've been modified and requiring FDA scrutiny.

As of today, one company owns 44.4 percent of those PMTA orders. That same company also

owns 87.5 percent of the MRTP orders. There was in 2009, one of the other competitors brought this up, that the Tobacco Control Act was actually designed to protect them. Almost 20 years later, I do think that we have the data that shows that.

The FDA's process of authorizing these less harmful alternatives of cigarettes is slow and confusing. I know that myself. Like, I deal with, you know, people that smoke. And I've heard so many times how vaping is more worse than smoking. And I've been doing 10 years of this research, I can tell you that's not true. We have decades of studies that are showing the misinformation campaign and how both consumers and physicians are misinformed about the role of nicotine causing cancer.

We also have public health agencies that are helping to lead to this confusion. We can go back to 2019 with the lung injuries and the EVALI. And the Centers for Disease Control and Prevention, you know, linking it to nicotine vaping, even though 99 percent of those injuries were actually caused by illicit vapes containing THC. We now have the FDA that is actually actively using user fees to block shipments of tobacco harm reduction products.

I need to point out that this meeting, I mean, the Center for Tobacco Products is completely funded by user fees. This meeting is happening during a government shutdown. The smokers are actually paying for this meeting to happen right now. And again, just kind of speaks for greater reforms to the tobacco, the TCA in general, you know. The MRTP is a redundant process in itself. The PMTA finds that these products are appropriate for the protection of public health. That is what the PMTA [unintelligible] says. But companies have to spend more billions of dollars to be able to convey that to John Q. Public.

Again, I'm not going to go—I'm just kind of speaking for, you know, we need greater reforms on this one. I live in a country where I have more access to different fast food, fried chicken alternatives than I have to alternatives to cigarettes, 81 products to 15,000. Again, thank you for your time today, and I'm happy to answer any questions.

Cristine Delnevo:
Thank you. Speaker number five.

Julie Gunther:
Hi, everybody. My name is Julie Gunther. Madam Chair, esteemed members of the committee, thank you so much for letting me speak. I am a board-certified family physician. I have spent the last 20 years taking care of people 5 days a week in the outpatient setting in Muncie, Indiana, and Boise, Idaho. Conflicts of interest, I first became aware of the IQOS in 2019. I've never been paid by Philip Morris or Altria.

But in 2019, I was invited to go to their research facility and their factory in Switzerland and Italy. And that was the first time I became very curious and very excited about the IQOS, which is sort of a contradictory thing for physicians to say. As other speakers have pointed out, our medical pathways for smoking cessation are very limited.

We're supposed to recommend pharmacologic intervention with behavioral interventions with

really limited options, which are transparent when you look at the success rate of cessation in the United States. Most traditional smokers have to do 6 to 10 to 30 attempts before they quit. And being on the other side of caring very deeply about people and their families and trying to help them quit, it's been exceptionally frustrating for my whole career.

So, in 2019, when I learned about the IQOS, I became exceptionally optimistic. The IQOS is a product that is very consistent with the work that most family physicians do, which sometimes if we can't get to perfect, a.k.a. cessation, can we get to better? Can we get to good? Can we help people transition in a way that we believe, or that there's robust data that supports that they are reducing their overall harmful effects of nicotine consumption?

So, from a boots on the ground, taking care of people day-to-day standpoint, this is a profoundly meaningful product. It's a meaningful product to what we assume are the exposures to the family members of people who smoke. It's a meaningful product to people feeling successful in their transition to a healthier version of themselves. And I support the renewal of the MRTP and anything that gets out of the way of making this product and other heat-not-burn products available to the average U.S. consumer. So, thank you so much.

Cristine Delnevo:
Thank you. Speaker number 6.

Diana Zuckerman:
I'm Dr. Diana Zuckerman, President of the National Center for Health Research. Our nonprofit think tank does not accept funding from any entities that have a financial interest in our work. So, we have no conflicts of interest. Research showing low IQOS use when they were very briefly on the market during the COVID pandemic is not relevant to future use. There is new research and a new understanding of the impact of these products on quitting smoking, on potentially harmful exposures, and on health.

We also know more about the marketing of these products, and about consumers' understanding of the risks. And I'll briefly summarize these issues. Number one, these products have the potential to help people quit smoking, but the most recent research shows they don't usually do that. In a study published this year in the Journal of Epidemiology, which was based on all published studies since 2022, 68 percent of users of heated tobacco products also smoked cigarettes.

Number two, although the short-term biomarker data says that traditionally identified toxic exposures are lower for IQOS than cigarettes, there is no long-term data that would be needed to show that IQOS products are a healthier alternative to cigarettes in the long run. Meanwhile, FDA has identified many other potential toxic exposures that we heard today are higher for IQOS than for cigarettes.

Number three, consistent with those findings, rodent studies indicate respiratory, cardiovascular, and reproductive harm that is equal to or greater than the harms of cigarettes. I don't like to rely on rodent studies, but we can't ignore these important findings. Especially because in research based on 55 studies of humans or human cells that were published this year in the journal

Healthcare, heated tobacco devices increased respiratory disease, hypertension, heart rates, and other predictors of serious diseases.

These products have been on the market for 10 years, and the company should have provided longer-term data to support their claim of reduced risk, rather than telling us that their short-term exposure data show that lower risk is reasonably likely.

Number four, the Campaign for Tobacco-Free Kids has described some of the marketing techniques that PMI uses to reach young consumers. These include ads in fashion magazines and sponsoring concerts that appeal to teens and young adults. Even more harmful, two of the HeatSticks you're considering today are menthol products. We all know that menthol appeals to nonsmokers and those just starting to use tobacco. Why encourage the use of a product that will encourage young people to become dependent on nicotine?

And number five, and last, I've worked with thousands of consumers to evaluate their understanding of health warnings. While many consumers may understand a statement that they've just read, that they would need to switch completely from cigarettes to reduce risks, that doesn't mean that they're going to remember that message exactly later that day, or later that week.

After all, health professionals always tell us that moderation is the key. We can eat fried foods, or ice cream, or hot dogs, or anything else in moderation. So, smokers will assume that using IQOS and smoking less is a good way to lower risk. But that's not what the data show. And the message about lower exposure to chemicals is inevitably going to be misunderstood as meaning less harmful. Thank you for the opportunity to speak today.

Cristine Delnevo:
Thank you. Speaker seven?

Lindsay Mark Lewis:
Thank you, and good afternoon. And I want to thank the committee for giving me the opportunity to offer my support for the MRTP for IQOS. And thank you for the work that the TPSAC committee does. My name is Lindsay Mark-Lewis. And I work at the Progressive Policy Institute where we focus on policies that hopefully improve outcomes for working class Americans. The conflict I have is I'm a proud user of the IQOS.

I want to start by saying that I am not a scientist, and I am not here to present research papers or technical reports. I am here to share my experience as a real-world adult smoker, and the impact switching to IQOS has had on my life. Access to safer alternatives to cigarettes should not be limited to folks like me, the wealthy or highly educated. It should be available to all adult smokers who want to reduce harm. Working class Americans in particular are disproportionately affected by tobacco-related diseases, and they deserve access to products that can help them.

I am a former smoker. And like millions of Americans, I struggle to quit combustible cigarettes. Seven years ago, my lung function was measured at the level equivalent to somebody 160 years old. I first discovered IQOS, back then in 2018, in Europe, and noticed other adults using it, and

out of curiosity, decided to try it for myself. I enjoyed using IQOS. But during the first year, I struggled with dual use of cigarettes and IQOS, frankly, because of the flavor I was using which was amber which is designed to mimic the taste of cigarettes. It wasn't satisfying enough for me, and I often slipped back to cigarettes.

Once I tried the blue flavor, with a different taste profile, the switch became much easier and I was able to stop using cigarettes completely. I smoked my last cigarette in 2019 after 20 years of smoking. Since switching, my health has improved dramatically. Today, my lung function is equivalent to that of a 54-year-old. This improvement is not just personal. It demonstrates the real-world potential of products that reduce exposure to harmful chemicals produced by burning tobacco.

Real-world experience in other countries also demonstrates the impact of heated tobacco. In Japan, where IQOS was introduced in 2014, smoking prevalence has declined from around 20 percent of adults to below 10 percent today. With the FDA, America has a chance to lead in this effort and ensure adult smokers have the same access and the same pro-harm reduction regulatory framework that Japan has.

From my personal experience, I just want to mention this, even though this is not what the hearing's about, the newest version of IQOS, the Iluma, is even easier to use and makes—and produces much less odor, which makes it more appealing in daily life. Small differences like this matter to me, and they make switching from cigarettes more practical and sustainable for adult smokers.

I was recently in Japan. And I want to point this out, it was a sort of unique data point, talking to users of the Iluma, and why it got them to actually switch in the end. And their consistent answer was because it reduced the odor and eliminates the impact on families and their neighbors. It's important.

I admit IQOS is probably not risk free. But in my own life, and the lives of millions of adult smokers worldwide, it represents a real pathway to reduce exposure and improve health outcomes. Working class adults, in particular, should not be left behind when effective options exist. With the correct regulation of these nicotine delivery systems by the FDA and stronger public awareness of the relative benefits of IQOS, I believe we could realistically see the end of combustible smoking in the United States by 2035.

I want to thank you for taking the time to listen to me as a former adult smoker. And I hope the committee will act decisively to provide access to these products and help adult smokers make meaningful steps towards a better health outcome. I strongly recommend the MRTP for the IQOS and encourage the quick consideration of the Iluma device as a next step. Thank you.

Cristine Delnevo:
Thank you. Speaker eight?

Connor Fuchs:
Good afternoon. I'm Connor Fuchs, Senior Staff Attorney with the Campaign for Tobacco-Free

Kids. And I have no financial relationships to disclose. Thanks for the opportunity to speak today. As detailed further in the written comments that my organization submitted, PMI has failed to meet the statutory standard for renewal of its modified risk orders for the following reasons.

First, independent research since the original risk order shows that consumers continue to misinterpret the authorized reduced exposure claims. The research is clear that consumers interpret the reduced exposure claims to mean that IQOS reduces a consumer's health risk. That alone is grounds for denial as the statute requires applicants seeking a reduced exposure order to show with actual consumer perception data that no such misinterpretation exists.

And PMI's own misleading and deceptive statements, since FDA issued the original order, have further exacerbated this misunderstanding. For example, during a webinar in the Philippines, a senior PMI official referred to IQOS as the company's "leading flagship brand in its reduced risk portfolio," and stated that the product was "granted the modified risk tobacco claim in the U.S." Our written comments detail additional examples of PMI's misleading statements.

Consumers also continue to misinterpret the authorized claims to mean that partially switching from cigarettes to IQOS will confer some health benefit when as FDA found in the original order, and despite what the applicant has insinuated today, complete switching is necessary to achieve the benefits mentioned in the claims.

Second, studies, including analysis by FDA, have found that IQOS aerosol can contain higher levels of certain toxicants in cigarette smoke, particularly when simulating real-life conditions in which substances deposited in the device during use are reheated repeatedly. And this data directly contradicts the reduced exposure claims that PMI is seeking to renew.

Third, independent data contradict PMI's claims about IQOS use in switching, which raises serious doubts about the public health utility of the product. Data from the U.S. is limited because until March 2025, IQOS was available only for a short time and only in certain markets. However, data from other countries show markedly lower rates of complete switching than what PMI has claimed, that dual use is the dominant use pattern among those using heated tobacco products. And that users' heated tobacco product uptake exceeds their reduction in cigarettes, thereby increasing their overall tobacco use.

Fourth, PMI's marketing of IQOS is not aimed at today's adult smokers who tend to be older. Internationally, the company has marketed IQOS as a lifestyle product, rather than a tool to help smokers completely switch or quit tobacco altogether. And here in the U.S., where the products were reintroduced earlier this year, PMI has sponsored concerts promoting the products in partnership with Rolling Stone magazine and Grammy-winning artists. And images from these events show many young people attending.

This is deeply concerning, particularly given the vast research tying exposure to tobacco marketing at music events with more positive views of tobacco products and a higher likelihood of trying such products.

And fifth and finally, the orders that PMI seeks to renew include two menthol-flavored HeatSticks. And since the original orders were issued, FDA proposed a rule prohibiting menthol as a characterizing flavor in cigarettes. Key findings that FDA made in the preamble to the proposed rule, including that menthol sensory effects encourage initiation, and that the interaction between menthol and nicotine in the brain enhances addiction, are directly relevant to IQOS and should preclude reauthorization of the claims for the menthol HeatSticks.

For these reasons, and those documented in our written comments, we urge TPSAC to recommend denial of the application for reauthorization. Thank you.

Cristine Delnevo:
Thank you. Speaker number nine?

Ross Marchand:
Good afternoon, everyone. My name is Ross Marchand, and I'm a senior fellow at the nonpartisan, nonprofit Taxpayers Protection Alliance. And on behalf of the millions of taxpayers and customers we represent, we're pleased to present the following comments before the Tobacco Product Scientific Advisory Committee.

For the roughly 30 million American adults addicted to cigarettes, including my grandfather, who was taken way too soon from lung cancer 20 years ago, quitting is no easy feat. Even relatively effective quit-smoking aids, such as nicotine patches, have a 6-month success rate of only about 20 percent. Fortunately, reduced-risk products such as IQOS allow users the sensation of smoking cigarettes without the significant health risks that accompany smoking.

Five years ago, the FDA recognized this and took the commendable step of allowing the marketing of IQOS as a modified risk tobacco product. As a result of this designation, PMI, the manufacturer, has been able to provide information to customers on IQOS' reduced exposure to harmful, cancer-causing substances. The FDA decided this after the producer demonstrated that because IQOS heats tobacco and does not burn it, it significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. That decision was supported by volumes of data submitted by PMI and corroborated by independent research.

In 2017, a research team affiliated with the University of Bern in Switzerland examined the level of carcinogens emitted from an IQOS puff compared to the traditional cigarette brand Lucky Strike. The team found that amounts of harmful chemicals in IQOS smoke were far lower than for cigarette smoke. And in the time since the FDA allowed for IQOS to be marketed as an MRTP, additional evidence has been released affirming the relative safety of IQOS for smokers looking to make healthier choices.

According to a comprehensive review of the evidence published last year, 2024, by health researchers at The Ohio State University, the use of IQOS is associated with significant decreases in exposure to harmful gases and chemicals such as carbon monoxide and benzene. The researchers also noted that studies using high-quality systems toxicology showed minimal harmful impacts from using IQOS compared to the conventional and deadly alternative. So, the evidence is vast, and the conclusion is clear. IQOS is a reduced-risk product that can save and

better millions of lives.

As the Tobacco Product Scientific Advisory Committee convenes to consider the renewal of the FDA's modified risk-granted orders, we urge the committee and the FDA to consider the significant evidence that IQOS is a far safer option for customers than cigarettes. We also encourage the FDA more generally to adopt a more flexible regulatory framework that allows customers access to harm reduction products. We thank you for your time and attention to this important issue. Thank you so much.

Cristine Delnevo:
Thank you. Speaker number 10?

Dallas Atkinson:
Hi. Thank you so much to the committee for having me. I'm Dallas Atkinson. I am here as an Army wife and in the veteran service industry full time. I'm here to raise an issue that's both personal and national. Persistently high rate of tobacco use among our veterans, the culture that drives it, and the opportunity through innovation and science that we have to turn the tide.

Veterans continue to smoke at rates far higher than the general population. According to the CDC, nearly one in three veterans uses tobacco, and more than one in five are current cigarette smokers. Among veterans enrolled in VA health care, the rate remains around 13 percent despite years of other programming. It's not just a habit, it's part of military culture.

Cigarettes are still used as stress relief in high-pressure environments, coping mechanisms for trauma, and bonds of camaraderie in deployment. Many service members start smoking during service, others relapse after exposure to combat. When they come home, they don't leave that culture behind, and the result is a chronic public health crisis that our system continues to absorb.

The Department of Defense roughly spends about $1.8 billion every year in tobacco-related medical and productivity losses. Department of Veteran Affairs spends about 2.7 annually treating smoking-related illnesses. Those are real dollars, real people whose lives are shortened by something that we're learning how to address.

As an advocate and as a military spouse, I've seen what that cost looks like up close in our veteran community. The caregiver trying to manage lung disease, or a veteran who can't climb a flight of stairs without wheezing.

We need to be honest, not every veteran can or will quit smoking. For many, nicotine is intertwined with trauma, identity, and survival. That is why harm reduction must be a part of our public health strategy. The FDA has recognized the potential in IQOS as a heated tobacco product developed to reduce exposure to harmful chemicals by heating instead of burning the tobacco.

IQOS doesn't produce smoke. And studies reviewed by FDA show significantly lower levels of many toxins found in conventional cigarettes. No one would claim that IQOS or any tobacco product is risk free, but the evidence demonstrates that IQOS is significantly—a significantly

validated alternative that can reduce harm for adult smokers who would otherwise continue to use combustible cigarettes.

For our veterans, many of whom have tried and failed to quit, IQOS could represent a bridge, not a barrier, for better health. Give them a ramp to reduce risk, regain control, take those first steps away from traditional smoking. Veterans have earned the right to know every option available that could reduce harm, prolong life, restore dignity. IQOS should be one of those options for our veteran community.

Our veterans fought for our freedoms. They didn't choose addiction. It was cultivated by the very culture of service that we asked them to join, and now it's our responsibility to fight for their freedoms from smoke, from the stigma, from outdated policies that deny them innovation. IQOS isn't an enemy. When science tells us that technology can lower harm, the question is clear. How quickly can we act?

I would urge this committee to embrace evidence and not complacency. And to consider these things, knowing that a veteran deserves access to every scientifically supported tool that could save their lives. Thank you so much.

Cristine Delnevo:
Thank you. Speaker number 11.

Travis Johnson:
Hi. Good afternoon. I'd like to thank you for the opportunity to join you today and to share the views of the International AntiCounterfeiting Coalition in connection with the Advisory Committee's consideration of the renewable applications for the Philip Morris modified risk tobacco products previously granted by the Food and Drug Administration.

Founded in 1979, the IACC is the world's oldest and largest organization dedicated solely to combating the trafficking of counterfeit goods, and the wide range of harms associated with trafficking. I should say at the outset that I am not a medical doctor or scientist, nor is my background in the field of public health. But I do have a great deal of expertise in the area of illicit trade having worked on those issues for the past 20 years, and that will be the focus of my comments here today.

For over four decades, the IACC has studied the production and distribution of counterfeit goods across every conceivable product sector, the factors driving illicit manufacturing and sales, consumer attitudes and perceptions related to the purchase and consumption of those goods, and the resultant impacts. Given the focus of today's meeting, it's worth noting that tobacco products consistently rank among the top 10 counterfeit commodities seized each year in our ports by U.S. Customs and Border Protection.

A common misconception about counterfeiting is that the harm caused by this illegal trade is limited to economic considerations. And while economic injuries are certainly one component, a more troubling and often overlooked harm associated with counterfeiting is the significant threat that these goods pose to consumers' health and safety.

It's important to consider the realities of the consumer market and the fact that counterfeit goods do not typically compete in that market on the basis of their purported quality, but on price alone. So, how do manufacturers of counterfeits maximize their profitability? While legitimate manufacturers of FDA-authorized products, products like the IQOS devices before the Advisory Committee, are required to adhere to rigorous safety, quality, and manufacturing standards.

The costs associated with that compliance are not borne by counterfeiters. They use low-quality components. They ignore every regulatory mandate on the books related to product safety or sanitary production environments. And they pay no heed to accepted standards of consumer protection, and why would they? It's not their name on the packaging, and it's not their reputation at stake. That's why we believe it's vital that consumers continue to have access to modified risk tobacco products produced and distributed in compliance with a thoughtfully considered FDA regulatory framework, one that ensures consumer trust.

It's often said that nature abhors a vacuum, and that sentiment has been borne out over years in the context of trafficking of counterfeits. When legitimate products are not available in the market, someone will step in to fill that void and to satisfy demand for those goods. Denying the renewal of the IQOS' MRTP designation would likely have the unintended effect of reducing availability of authentic, regulated products while incentivizing bad actors to produce and distribute illicit alternatives that fall far short of the FDA's existing framework for ensuring product safety and quality.

Accordingly, we support the renewal of the MRTP authorization for the products before the Advisory Committee as a means to preserving consumer choice, access, and protection, and thereby minimizing the risks associated with the distribution of counterfeit substitutes. Thank you for your time.

Cristine Delnevo:
Thank you. Speaker number 12?

Lonnie McQuirter:
Thank you, Madam Chair, and members of this committee. I do not have any financial interest in PMI, nor am I being compensated for being here today. My name is Lonnie McQuirter, and I'm the Director of Operations at 36 Lyn Refuel Station, which is an independently owned convenience store located in South Minneapolis of the state of Minnesota. Appreciate the opportunity to speak to you guys today.

I urge the Tobacco Products Scientific Advisory Committee, or TPSAC, to recommend the renewal of IQOS modified risk tobacco products designation. As a retailer serving adult customers every day, I see firsthand the challenges many face in quitting smoking. Many are actively seeking alternatives like IQOS. The MRTP designation empowers retailers like me to provide clear, truthful, and scientifically vetted information that helps consumers make informed choices about less harmful products.

The FDA authorization is essential for retailers. It safeguards public health, builds consumer

trust, and protects against legal and financial risks. While not every product in a store is FDA approved, FDA oversight is critical for items that impact consumer health and safety. And IQOS is one of those products. The MRTP designation enables accurate and reasonable communication. It ensures that any reduced risk messaging is evidence based, legally compliant, and thoroughly reviewed by the FDA.

This is not marketing hype. It's science-based information that helps adult smokers transition away from more harmful combustible cigarettes. Retailers committing—committed to selling FDA-authorized products demonstrate a dedication to compliance, safety, and responsible sales practices, including strict age verification. This builds consumer trust and reinforces our role in supporting public health.

Finally, carrying FDA-authorized products like IQOS protects our reputation and ensures continued market access. Consumers know these products meet rigorous standards, and retailers avoid enforcement actions while maintaining credibility in communities we serve. I respectfully ask TPSAC to support the renewal of IQOS' MRTP designation. It is a decision that supports harm reduction, empowers adult consumers, and strengthens the role of responsible retailers in advancing public health. Thank you for your consideration.

Cristine Delnevo:
Thank you. Speaker number 13.

Graham Boyd:
Okay. Thank you. I'm Graham Boyd I'm the Executive Vice President for the Tobacco Growers Association of North Carolina. We're the commodity organization that represents the 2,000 farmers in our state that grow principally flue-cured tobacco. In terms of full disclosure, obviously, Philip Morris International is an important customer of buying our product from the farmers. In addition, they are supporting a corporate sponsor member of our organization. This is important as we interact together in the market space.

We last presented to you in 2017, when you were given consideration to the initial application for heat-not-burn products, specifically the PMI product that we have already heard referenced all day as IQOS. And so, we're coming back to you today in support of their application for renewal.

You might be interested to know we had two conditions of support. And we made these to Philip Morris International as they were advancing this technology around the world. And as it had evolved in places like Japan and in Italy, initially. And those two conditions for us were that it had a high content of U.S. grown tobacco. And that when they would make a manufacturing facility in the United States, selfishly, we would like it to be in North Carolina.

And since 2017, I can confirm to you that both of those things have transpired. They continue to buy a high content of U.S. tobacco as a key ingredient source. And that means that they are using, as the basis for this product, the most compliant tobacco in the world. We are subject to an array of government oversight and inspection processes from the Department of Agriculture through the Department of Labor. And indirectly, even the FDA, which doesn't have authority

over the farm, but your policy decisions impact our farmers.

So, we've been convinced and appreciative that those two things are—have been a priority, with Philip Morris International and this product, IQOS. We've toured their facilities. We've seen their product, and it's quite impressive in the facility that they built in Wilson, North Carolina. As recently as last week, a new announcement came as they continue to evolve new products, and they have petitions before you considering approval for things like Iluma. They are going to spend $37 million in Wilson, North Carolina, which is a rural part in the eastern part of our state. That's a lot of infrastructure and a lot of jobs as they expand into this footprint.

Again, our two conditions remain on that product and the renewal of this product. Continue to buy U.S. content, American-grown tobacco, continue to make those products here in America, very important, particularly as this product largely has an opportunity for export into a growing segment. We don't condone or advocate people to use any particular tobacco product but we do think consumers should have a choice. And they should be free to use products when they have an informed choice about the risk. And for that reason, we again support the continued application approval.

I'd like to spend the balance of my time, which is about a minute here, to echo a few things that Mr. Johnson mentioned earlier, and that's the topic of illicit trade. If you really want to do your job at FDA and help protect consumers, crack down on this issue. It's hurting farmers as we see double-digit decline of the legitimate product that you actually have enforcement authorities over. And mark it down in this recording. It's a matter of time before all this illegal, illicit vape when we see an episode of a fentanyl outbreak or something of that kind. These products are unregulated. We don't know where they're made, what's on them, what's in them.

And the last comment would be that we oppose synthetic nicotine being used in these products as well. And so, as you look at the non-combustible space, we would ask this committee to put high emphasis on the fact that nicotine—these are all nicotine delivery devices, and nicotine is a stimulant. We know it's a drug, but it's not carcinogen. We know that people chase nicotine, like caffeine, or sugar, or any other thing that our bodies crave.

Here's the important thing. It should come from naturally grown tobacco, and to be selfish, American-grown tobacco. This means jobs. It means compliance. It means tax revenue for our government system. And that is a priority that FDA should make very high in this review of any new products coming online. And I thank you for the opportunity.

Cristine Delnevo:
Thank you. And now we will have our last speaker, number 14. And as a reminder—and I know it's difficult, not everyone can see their timer, I will give a 1-minute warning when there's 1 minute left.

Kanagavalli Mathivathanan:
Thank you, Madam Chair. And thank you, committee members, for providing me with the opportunity to talk about this MRTP application. My name is Kanagavalli Mathivathanan. I'm a tobacco control advocate. I have no conflict of interest, and I have no financial interest or

affiliation with any tobacco manufacturers or importer or distributors or retailer, nor with any organization supported by tobacco industry.

I'm here to talk about PMI's MRTP renewal application. This clearly does not meet the statutory standards. I would like to focus on three statutory standards: population benefit, youth initiation and disparities, and consumer perception. Next slide, please. Next slide. Thank you very much.

Yeah. Population benefit. PMI cites that 20,000 users completely switched to HeatSticks from other cigarettes, but there is no net population level benefit data that has been shown. Dual use reminder common use, even after this IQOS has been introduced. Nicotine and the HeatSticks are highly addictive. Remember, we are talking about the products which are harmful and also very addictive. Emissions from the heated tobacco products expose users and bystanders by toxicants. We have clearly seen by the biomarker studies that is also presented by PMI, which show that is not risk free, that also contains all very toxic and carcinogenic materials.

In PMI's original application in the page number 64, it has been shown that this heated tobacco products, especially with the menthol flavor, which has been more attractive to Black or African Americans and Hispanic or Latino people. And in a BBC article, all the three Big Tobacco companies, including PMI, has admitted that it is incorrect to say heated tobacco products are safe or risk free. Next slide, please.

Next, I would like to focus on the statutory standards, youth initiation, and disparities. Even though PMI stated that it will not target the youth consumers, research after research studies has been very clear, it has been shown, especially with the menthol flavors, which increases the youth appeal, and also make the end consumers to experiment and initiate this new product.

Disparities, as I mentioned before, disparities are very common among Black and Mexican Americans. Menthol flavors especially make the quitting more difficult, which is the very reason that PMI is stating that it will help the consumers to quit cigarette smoking. But, that's not the case with the reality. From PMI renewal application, it shows that only 6.49 percent Black Americans preferred menthol heat sticks, which is a very contradictory statement by its original application, which the data I have shown in the previous slide, in the page number 64 from its original application.

And research studies have been very clear; the psychoactive effects of the menthol increase the addiction. Renewal of the flavor HeatSticks undermines the public health effects. Next slide, please.

Cristine Delnevo:
You have 1 minute left.

Kanagavalli Mathivathanan:
Okay. Yeah. Thank you. Consumer perception, it is very, very evident that consumers often misinterpret that reduced exposure means reduced harm. That's the modified—the word modified risk, often the consumer is misinterpreting as safe. So, consumer perception is often favorable for the design appeal and also for the flavor. Next slide, please.

There is definitely evidence gap. It has been very understanding that the product is not available from October 2021 but there is still limited U.S. data. And if you see the sampling of the studies represented by—presented by PMI, that is short-term convenience sampling and perception surveys. There is no robust post-market surveillance data, industry-sponsored data. We always know there is a bias.

And also, the evidence conducted by—the research study conducted by the National Technical University of Athens, they didn't—cannot be able to identify all the toxic chemicals or all the ingredients present in the aerosols of the HeatSticks. Next slide, please.

Cristine Delnevo:
Time's up.

Kanagavalli Mathivathanan:
Okay. Yeah. And, finally, I would like to recommend the committee, do not renew the applications of modified risk tobacco products by Philip Morris International, as it does not meet the statutory requirements without the robust independent study. Thank you so much for the opportunity.

Cristine Delnevo:
Thank you. I'm just going to ask again if our first speaker is here. I don't think that they made it. But before we close the open public hearing session, I just want to double check. Okay, very good. I'd like to invite Dr. Ben Apelberg. Dr. Apelberg is the Deputy Director of the Office of Science at CTP. Take it away, Ben.

Ben Apelberg:
Great. Thanks. Thanks, Dr. Delnevo. And thanks to all the individuals who participated in today's open public hearing. Public participation in the regulatory process is an important part of the work we do here at FDA. So, we really appreciate you all taking the time to speak to the committee today.

So, as Dr. Delnevo mentioned, I am Dr. Ben Apelberg. I'm Deputy Director in the Office of Science at the Center for Tobacco Products. And for the rest of today's meeting, our committee members will be asked to discuss and deliberate on three discussion questions. CTP developed these questions based on topics identified during our preliminary evaluation of the MRTP renewal applications for these Philip Morris IQOS products.

Two of the questions center on new toxicological evidence about IQOS use. And we're grateful to have three consultants here today with the committee who will bring additional toxicological expertise to the discussion. The third question asks the committee to discuss the likelihood that people who use combusted cigarettes will switch completely to IQOS products. We have many staff listening in from the Office of Science. We'll be paying close attention to the committee's discussions. And these discussions will be used to inform our evaluation of the MRTP applications, moving forward.

A few things to keep in mind before I turn it back over to our chair. First, we really encourage committee members to focus on the questions that CTP has developed. A lot of thought went into these questions, and they really reflect the areas of scientific evidence where we're really most seeking TPSAC's scientific input and advice.

Also, as scientists, we encourage you to use your scientific expertise to objectively consider the evidence that's been presented. And keep in mind why we're here, to provide scientific advice to CTP as part of our evaluation of this MRTP renewal application. So, with that, I'd like to turn it back over to Dr. Delnevo to lead what I'm sure will be a robust and engaging discussion about the evidence that's been presented. Thank you all.

Cristine Delnevo:
Thank you. Next slide. Next slide, please. Next slide. So, we're going to start with the first discussion question for TPSAC, which is focused on IQOS and nonclinical toxicity evidence. The background here is that the findings from most nonclinical toxicological studies published since the issuance of the modified risk granted order and reviewed by FDA did not identify new toxicological concerns about IQOS.

However, four newly published nonclinical studies that used rodent models to study IQOS aerosol exposure found that exposure to IQOS aerosols had respiratory, cardiovascular, and reproductive developmental toxic effects that were comparable to or more severe than combustible cigarette smoke exposure.

And so, we're being charged now to task with the discussion about the strength of the noncancer toxicity evidence from the four animal studies in the context of the totality of the toxicological evidence, including any limitations of these and any studies that may limit their conclusions.

Cristine Delnevo:
Dr. Zelikoff.

Judith Zelikoff:
Yes. I'm going back to the questions that I asked. It's very hard to interpret the data from studies that we don't know the details for, again, dose, duration, method of exposure, et cetera, et cetera. But with that said, it raises concerns in my mind. And, if somebody could get back to me with that information, that would be helpful. But as I was saying, the animal studies, though probably pilot in nature, raise concerns about indications of the toxicological effects. And there's many other toxicological effects that are potentially there that have not been considered, have not been studied.

So, I just feel that, you know, there's controversial data. But if you're going to take the precautionary principle, then you're going to consider those studies—can begin to start showing. And again, the limitation of time is a real concern for me. So, that's what I would say about the toxicological data. I also happen to know some of these authors, and I know the quality of work that they do.

Cristine Delnevo:

Thank you, Dr. Zelikoff. I think it's a good reminder for us that there were some questions initially after the FDA presentation. And Dr. Koblitz was going to get back to us, with some answers to those questions. And so, if it's possible for FDA to follow back up with—I'm not—I didn't fully keep track of what all those questions were. I just remember you saying, Amber, you were going to get us answers to some of the questions. And this would be a good time for that.

Amber Koblitz:
Absolutely. And I'm going to have Dr. Wagage join me as well to answer that. But, questions came from Dr. Zelikoff and Dr. Madl, both about kind of how we weigh the evidence that we're seeing where things don't match. There's not comparisons, right? There's not, I believe, equimolar was thrown around. But, how do we actually factor in these difference and these comparisons and the different potencies when we come to a conclusion?

And so. I'm going to have Dr. Wagage answer a little bit. But I am going to say, just to start, we generally—we have to figure that out on our—so this is the problem that we deal with as well, right? There are limitations in every single available study. We have to evaluate all this evidence including those limitations. And there's not a set way to do it that is, you know, super helpful. But I'm going to—Sagie, if you're available, I'm going to let you weigh in if you've got anything to add to that.

Sagie Wagage:
I can speak a little bit to the specifics of the studies. So, these were all studies in which, either mice or rats were exposed by inhalation, either whole body or nose-only inhalation. One of these four studies did evaluate serum cotinine levels. The other three studies did not have data on biomarkers of exposure.

In terms of dose, like, specific doses, in general, there wasn't a lot of specific information. The studies in the methods section did speak to, for example, how many cigarettes or how many HeatSticks were used for the exposures. And those were similar. So, for example, in one of the emphysema studies, mice were exposed to the same—to aerosols from the same number of HeatSticks, and cigarettes. But please let us know if there are other questions about this.

Cristine Delnevo:
Thank you. Dr. Jordt?

Sven-Eric Jordt:
Thank you. So, in reading the more detailed document that FDA distributed about these questions, and also their analysis of these studies, I came to the conclusion that the exposures that were used here are likely less what a human user would receive. In some studies, the animals were only exposed once a day or twice in the study by Yoshida. I believe only twice, basically. So, they were—just got two exposures. The exposure atmospheres were also quite strongly diluted with air in one study, down to 3.5 percent.

The study by Gu was criticized by FDA because of the use of the t-test only. This is definitely a legitimate concern and this is insufficient to compare groups. But the study by Qiu does that, and the study between—no, excuse me. The study by Nitta, et al. does that and it's very similar to

Gu, and they come to the same outcomes. What gives me more confidence even is now that we have, in fact, clinical studies available with human subjects that reflect some of the outcomes of the animal studies.

A recent study by Jung from Germany has shown that IQOS use by test subjects in a controlled clinical trial can affect small airway function, and has very similar cardiovascular effects affecting the endothelium, heart rate, and other essential parameters. So, I conclude from—basically that, yeah, the exposure that were done is likely lower than what humans get. And that these studies—now that we have clinical studies, in fact, reflect what we see in those clinical studies. Thank you.

Cristine Delnevo:
Thank you, Dr. Jordt. I do have a question. PMI has raised their hand for—to participate but my understanding is this is about the non-clinical study. So, if you could just quickly unmute yourself and clarify. These are not nonclinical studies that PMI did.

Keagan Lenihan:
Correct. They're not clinical studies that we did. I just feel like there's been a bunch of questions related to the tox profiles of these, as well as the limitations. And I think it would be nice to have Dr. Picavet to explain the difference in between the two.

Cristine Delnevo:
Well, I don't see committee members asking questions about those particular studies.

Keagan Lenihan:
He wants to comment on the four studies that have been cited, that folks have rightly questioned the limitations around those studies from animal models versus the human studies that we have.

Cristine Delnevo:
The four nonclinical studies that are posed in question one. Is that correct?

Keagan Lenihan:
Correct.

Cristine Delnevo:
That were not done by PMI.

Keagan Lenihan:
Correct.

Cristine Delnevo:
Then I'm going to rely on the expertise of TPSAC to have that discussion.

Keagan Lenihan:
Okay.

Cristine Delnevo:
Thank you. Scout, do you have any comments to make or questions about the first question?

NFN Scout (they, he):
Yes, I do. The—it definitely concerns me that we have evidence which directly contradicts the reduced exposure claim from independent studies. I also am concerned because if we think about it, so far, we're still using an HPHC that was developed before this item even came to market. And in 2019, TPSAC did suggest adding a bunch of chemicals that were more relevant to this type of product to the HPHC and updating it. And here we are in 2025, and those chemicals are still not actually on the HPHC yet. So, I would strongly encourage TPSAC to use their own updated HPHC.

But then, the last piece related to this that I think is of concern when we hear this is that, as we saw, so many of these studies only talked about a very minority percent of all the cases since the independent studies show that really, what we're dealing with is a lot of dual use. And so, it strikes me that it seems like we've got a fair amount of limitations if we're only looking at studies that look at single use, which only affect a small minority of the number of people using IQOS. Those are my concerns.

Cristine Delnevo:
Thank you. Dr. Upson.

Dona Upson:
Thank you. And adding to what Dr. Jordt said with the clinical studies supporting the rodent studies, there were also some studies of human lung epithelial cells that were referenced in the background documents that showed similar findings. And to Dr. Scout's point, one of those studies showed that the exposures were highest for dual use compared to conventional cigarette smoke or IQOS by itself.

And I'd like to reinforce that all of these are short-term studies, but they support background effects that are likely to have or that may have long-term effects. We don't have any long-term data yet. Thank you.

Cristine Delnevo:
Thank you. Dr. Madl?

Amy Madl:
Hi. Amy Madl of Valeo Sciences. I'd like to just bring up my prior comment about the importance and need for appropriate aerosol characterization and dose delivery to the animals. And ultimately, the question at hand is, what is the exposure comparison of IQOS to combustible cigarettes, and how that translates to the overall harm reduction of IQOS compared to combustible cigarettes.

And of the four studies that were covered by FDA, only one of those studies actually characterized the dose delivered to the animals, comparing IQOS to combustible cigarettes. And the remaining studies did not do any aerosol characterization or any biomonitoring to really,

truly understand whether there was an appropriate apples-to-apples comparison of doses, as well as allowing one to interpret the relative difference between IQOS and combustible cigarettes with respect to the health outcomes.

So, I would go back to just the overall totality of evidence that has been presented, both by Philip Morris and FDA today, about the relative comparison in risk or exposure reduction of HPHCs from IQOS. And ultimately, there's a very large reduction, 80 to 90 percent reduction, in HPHC exposures that translates to a tremendous reduction in biomarkers of exposure. And we then further see that in a reduction of—or comparable biomarkers of harm of individuals that completely switch away from IQOS compared to smokers that have ceased smoking over the last 8 years.

So, I would—in terms of these four studies, I don't think that these four studies necessarily meaningfully or materially change the overall weight of evidence that IQOS shows a tremendous exposure reduction that would be beneficial to smokers looking for a reduced harm or reduced exposure alternative to nicotine.

Cristine Delnevo:
Thank you. Dr. Zelikoff.

Judith Zelikoff:
So, I have a number of things. But one clarification point, and that is that I am not dismissing the additional toxicological data from the independent authors. I would recommend that—and I don't know if this is possible. But I would recommend that the FDA reviewers do take a second look at some of these papers, just to be able to answer Dr. Madl's and my own questions. And, that would be a recommendation. But please note that I in no way are dismissing these studies, just require more information. That's all.

And a couple of other things. The fact that certain toxicants are reduced in concentration does not mean that there aren't biological effects. Statistical analysis versus biological analysis, and how that could focus on human health are very different. Also, we know that even if you reduce the concentration of a certain chemical, the potency of it may be such that even at low concentrations, they're harmful or adverse. So, I would take that into consideration.

I also have read the in vitro studies, which are compelling and of epithelial and endothelial cells. And in any case, that is the first tier, in vitro studies, followed by animal studies, followed by human studies. And so, I think that the data between the in vitro studies and the in vivo studies are trending in similar directions. In vitro allowing us to see mechanistic actions that the changes that were observed were—could lead to cardiovascular and pulmonary outcomes.

I also have experience in reproductive toxicology and that is a very complicated findings. But with pregnancy, I'm still very concerned about the use by pregnant women. Because they are still getting nicotine, and they are still getting low doses of chemicals, albeit reduced. But again, it depends on the potency and the body burden of those particular chemicals.

I had one last point, sorry. Oh, menthol. So, this was brought up during our open discussion. And

menthol is a coolant, and it's one that specifically targets Black Americans and African Americans because of their more addictive behavior. In this case, because of a variant of a gene. And so, there is genetic evidence, clear genetic evidence, which shows that the addition of menthol is more highly used by African and Black Americans.

So, again, we're going back to the targeting. And my final thought was also brought up, and that is that this is a 1-year, one-and-a-half-year data collection. And despite the fact that it was mentioned that these data will reflect future data, I humbly disagree with that. I think that it's certainly the more numbers you have, the more people, all surveys, for the most part have some bias within it. They're self-reported.

And so, I think that we have to consider that as well. So, there are, on many basis, toxicological basis, public health basis, I disagree with some of the things that were said. But I also wanted to echo what someone else said. And that is, according to the background document, they have found that dual users do have greater health effects than just independent users on their own. And I don't think that people will actually take into account exclusive use only. So, thank you very much for the time.

Cristine Delnevo:
Thank you. Before we move on from question number one, I did want to pose to the committee a question about what type of studies you think might be needed to fully address the scientific issues that we're discussing that's listed under discussion question number one, if individuals have thoughts there. Dr. Rigotti?

Nancy A. Rigotti:
Yes. Just following up on what I've heard. I'm not a toxicologist. But from what I've heard from my colleagues, it seems like because of the concern about how much dual use there's probably going to be when this product is in real-world use, I think it's going to be important that looking carefully at what that means and how much risk reduction actually occurs, compared to cigarettes, but also compared to HPHCs only, would be very helpful going forward. I guess that would complicate the models, but I would wonder if that's possible.

Cristine Delnevo:
Thank you. Dr. Stepanov.

Irina Stepanov:
Yes, I would second that. I do agree with the concern. And, you know, as we've heard some of the evidence that, I think over 83 percent of people who use IQOS report reduction in cigarettes per day, but we weren't given any numbers, actually, by how much. There were results presented, you know, showing reduction in people who are predominantly IQOS users, which was pretty, you know, impressive, going in a positive direction.

However, you know, what is the proportion of the overall population that are predominant IQOS users versus people who just reduce their cigarettes per day by one or two cigarettes and are likely to be exposed to a more complex and potentially higher levels of toxicants, including some unique chemicals that come from these products?

So, just to second the proposal that dual use needs to be taken into consideration in these models. And another point, you know, there was a discussion about the dose, how do—that exposures are not well characterized in some of these studies. I think it is important to look at per nicotine dose delivery, whatever it means, if studies look at the same number of cigarettes as IQOS sticks.

Because we know from human product use studies that delivery of nicotine, even though that IQOS stick is really small but it delivers the same amount of nicotine as a single cigarette. So, normalizing for nicotine to better interpret the outcomes of these animal studies would probably be helpful.

Cristine Delnevo:
Thank you. And just so folks know, we will be talking about patterns of use in a later question. And so, I think there's another opportunity for questions or concerns regarding dual use to come up there as well. Dr. Upson.

Dona Upson:
Thank you. Just briefly about the dual use. I think one of the papers I read said that there was a significant number of people who had used more than two forms of nicotine. It didn't specify which ones, but I would guess that e-cigarettes fit in there, along with IQOS and cigarettes, maybe other forms of tobacco. So, I think future studies should look at multiple forms of tobacco use used together, but we can talk about that more later.

The other concern I have that could be studied would be the epigenetic changes that were mentioned in the animal studies. We're learning more and more about the DNA changes that are passed down through generations, and the impacts even on neonatal or prenatal exposure to paternal smoke. So, I think more studies looking at generational changes epigenetically and on lung function especially. Thank you.

Cristine Delnevo:
Thank you. Dr. Jordt?

Eric Jordt:
Thank you. Yeah. I second the opinion by Dr. Rigotti that dual use needs to be studied in animal models. And it is especially also important to look at sex differences in this context. Just adding to what Dr. Zelikoff said about concerns about use by pregnant women. I think we need additional studies in pregnancy models. This is important.

Just recently, an epidemiological study out of Japan demonstrated that IQOS use is linked to placental abruption. This is likely due to the effects of nicotine have been shown for cigarettes too. So, this needs to be also studied in animal models, if possible.

Cristine Delnevo:
Dr. Madl.

Amy Madl:

I'd like to just reiterate the importance of this dosimetry. And I agree with the prior comment about characterizing dose and normalized in nicotine. That really provides the platform to compare doses, as well as effects across different treatment groups or different products. And I would just say that these studies are noteworthy. It's worth further study. But it needs to be done in a context where dosimetry is appropriately characterized.

And I would say that that is a need not only for in vivo studies, inhalation studies, but also in vitro studies, as we are advancing in the field of toxicology to extrapolate findings in vitro to what that might mean in in vivo systems and even mean for humans. And I think there is a really strong need to contextualize and understand the doses that are delivered in these types of studies, and how that really translates to doses and exposures in humans.

Cristine Delnevo:
Thank you. Can you move to the next slide? I'm going to move us to discussion question two. I'm going to read discussion question two and then open the floor up for discussion. And recognize that, you know, we do have crossover between all three questions. And so, don't hesitate to contribute if it's not cleanly, like, linked right to the single question.

So, question number two focuses on the totality of evidence and long-term disease risk. By way of background, there is evidence of large overall reductions in harmful and potentially harmful constituents in IQOS aerosol compared to combusted cigarette smoke.

However, newly available nonclinical data from predictive computational toxicology studies and rodent models raise questions about the genotoxic and noncancer toxicological effects of exposure to IQOS aerosol. Consider the totality of the toxicological evidence that is now available and discuss the implications for long-term disease risk of exposure to IQOS aerosol relative to combustible cigarettes. Dr. Zelikoff.

Judith Zelikoff:
Well, we know from long-term data that acute exposures or acute effects from short-term exposures are very different from those effects that you either might see after long-term exposure or delayed effects. And at this point, we have no evidence that convinces me that there will be no chronic concerns coming off. I mean, I'm not sure if I'm allowed to say some of the things that have happened with e-cigs.

Just in point of reference that the more we study. the longer we study, and I'm not proposing, you know, year-long studies, I'm just saying that you can't identify accurately, or reproducibility is minimized when you don't have subchronic or chronic exposures. And then you wait 6 months, 3 months, and you see what long-term effects might arise. Maybe there's none. But there's no, in my mind, there's no extrapolation between acute or short-term and long-term effects and persistent or effects that come about after a longer period of time. So, I don't think you can compare these studies to long-term effects. Thank you.

Cristine Delnevo:
Dr. Jordt?

Eric Jordt:
Thank you. I would like to reiterate Dr. Scout's concern he just voiced about the deficiency of the HPHC list the FDA is working with and making conclusions on these. The list is completely outdated, it's from 2012. It only basically lists compounds that are present in combusting cigarettes but not even in e-cigarettes or in these heated tobacco products. And we just learned that in addition to the standard HPHCs that, some of them were reduced, there was an increase in some other compounds that are not on the list, but that are carcinogens. We're talking about, like, glycidol. We talk about 2-Furanmethanol. There are compounds that have cardiovascular effects, such as 2-chloro-1,2-propanediol that was also mentioned. I don't even know where this comes from. PMI has complete control over the constituents.

Why is there a chlorinated compound being formed? Where is this from? Is it from a sweetener, like sucralose or other compounds? So, I'm concerned FDA has insufficient tools to make conclusions based on the deficient HPHC lists and neglects concerns related to these compounds that are not on the list but are known carcinogens or cardiovascular toxicants. Thank you.

Cristine Delnevo:
Thank you. And I do want to clarify for the committee that a focus for our discussion here is about the harms of this product relative to cigarettes. So, think about that in your contributions. And also consider are there biomarkers that could be helpful to show meaningful change? How long might those take? And is there any additional evidence that would be valuable in assessing the health effects of IQOS relative to combusted cigarettes? Dr. Stepanov.

Irina Stepanov:
Sorry, it took me longer to turn my mic on. So, I, again, I want to support the concerns. Actually, it was highlighted by the FDA review that we need more information on unique chemicals that are present in IQOS aerosols. There is no quantitative data on the levels of these chemicals. And not really enough information, at least from what was presented on what those compounds are. And the actual methods, I think, are also relatively deficient in trying to identify the complete chemistry of emissions. So, that is one point.

The second one is, again, as was reviewed through independent studies, that biomarkers of potential harm in long-term users of IQOS are not—even though they're slightly reduced compared to smokers, but not statistically or substantially different from smokers. So, that is a concern and indicator that the picture is not clear cut. You cannot just simply extrapolate reduced exposures to harmful and potentially harmful constituents and long-term biological effects.

Another point I would like to raise is the carcinogenicity. So, if you think about the model of chemical carcinogenesis, it's a multi-stage model. And we are talking about long-term effects in people who smoke. Predominantly, people who use IQOS are people who smoke. So, in multi-stage model of chemical carcinogenesis, cells are first initiated by a carcinogen. And then you need continuous and repeated exposure to tumor promoters to actually push the process towards carcinogenicity.

And at least from what we see from the chemical analysis and biological effects that are observed in people who use IQOS, there is a high likelihood that this process can happen. So,

closer attention to reactive oxygen species, inflammatory agents that are present in IQOS aerosols would be needed to better understand the potential long-term carcinogenic risk from these products. So, I would humbly and respectfully disagree that there are no new toxicological concerns coming from these assessments of 80 compounds that close to half of them have some carcinogenic and mutagenic potential properties.

Cristine Delnevo:
I want to encourage folks to think about the specific question in front of us now. And in particular, are there any biomarkers that would be helpful to monitor? And also pointing out that while IQOS has not been on the market for extended periods of time in the United States, that's not the case internationally. And so, encouraging folks to think about what additional evidence could be used and could be useful to FDA as they consider this particular question. Dr. Madl.

Amy Madl:
Hi. So, I'd like to just bring it back to the question at hand with comparison between IQOS and combustible cigarettes. IQOS at least in the U.S. is a relatively new product. But it's not new internationally or globally. And when we're looking at this question about potential risk, we've got different tools that we can apply to better understand and characterize the potential risk reduction, harm reduction of IQOS. And that is the quantitative risk assessment, both noncancer and cancer risk assessment. As well as clinical tools, as well as toxicology studies to really inform what would be the relative harm and reduced harm, reduced risk of IQOS.

So, based on the evidence that's been presented, there's been there's a decrease in HPHCs, for IQOS compared to combustible cigarettes, up to 94 percent. When you evaluate the HPHCs, even those that are increased or unique in IQOS compared to combustible cigarettes, the quantitative cancer risk assessment still shows that there was an 80 percent risk reduction compared to combustible cigarettes. And then that aligns with the toxicology studies that have been conducted and compared IQOS to combustible cigarettes showing that IQOS has reduced potency in toxicology studies that were presented or submitted to the FDA.

And then that further translates to biomarkers of exposure. So, there was evidence that presented that biomarkers of exposure reduce upwards between 50 and 95 percent in IQOS users compared to smokers. So, I think that provides a pretty compelling argument that the IQOS is reduced in exposure. It's not harm free. It's not risk free. But it's certainly reduced compared to combustible cigarettes.

Cristine Delnevo:
Dr. Zelikoff.

Judith Zelikoff:
Yeah. I'd like to add to that and say that, again, keeping in mind, compared to combustible products, and in answer of your question, considering the toxicological evidence. I think that there is, while some studies may have—do have limitations, and we're not familiar with all of the methodologies, et cetera, that, number one, we have more sensitive equipment and instrumentation now that could be used. And I'm sure that companies have this instrumentation available that they could use, which may not have been around when they did some of these

studies.

And, to answer your question specifically—oh, and to say that biomarkers of effects and/ or of potential harm can be identified by use of these instruments. And so, I would recommend that additional studies be done in light of 2025 and what's available for testing. I'd also like to see more animal studies being done that are guided by the toxicologist at the FDA or by this group. So that we know it's actually—all of the controls are done, all of the parameters are measured. So, I would also recommend that.

And I think that there's enough evidence between in vitro studies in the beginning of in vivo studies to say that there will be long-term disease risks from the studies that we've seen from IQOS aerosols.

Cristine Delnevo:
You mean, long-term disease risk relative to combusted cigarettes?

Judith Zelikoff:
Oh, that is the caveat. Isn't it?

Cristine Delnevo:
That's why we're here.

Judith Zelikoff:
That is the reality. Yes. I—in comparison to combusted cigarettes, I think there will be long-term effects, but they will probably be less.

Cristine Delnevo:
Dr. Rigotti.

Nancy A. Rigotti:
I'll follow up on that. It is challenging what we're being asked to think about because this is the nature of science, you know. It's very—a little bit forward, and then a little bit back, and then a little bit forward. And the question here is almost like is there enough a little bit forward concern about risk that we need to think about the decision that has been made in the past? That's really the question that I think we're being asked here. So, I guess I would agree with others who've said that the point is that compared—we really need to compare this to combustible cigarette use.

And I think the data is pretty clear that it is going to be less harmful, no matter what, than combustibles. It looks like we're maybe finding out that maybe the aerosol in these products is not as harmless. We never thought it was harmless, but it was—it's less—I don't know how to say it. But it's a little bit more harmful than we thought it was maybe going to be. And if people are not really switching completely, then the amount of actual risk reduction that the human would have is going to be less.

Still, I'm not sure we're at the point where we say, you know, we've got a—that we can't move forward with this. I would say that if the FDA does decide to move forward with the renewal of

this status, that probably what would be very helpful, it would be to be very clear about what sort of studies need to be done for it to remain on the market and remain approved. And sort of to fill the gaps that we're painfully struggling to imagine how to fill now. And I'll stop there.

Cristine Delnevo:
Thank you. I do have a clarifying question for FDA, if that is okay. And that is, it's something that came up during the open public hearing, and then a comment that Dr. Rigotti made as well, reminded me of this. And so, that's about the access and the availability of IQOS. IQOS does have a PMTA. It does have a marketing authorization. And that at least my understanding is about the action that is in front of FDA right now is about the MRTP renewal.

And so it's not about the availability of the product in the U.S. marketplace, but whether or not IQOS should be allowed to continue to make a reduced exposure statement in their marketing. And I'm wondering if someone at FDA, either Dr. Koblitz or Dr. Apelberg can either comment on that.

Amber Koblitz:
Yeah. I'm happy to comment on that. And Dr. Apelberg, if you want to hop in, feel free as well. But you're exactly right, Dr. Delnevo. We are discussing the renewal of the MRTP and the usage of the claim. These products are on the market. They have a PMTA. So, we're not discussing that piece. We're really looking at the applicability of the claim and the renewal of that claim as we move forward.

Cristine Delnevo:
Thank you.

Amber Koblitz:
Yeah. Thank you.

Cristine Delnevo:
Yeah. No. I just wanted to be clear, because there were comments that raised concern that the outcome of FDA's decision could remove a product from the marketplace that could be used by some people to move off of combustible cigarettes. And the authorization of the product is not what is being considered with this meeting and this renewal application. With that, Dr. Jordt?

Sven-Eric Jordt:
Thank you. I would like to respond to your question about potential new biomarkers that could be used. Again, I'm especially concerned about compounds that are strongly increased in the aerosol of IQOS compared to combustible cigarettes. And one of them is glycidol that's likely produced from the glycerol that gives the aerosol the body or this vapor form. It's actually quite similar to what e-cigarettes do.

So, there are human biomarkers known for glycidol. One is 2,3-dihydroxypropyl mercapturic acid. And those have been identified through dietary studies. So, this has to be adapted to inhalation studies, but I think those can be identified. And I would recommend that human studies and also potentially animal studies should test for these compounds to assess how much

of this class 2 carcinogen is inhaled from IQOS.

So, this has been determined by the institute for the IARC, the International Agency for Research on Cancer. It's a class 2 carcinogen. And I strongly support that it should be tested for presence as with biomarkers, such as I just mentioned. Thank you.

Cristine Delnevo:
Thank you. Dr. Upson.

Dona Upson:
Thank you. A couple of points regarding the—I think that the question is very limited. And that the evidence is also, in terms of what we're saying and in terms of decreased exposure compared to conventional cigarettes. And that seems to be true. But some points that were raised that are very concerning are that the public, and consumers in particular, think that there may be an equation between decreased exposure and decreased risk. And we don't have evidence of that.

So, I'm concerned about that. And that might mean that FDA needs to be more careful in how things are labeled and advertised going forward. Another is an indirect effect, perhaps, of use of IQOS and its effects on cessation of tobacco products. As we've heard, IQOS does not lead to cessation of IQOS, or of, well, some people stop their conventional cigarettes. But I wonder if it is—the use of IQOS is decreasing overall cessation of all tobacco.

We know that even though success rates are not great, they're better than they used to be. And still, maybe 10 percent of people on higher with good treatment stop smoking cigarettes every year without switching to other forms of tobacco such as IQOS or e-cigarettes. So, I worry about the impact on overall cessation of tobacco products.

And then the other things, I think we'll probably talk about with the third question, as has been mentioned, is the concern for dual use. And in many studies, the predominant form of IQOS use is dual use. Even in the applicant's statements or their presentation, it's almost 50 percent. And that the trajectory is showing that that's going to become even more higher percentage of people will be doing dual use. And that's really, I think, the concern that we're going to have is the increased risk with dual use compared to conventional cigarettes. Thank you.

Cristine Delnevo:
Thank you. Dr. Stepanov.

Irina Stepanov:
Yeah. Thank you. Just a couple of points to add, that we definitely, we don't argue that levels of HPHCs are lower in emissions from IQOS compared to conventional cigarettes and inherent risks of those chemicals are likely to be decreased. I think the main question here is those—that panel of compounds that are present at higher levels in IQOS or that are unique to IQOS.

So, in addition to what Dr. Jordt said, maybe a suggestion would be to identify that panel of chemicals, and do a search, identify potential biomarkers for the whole panel to monitor in people who use these products. And focus on maybe co-exposure studies to these unique

chemicals and cigarette smoke in in vitro and in vivo models to better understand those unique risks that we cannot predict at this time. So, I think that would be a potential, you know, suggestion how to move forward to better understand risks.

And another point is, I don't know, just a suggestion for the wording, what is on the label. Because at this time, it does imply that overall, there is a reduction in exposure. And it communicates that there is a proportional reduction in risks. Maybe there is a need to revise that statement to add that, however, there could be unknown, unique risks posed by IQOS compared to cigarettes that are not known at this time. That could give a little bit more, you know, information to users so they can make informed decisions about using these products.

Cristine Delnevo:
Thank you. And about to wrap up discussion point two. But I do want to—as a teaser going into the third discussion point where I do think we're going to be talking about dual use is that broadly, in the totality of evidence and long-term disease risk, if in fact dual use is a dominant behavior pattern that that in and of itself, could raise different disease risks, as Dr. Jordt referred to, different exposures to different constituents present in IQOS that's not present in combustible cigarettes.

And with that, we are going to take a 10-minute break. We will come back at 3:02. And we will resume our discussion with question number three. Thank you.

[Break]

Welcome back, everyone. If we can move to the next slide.

Gideon McMullin:
Give us 15 seconds, then we'll go live.

Cristine Delnevo:
Oh.

Gideon McMullin:
Good to go.

Cristine Delnevo:
Okay. Welcome back, everyone. Can you move to the next slide, please? Next slide. So, we're going into discussions for question number three, which relate to IQOS patterns of use. By way of background, the applicant was unable to conduct all the planned post-market studies, including the cohort study designed to evaluate the impact of marketing IQOS with the modified risk claim on tobacco product use behaviors.

Accordingly, FDA received limited evidence regarding the impact of marketing IQOS with the claim on patterns of tobacco use. And so, we are to discuss the likely patterns of IQOS use behavior when marketed as an MRTP in the United States. Based on the available evidence, we are asked to consider the likely patterns of use with a specific focus on the likelihood that people

who use combustible cigarettes will switch completely to IQOS. And the likelihood that they will dually use IQOS and combusted cigarettes.

NFN Scout (they, he):
I have my hand up. Can I go? Can I start?

Cristine Delnevo:
Yes, Scout. Go ahead.

NFN Scout (they, he):
Great. So, it seems from all available independent studies from other countries, we should presume that there is going to be a strong level of dual use. I'm particularly concerned about the static level of dual use in at least one of the studies, saying that it's going on for longer. And that dual use is going to affect, it looks like between two-thirds up to, like, 85 percent of the people who might be moving from combustible cigarettes over to IQOS.

And that being the case, it makes me really wonder about the way this is set up right now, the claim is about complete elimination. But if most all of the people go through the journey where they have at least a period, if not an indefinite period, of dual use, then it seems that there is at least a potential harm step in the middle that is not being considered in the larger calculus of the route, even if they are among the smaller group that end up solely using IQOS at the end.

I think, just to also touch on a few other things that are related to this, I'm also concerned about the idea that from independent studies, the public is not understanding what reduced exposure is versus reduced risk. And that we have information showing that, I mean, not only is there a consistent difference between the independent studies and the studies presented by PMI, but we have information showing that from the comments that were submitted, the number of times and ways that PMI has misrepresented the reduced exposure as reduced risk.

And it makes me very concerned that there is—I don't know, and I would like to ask FDA. What is the mechanism when an agency like PMI falls outside the acceptable usage of the risk and warning statement, what happens to then correct that company so that they can understand what lane they're supposed to be in, and not just willy-nilly decide to make some new ones of their own?

Cristine Delnevo:
Thank you. So, I just wanted to add some thoughts that I had around this. The first is, you know, I understand that there was disruption in the marketplace with the availability of the product which did prevent some of the studies from going ahead. It was a little disappointing that supplementary studies on the perceived understanding of the reduced risk claim couldn't have been done, even if the product wasn't available. You're not testing necessarily the use or the uptake of the product. But still understanding that people who smoke cigarettes understand the modified risk claim seemed like that was something that could have been done, even in the absence of the product in the marketplace.

And it's not like the product hasn't been available in the marketplace, and it would have been

useful to at least hear a little bit about what has been happening in the Austin test market, which has been going on for several months, with regards to the types of consumers that are using that particular product. It seems like it would have been possible to at least share and present at least a little bit of data on that.

And so, just some thoughts that I have with regards to question three. I kind of reserved my comments for question three, because areas one and two are not my area of expertise. But looking for other committee members to contribute to this discussion. Dr. Popova.

Lucy Popova:
Thanks. My—I have a bunch of comments, but I'm going to start with one. I think what we've seen when IQOS was first introduced here, there was very little uptake of it. So, in terms of what is the likely pattern of IQOS use behavior will be, based on what we've seen here, it's—it will be very few people who actually take it. And among those who do take it, it's highly likely they will be mostly dual users.

So, when we are discussing the toxicological evidence and trying to answer the question, how much of the risk reduction, how can we translate the reduction of exposure to risk reduction? I think we really need to consider how people will be using this in the real world.

And from what we know now, it's really people will be dual using. That will be very—and based on what we know now, again, there should be more studies, as we discussed in previous questions, should be more studies on the actual effects of dual use. But from all the evidence from other products and what we know before, it's highly unlikely that dual use will provide reduction in exposure and reduction in harms. And it's much more likely that we'll actually increase the risk in both of those.

And I want to reiterate a point that somebody else was brought up—and actually, I wrote it up earlier—is in all the presentations we've heard was this product will benefit smokers. And it's good we're marketing to smokers, and we want smokers to use it. But smokers are not a homogeneous group. There are people there who are more and less likely to quit. And there are some people who really want to quit, and they try it every year.

And what we've seen in our studies and in a bunch of other published research is that those are the people that are interested in alternatives. Because they've been trying to quit, they want to quit, and they're willing to try all the different things. And I am concerned that IQOS might be poaching them from quitting. So, that would be something—we don't really have evidence on that, because we haven't seen that being on the market that much.

But this is something we should be looking at to see, do people who—because people who are—who would be interested in IQOS are going to be most likely those who are also interested in quitting. But would having that IQOS and having the less harmful, or less exposure to harmful chemicals in it, actually prevent them from switching or delay absolute quitting.

Cristine Delnevo:
Dr. Upson.

Dona Upson:
So, I'd like to add that in terms of patterns of use, from other alternate forms of tobacco use, we've seen a huge uptake in the youth. The data presented showed that there wasn't much when IQOS was first available. It was only for a few months. And at that time, online sales were not allowed. And I think what we've seen with e-cigarettes is that youth often get their products online. So, I don't know that that's comparable.

And we've also heard testimony that IQOS is, in fact, being advertised to youth populations. So, my concern is that, especially with the reduced exposure, modified exposure risk, that youth in particular will be vulnerable to that. And maybe not understand the implications. And certainly not understand the level of addiction risk.

So, that's part of my concern is with the users getting just as much nicotine as with conventional cigarettes. The health effects of nicotine, which are not insignificant for youth in terms of brain development, pregnancy, and other things that we don't even know about yet. Diabetes, things like that. That we're putting our youth at even higher risk of nicotine addiction than we are now. Thank you.

Cristine Delnevo:
Dr. Stepanov?

Irina Stepanov:
Yeah. Thank you. I just wanted to bring up something that I referred to earlier. So, studies are limited. They were halted, unfortunately. But there is a trend. If you look at the data, there is a trend that over the 18-month period, I think, in both studies, the one in 2020 and 2021, that there is a time trend where exclusive or complete switching—the proportion of study participants, that sample size is increasing.

The proportion of participants who use IQOS exclusively trends to go down. And the proportion of the study population that are dual users report smoking is going up. So, and also, kind of thinking, it has been emphasized several times that more than half people who use IQOS are exclusive users. But that more than half, it's actually pretty close to 50 percent.

So, I want to acknowledge, and I am not an addiction expert, but I do know that 50 percent is a pretty significant number when you think about, you know, nicotine replacement therapy or other products. But I would like to see more attention being paid to this trend that was seen consistently across these two studies that, you know, initial larger proportion tends to go down when we look at people who completely switch to IQOS. Thank you.

Cristine Delnevo:
Dr. Rigotti?

Nancy A. Rigotti:
I would like to agree with what others have said, which is that, I think that if as IQOS is reintroduced, I think the most important thing would be to collect data. Already great plans were

made the last time, and perhaps even stronger ones need to be suggested as part of the approval if the marketing—I mean, if the reduced exposure claim is allowed. But even if it—regardless of whether it is, I certainly hope that the company will be looking very carefully at how it is being used and who it's being used by.

Cristine Delnevo:
Dr. Popova.

Lucy Popova:
Well, let me bring my other comment which relates to what drives behavior, and sometimes it is those perceptions. Some of the comments mentioned that we do need to look at comprehension of the claims and what people perceive. And the industry's presentation talked that the consumers continue to understand the reduced exposure claim. But what does it actually mean to correctly understand the claim?

The way their studies measure it, they have a very specific answer in saying is using IQOS less—expose people to less harmful chemicals. And it's very hard to answer this question incorrectly. Although even then, some people do. What we are seeing in our studies and studies done by other people in the U.S. and in other countries where IQOS has been done, is that people—one, the— the answers often depend how you ask the question.

But then the bigger issue is people—and this is statutory question. Because the law itself says reduced exposure claim cannot be confused with reduced risk claim. And all the data show that people are very good at confusing them. When you ask people, does having less exposure to harmful chemicals mean you have less risk of disease? They say overwhelmingly, yes. So, there's no way of going around this question.

And the other issue that goes with the pattern of dual use is even though the claim says, switching completely, people do not understand what that means. We've done a study where we ask this question, what does switching—if you switch completely, how many cigarettes per day can you smoke? Zero? One to two? Three to four? Five to six? I don't know. As many as you want.

And when we ask this question to people who don't smoke, like, over 70, like, upper 60, 70 percent, they correctly say zero. When we ask this question to people who smoke, only about 10 percent say zero. Everybody else says—like, a very large number says, "I don't know." But a lot of them say, like, "A few cigarettes a day is okay." It is complete switching. And even when we added a very clear statement that we thought—it says, "Complete switching means smoking no cigarettes and only using IQOS product," only 20 percent of people correctly said. And this was a randomized experimental study that we published.

So, that switching completely in the current language, how it is shown there, is not going to give people full understanding that they do need to switch completely. So, this is something that needs to be potentially done with that. And either really do a very much better job explaining to people what switching completely means. Because smokers are like, "Oh, yeah. I'm switching completely. I just had a cigarette. Oh, yeah. But I switched."

And so, this is—and that gets us back to this dual-use pattern, where people have to really understand what it is. And only then can we realize any potential benefits from less exposure to harmful chemicals.

Cristine Delnevo:
Thank you, Lucy. I mean, you kind of took the words out of my mouth when you tied the pattern of use to understanding the behavior. Understanding the risk, because if you don't understand what—like, how complete switching is understood, then dual use is—it could very well be an inevitable behavior, depending on how people understand that. Ms. Becenti.

Alberta Becenti:
Yeah. I just wanted to also express my concern about the dual use and the long-term health effects of the products. And then also, about the 36 potentially genotoxic carcinogen compounds that were found at higher levels in IQOS aerosol and that weren't on the list. And then the effects of IQOS use among females, especially those of childbearing years.

And then there needs to be—if there's going to be a future study, their recommendation would be to actually, the inclusion of those populations that use combustible tobacco products more than the general population, like American Indian and Alaska Native populations. And then also have some issues with the verbiage on the reduced exposure. Some people may not really understand what it means. And reduced exposure may be interpreted as reducing risk.

Cristine Delnevo:
Thank you. Dr. Zelikoff.

Judith Zelikoff:
Yeah. I just wanted to emphasize again what I've heard. And number one, I totally agree that more specific language has to be used on the warnings. From what I saw, it's highly -- it needs a bit of clarification and a bit of scrutiny. And it needs to be right on top of things, as was stated in terms of risk versus exposure.

The other thing I wanted to echo was the use of—I think it's Dr. Upson—the use by youth. And, you know, nothing is going to stop them from having their friends who are over 21 buying it for them. And I think one of the reasons there was low youth participation when it was first questioned was there was nowhere near the amount of marketing and knowledge or awareness of the product that we will be ascertaining and reaching once all the social media gets on, and the concerts and everything else. You're going to see an explosion of awareness to IQOS.

And so, to think that youth won't be using it, no matter what kind of bars you put up, there's always ways around it. So, I just want to echo and emphasize that I really see this going towards the youth and adolescent populations. Thank you.

Cristine Delnevo:
Thank you. Dr. St. Helen.

Gideon St. Helen:
Yeah. I really struggle with tying an MRTP to the issue of dual use. Because dual use is so complicated. How do we even define dual use? Is it somebody who smokes—who uses the IQOS and they smoke one cigarette a day? Is it somebody who uses the IQOS more frequently, and then smokes one cigarette a month? How do we even operationalize that? And how do we even understand the toxicological risk of that, given that dual use is such a diverse behavior. It's not monolithic. How do we even operationalize that? Not we, but FDA.

Cristine Delnevo:
It's a great point. And I want to bring people back to this concept of dual use, right? And it is complex. And so, a question before us is, is dual use, the use of combustible and IQOS together, likely to be a sustained pattern that has been suggested at some of the international studies? Or is dual use more indicative of a transition to switching? And is there any benefit to dual use? And I want to put that out to the committee to think about. Dr. Rigotti.

Nancy A. Rigotti:
Well, you are asking excellent questions. And I think that we need the answers, and the answers will come from studies when this is in the market, and we'll see what happens. I think that that's really where we're—that's the only way to get the answer.

Cristine Delnevo:
All right. I do want to pose one more—Dr. Upson.

Dona Upson:
I think from the FDA's presentation in the question and answer part, it was stated that there was no benefit to dual use, compared to conventional cigarettes even, and potentially more harm than conventional cigarettes alone. I think other studies have borne that out. And we're getting more and more evidence that that's true for e-cigarettes, even in terms of long-term health effects, such as COPD, that we wouldn't expect to see so soon after the introduction of e-cigarettes.

And I think that all the data support that dual use will be, if it is not already, the predominant form of use with IQOS. And it seems to be increasing, that dual use is becoming more common than only using IQOS alone. Thank you.

Cristine Delnevo:
Dr. Jordt?

Sven-Eric Jordt:
Yeah, I just wanted to point out, no matter which international study you look at from markets where IQOS is marketed, from Japan, Korea, Germany, other European countries, it's always young men who are the major users of these products, between 17 and 32. It's not necessarily the group of older smokers who are enticed to switch. And obviously, yeah, the marketing is the same overall with reduced risk or harm claim, but it always ends up with this population. And it seems something is wrong here, and that there are other forces in play that favor this population or makes it more susceptible to the marketing. So, there is some bug there, and I don't really understand what's going on. Thank you.

Cristine Delnevo:
Thank you. Along those lines, and that speaks to kind of the different populations that the product may appeal to, and we do know, at least in the United States. There does not seem to be great receptivity to using e-cigarettes, for example, among current smokers who are older, right? And so, we see the appeal of this product might skew younger.

And in the context of that, I do want to pose a question in the context of the diverse marketplace, which doesn't look today like it did 5 years ago, when this MRTP order was issued. Do people have thoughts about the uptake of IQOS among adults, that currently do not use cigarettes or might be using a potentially less risky product? Dr. Scout.

NFN Scout (they, he):
I think the available evidence that you can see the marketing strategies by PMI that are occurring currently in other countries strongly shows that they are attempting to get into the youth-adjacent market. And that is a very visible play on their parts. We're not, obviously, you can have all the guards you want on who actually gets access. But we also know that those guards have not yet proven effective in the history of tobacco control in this country. And so, I think a lot is to be gleaned by the marketing tactics.

So, the idea that, you know, we're talking electronic dance music concerts and special drops of clothing and, you know, DJ collaborations and things like that tells us a lot about whether this is actually being targeted at people who are existing smokers, who are looking to convert, and reduce that smoking risk. Because that's not a population with the highest smoking rate, and that's not the population that's even looking to consider cessation seriously. So, there's a lot of evidence on the table about what's happening internationally, and it's not good.

Cristine Delnevo:
Dr. Popova.

Lucy Popova:
To answer your question, I think what we are seeing is that people—I completely agree that we're in a very different marketplace. And we have studies that show there is, like, the gateway effect. There's—for youth particularly, there is a lot of evidence showing that those who start with e-cigarettes, there's a higher chance they might try cigarettes.

We don't know -- and this is a really good question, and it should be studied. But, like, what is the gateway effect of would people switch from e-cigarettes to IQOS? And would this be a higher or lower harm, based on just the fact that it's tobacco. And there is potentially some combustion that actually does occur with higher temperatures, or in all the chemicals we've seen. Would this be a risk reduction or not? And then with the proliferation of the nicotine pouches, do we have now which is quite popular among the young male population, would this be the easy shifting side by side? So, I think these are very valid questions.

Though they will happen—I feel like our discussion about the youth use and all of that, this will be happening because the IQOS is on the market. And how it's advertised, depending on what

we're seeing, it might happen. I don't think it's really predicated on whether or not it is advertised with the reduced exposure claim.

What we've seen is reduced exposure claim has not been used really widely in the U.S. As I mentioned, we visited IQOS store in Austin. We did not see the claims, aside from the product itself, saying that this is less harmful. And the whole discussion wasn't really emphasized when we went in there. And, but what we've seen is that the U.S. uses this reduced exposure claim to promote—sorry, the PMI uses this reduced exposure claim to really promote it abroad.

So, this is—and studies have asked the question whether this is something that is actually benefiting smokers in the U.S., or is it something that's really just a marketing ploy to get the rest of the countries to lobby and ask for various things? So, this is something also to consider. This is not something has been raised before, but, again, what is the purpose of the modified risk claim, given that we don't really—people don't really understand it. They don't really switch. And it's predominantly used abroad to get people to start using them there.

Cristine Delnevo:
Dr. Rigotti.

Nancy A. Rigotti:
I just wanted to ask Lucy to follow up on what you just said. So, if the marketing is not to reduce risk in the U.S., what is it that they're marketing? What's the reason? How are they trying to sell this in the stores that you've observed?

Lucy Popova:
It's the lifestyle marketing. It's technology. It's cool. It's helpful. It's really bright colors. They have all these different accessories. They do say, like—they do check to make sure you are a smoker, and they come in. But the main claim is not, this is "You need to switch completely, and this is what reducing—what will reduce your risk." The main thing is, like, "This is really cool. You should buy it. And let us show how to use it, and you'll enjoy it very much." It's like enjoyment. No smoke, better taste. So, that kind of stuff.

Nancy A. Rigotti:
Well, it seems like if we're going to—what we maybe need to do, and I don't know how we would do this. But that the manufacturer of a heated tobacco product like this maybe needs to really consider that it's not just getting people to use the product. But it's getting to people to get off of cigarettes to be—and to sort of have—somehow that becomes a marker or a measure.

I don't know if that fits into the regulatory structure, but I'm just trying to think that if there's some way that the actions of the FDA could help to position this more correctly in a way that could be more helpful, to adults. And I certainly would agree that we have done a bad job of trying to get older adults to use alternative products if they're not able to quit. But there is some evidence that you can get them to do it if you help them. So.

Cristine Delnevo:
Nancy, I think that's a great point about data that we'd like to see down the road. And I think

that's data we had hoped that we would be seeing today, but don't have access to today because of the interruptions for the post-marketing surveillance studies. You know, in another world, we might be looking at data like that today, but we don't have it. Dr. Jordt.

Sven-Eric Jordt:
Thank you, Dr. Delnevo. You mentioned briefly that it could happen that people who are using another MRTP product, or a supposedly safer product, who then switched to IQOS, right? And I have a question to FDA. Last year, the FDA leadership presented this concept of continuum of risk. Is it the intent of FDA to rank MRTP product along this continuum? And where would IQOS be positioned?

I mean, there is a concern that people who are using safer product with less carcinogens, let's say maybe a snus product or an e-cigarette. But then they see these reduced risk claims for IQOS, and then, "Hey, I like how this looks and it tastes better. So, I'm switching to IQOS, although it has more carcinogens." How does FDA want to avoid this to happen? And will there eventually be a ranking of MRTP products along the continuum of risk?

Cristine Delnevo:
I'm going to hazard a guess that FDA is not going to answer that question here today. But if someone is going to, feel free to turn your cameras on. But I will at least kind of, from my perspective, weigh in briefly. And I see Ben has turned his camera on. What I was going to say is, a PMTA is about the protection of public health, right? I think that the introduction of a product is not going to make public health worse.

But a MRTP is supposed to be for the promotion of public health. And when I hear the term or the phrase promotion, I think that it should be improving whatever the status quo is. And so, in the context, from my perspective, and this is me speaking, in the continuum of risk, you have to consider who's using the product. And if you're appealing to people that would have used or are using a lower—a potentially lower risk product, that's not promoting health. It might be protecting health, but it's not promoting health. But I can't wait to hear what Ben has to share with us.

[laughter]

Ben Apelberg:
No, thanks for the question. I mean, I'll just kind of emphasize, Cris, what you just said. You know, when we're—in the PMTA world, when we're evaluating, you know, new products to be marketed, you know, we're obviously, we're looking at the risks and the benefits to the population as a whole.

And that requires understanding who are the groups of the population that are most likely to use the products, and what would be the impact to them. Is it that they're switching from cigarettes? Are we concerned about, you know, nonusers taking up the product? And so that can include, you know, if there's evidence moving from one type of product to another, that would be part of the evaluation.

In the MRTP context, we're evaluating, claims that companies are proposing to use to market their product. So, we're not providing those claims to the companies. So, there's a level of us evaluating, are those claims substantiated, and what do we anticipate the likely impacts to be because of the—who the products would be marketed to, and the likelihood that they would—that would result in individuals taking up the product.

So, you know, I hear what you're saying in terms of, like, trying to think about the various trajectories of use that could occur. But, ultimately, in this context, we need to just look at, with this product, as it's marketed, you know, what do we anticipate the likely impacts to be? Who are the individuals most likely to use the product? How are they going to use it as a result of the claim? And, you know, that goes into our evaluation.

Sven-Eric Jordt:
Thank you.

Cristine Delnevo:
So, thank you, Ben for saying that. And so, one of the things that I've been thinking about in the context of this product, and thinking about MRTPs broadly, right? And you get questions one, two, and three that are kind of focused on that. And question three, the pattern of use is really important, right, when you're weighing the pros and the cons of whether or not there is a benefit to population health.

And, what we see from the international studies, Dr. Jordt has kind of referred to this himself, about who the IQOS users are internationally. And just seeing some of the marketing rollout in Austin, Texas, it does seem like at least initially, those consumers skew younger. And these are groups of individuals that right now have very low rates of combusted cigarette use. So, to the extent that this product can appeal to a broader swath of cigarette smokers, people who smoke, I think, is an important piece of the puzzle. And certainly, obviously youth uptake, or the potential for youth uptake is part of that as well.

Wondering if anyone else has anything additional to weigh in on, with regards to the third question. All right. In seeing, no additional people weighing in, what I'd like to do right now is give the committee members and our expert advisors an opportunity to make some final comments, conclusions about today's meeting, the data that's been presented, and the three questions that have been posed to us.

And I'm going to ask individuals—I'll basically follow the roll call order and call on individuals to make their kind of final comment. It can be about questions one, two, and/or three. And as a reminder, if we can—I'd actually like to go back in the slides and remind people what our three discussion questions were. So, if AV folks can go back to the first question? Just kind of refresh people, where we are.

So, question one focused primarily on nonclinical toxicity evidence. Next slide. Question two focused on the totality of evidence and the long-term disease risk. And then, question three, next slide, really focused on the patterns of use and understanding that there was limited data available to us because of the interruption of the sale of IQOS in the United States. In relation to

all these questions, FDA is also curious about what other studies or evidence could be useful to them in the future. And with that, I'm going to actually start with Dr. Jordt first.

Sven-Eric Jordt:
Thank you very much. As I've mentioned in my many questions, I remain concerned that the HPHC list as it currently is deficient, and it does not reflect the whole spectrum of toxicity products such as IQOS have. And FDA has presented evidence that there are additional carcinogens and cardiovascular toxicants being measured. Some of them have risks parameters associated by IARC. So, once we have sufficient biomarkers, this can be assessed in terms of their risk.

I remain concerned that the HPHC list is not being modified at all. I remember there was a docket request, and I myself put in a response. And there was basically no outcome based on that. So, I'm just concerned that we are working here with parameters that are deficient in general. I remain also concerned about the marketing tactics of PMI that supposedly emphasized modified risk or reduced risk but always end up with large numbers of young users who, usually have lower smoking rates than older users, especially male young users.

I agree with Dr. Scout. Having been to Europe this summer, I've seen IQOS advertising at Pride parades and other big, big festivals. So, that I assume the same will happen here in the United States, and this incompatible with the assumed targeting of older smokers. I also want to make some additional comments. I'm very concerned that FDA didn't ask the applicants to do another environmental impact assessment. We now have data from all over the world that IQOS HeatSticks are being littered. And that small children are ingesting these HeatSticks and experiencing severe injuries upon ingestion. There are several papers of this, and this has not been discussed here at all.

We know that PMI's other product, ZYN, is being ingested by small children in the U.S. And FDA called out ZYN to provide child protective packaging. This will be more difficult with IQOS. And I'm concerned we will see similar patterns of accidental ingestion here in the United States. In addition, we know much more about particulate matter—yeah, microplastic toxicity compared to 10 years ago. And there is a risk from IQOS HeatSticks to produce these, and this should also be reassessed. So, I think the FDA's statement that no impact assessment has to be done is deficient. Thank you very much.

Cristine Delnevo:
Thank you, Dr. Jordt. Dr. Popova?

Lucy Popova:
All right. So, the question in front of us is how do we use available evidence to make judgment on whether the MRTP claim—MRTP authorization should be renewed or not. And what I've seen in conversations today, and based on the available evidence, the new stuff that came—so when the decision was made in 2022, there was preponderance of evidence that the exposure to harmful chemicals is definitely lower than cigarettes—than in conventional cigarettes.

Since then, as we've seen today, we've had some additional studies come up. And we also have

comments saying that the list of chemicals needs to be expanded. So, that raises new questions and brings up the issue of whether the previous conclusion that this is definitely less harmful is—might not be as solidly yes as before. And there might be more stuff coming in. So, we need to continue monitoring that.

The other thing is that FDA is really good at looking at all the little things and asking very specific questions. But in making decisions, we should look at the full picture and as the questions themselves ask, the totality of evidence, including how do people use those products in the real world. And we haven't really had much evidence in the U.S. because the products were there only for a short time, and also people weren't using them. We've monitored when the first stores were opened in Atlanta, we went there. And there were days when there was nobody there.

So, the product itself might not be too appealing to smokers. And my concern is that with the modified risk—modified exposure claim, it might be more appealing to smokers who would have quit otherwise. So, we need to really look into that to make sure we are not increasing the harm by taking people away. What we've seen is we ask people who are not interested in quitting. And those are the people that this product would be the most beneficial to. They don't want to quit, so switching them to less harmful product that has less harmful chemicals would be beneficial.

But those people are not interested in any switching or any products, and they also don't believe cigarettes are harmful. So, we need to have a different approach to that. So, what the PMI and other companies should be doing is really telling those smokers, and they have the list of them, they know who they are. It's like, "Cigarettes are really, really bad. If you—you should switch to this product." And that's what should the marketing be, instead of advertising at the electronic festivals or in the Austin music stuff.

So, that's my point. Look at the totality of evidence, look how people are using the products in the real world. What we see from other countries is dual use is really predominant. In response to Dr. St. Helen's question, there's really good data from ITC studies that show with the dual use, and how many numbers of cigarettes go up? How many IQOS—if cigarettes go down by a little bit, number of heat sticks go up by a lot. And so, there's evidence there that shows that overall, dual use actually increases intake of tobacco products. So, looking at all the evidence should give us a good answer. Thank you.

Cristine Delnevo:
Thank you. Dr. Rigotti?

Nancy A. Rigotti:
Okay. So, I guess the way I'm thinking about it is that IQOS is about to—it's almost like it's having its first launch because it really had a launch for such a short time. So, we're about to see what happens when it comes to the U.S. market. And the question is, do we want to see it come—when it comes to the U.S. market, do we want them to be able to make claims about reduced exposure or not, in a way.

The judgment was made previously, 5 years ago, that the data supported a reduced exposure

claim. But we've heard some evidence since then that, today, of subsequent evidence that we've learned more. That, you know, it's not as simple as people maybe thought it was going to be. And that's where we, you know, spent a lot of time talking about maybe people are actually going to use it and not quit combustibles. And, you know, who is going to use it, and will young people use it, and all those questions.

So, we're about to have a time where an enormous amount of data would be—an enormous watching would be very helpful. And so, I guess, mostly, my advice to the FDA would be to think about how can you maximize the amount of information that you can get as we're going into this new experiment. And some of that, you can expect the company to produce. But we've also seen that that is not the classic, you know, longitudinal careful study, maybe with biomarkers, so we can really know what's going on.

It would be important for the company to be doing that data. But the way that we've also seen from some of the public comments that came in, that you need to have some third-party or independent information. We will have the PATH and other data sources that fortunately, we do have. And maybe FDA would even want to invest some of its own research funding resources to make sure that they carefully watch this natural experiment. So, I guess being a scientist, I keep thinking about we need more information.

I was struck in our conversation at how difficult it is to make a difference between exposure and risk. And I think that's really hard to do. I'm sort of surprised that there is that second category of reduced something, reduced badness. Because even in my mind, I have a trouble keeping it apart, but perhaps the company would need to be tasked to figure out how to communicate that better. Because it sounds like they are not.

And let's see, what else? I also think that their communication, if they're going to have a reduced exposure ability for marketing that they would—it would be really important that their public communication does a better job of getting that across. I was just so struck when I looked at their marketing materials that their warning statement was—or their statement of reduced risk was not something that a lot of people would understand easily.

So, I'm really struggling to think about, you know, is it really worth taking the risk of having the product with an exposure reduction marketing claim. Is it worth it? I'm not sure. I'm not sure. I'll stop there.

Cristine Delnevo:
Thank you. Dr. Scout?

NFN Scout (they, he):
Sorry about that. Okay. So, in summation, we do have evidence since this original claim was approved that there is increased risk. And that evidence is despite the fact that we still don't have even great information on dual use, which looks like it applies to practically everybody who might be an original cigarette user and moving in some capacity over to IQOS.

We also have new information showing from the independent reviews that there's no notable or

measurable cessation benefit related to this. We also have some concerns that with the dual use, that it may outweigh even the potential benefit with cigarettes reduced because of increased use of IQOS in replacement. And then, in addition to that, we've also got information from studies showing that the public does not easily understand what reduced exposure means. And that PMI has strategically sowed more confusion into that field by advertising this as reduced risk in other countries.

It was curious to see someone talk about -- I'm forgetting exactly who, that maybe that was the main reason. Since they're not even advertising reduced exposure in Austin, maybe that's the main reason that they get this. It's so they can go to other countries and say that, "Oh, but the United States said it was reduced risk."

In addition, we have proposal, and we heard from the user earlier that, yeah, those two menthol products, which are in this group to be reviewed, are much easier for people to tolerate. But that goes contrary to FDA's own position on menthol, and whether that should continue to be included in tobacco products at this point.

And we have we have a fair amount of information that the marketing on this, I think it was a really great point. It was just brought up, that, you know, we all understand from Marlboro merchandise, and the backpacks, and the—you know, the bags, and everything like that that was put out so many years ago, that if you're really trying to get a hold of the combustible cigarette population in the United States, or probably every other country too, that is middle-aged, or has been long-term cigarette users of some nature, and is really at the point where we understand people are really looking for cessation or risk reduction options, PMI has the list of those users. They have the list. They do not need to go to youth-adjacent music festivals and other such community festivals. That, to me, shows an incredible disingenuousness of the marketing strategies here, and a manipulation of this reduced exposure claim.

And I would say that with all of this, it still is a standing question that if PMI continues to misuse these claims, does FDA currently, particularly in light of all of their regulatory staff being RIFed, does CTP have the option to even do anything to try and make sure they only use these claims as intended if they have a pattern of using them beyond as intended thus far. That's my summation.

Cristine Delnevo:
Thank you. Dr. Upson.

Dona Upson:
Thank you. And I agree with the previous speakers. And to some of the first couple of questions, I would say that there is increasing evidence of toxicity in the animal models and the in vitro studies. And that I think that information provides a basis that there will be long-term harms and disease that we, you know, of which we do not yet know. The evidence for dual use and triple use is compelling.

And I think that it's going to be shown to increase, so that the vast majority of people who use IQOS will be dual or triple users. And the risks inherent in that are greater than using combustible cigarettes alone. And the labeling is easily misinterpreted or not understood by the

general public. And I think that will contribute to increasing use of the products.

And I'm very concerned about the youth, adolescents, youth, young adults, to whom the product is already being marketed. I think—especially with the inclusion of menthol, it's going to lead to increased nicotine addiction in our country. And with the harms, healthful implications associated with nicotine addiction. And it's true that the youth aren't—may not be impacted by the labeling, but their parents will be. And as much as we like to think that youth are driven by peer pressure and things that are cool, messaging from their parents has been shown to be the most important thing regarding tobacco use. And most kids think that they're going to stop using whatever tobacco product it is within 5 years. They don't take seriously the addiction potential of any nicotine product. So, I think that's important to keep in mind.

And on top of that is the fact that CDC has had very successful programs to decrease nicotine uptake among adolescents, youth, and young adults. And that program is pretty much gone, as Dr. Scout mentioned. So, I think we're setting things up for a perfect storm of increasing tobacco use in our kids. And I agree, going forward, we'll certainly need to include IQOS in our national surveys. We'll need more population studies and epidemiologic studies to find out the results. But that's going to take some time. Thank you.

Cristine Delnevo:
Thank you. Dr. Bailey.

William "Andy" Bailey:
Oh. Let me get my camera on. Okay. Thank you. Just a couple of comments that I had, although there's been a lot of discussion and concerns about some of the data presented versus independent studies in the marketing of IQOS products in other countries. If we take all this as a whole, all the data presented, as a whole, I think the benefits to the overall population still outweigh the risk. This product still qualifies as a modified risk product, and I think it should be renewed as such. And that's all I have.

Cristine Delnevo:
Thank you.

William "Andy" Bailey:
Thank you.

Cristine Delnevo:
Dr. Madl?

Amy Madl:
Yeah. So, I think, there's been some really great points raised on this panel, and a lot of questions also about needing to better understand consumer use patterns, and what that means in terms of, ultimately, risk reduction, And I'd like to first just echo a comment that Dr. Rigotti had, is that there is an opportunity here to really gain a lot of great information on consumers that would use the IQOS product. And further inform on how the exposures and use will ultimately influence exposures, biomarkers of exposure, biomarkers of harm. But we just need to continue to monitor

that.

But with—the question at hand is whether the claim is accurate. So, the claim is, does IQOS present a reduced exposure compared to combustible cigarettes? And what has been presented today is that there is a substantial reduction in harmful and potentially harmful constituents. And that includes testing that was targeted testing, as well as untargeted testing, and a further exploration of what that translates to in terms of noncancer and cancer risk reduction.

And so, even with the exposures to unique compounds that may present a risk of genotoxicity or carcinogenicity, that still presents a risk reduction when you compare that to combustible cigarettes. So, with that respect, the claim is accurate. And that seems to be supported by the toxicology studies, as well as the biomarkers of exposure studies, as well as the biomarkers of harm studies.

What I think is very encouraging is that you have users of IQOS that upwards of 51 percent completely switch away from combustible cigarettes. There is a reduction of approximately 83 percent of reduced use of cigarettes per day. So, as we move forward and further study the consumer use patterns, I think it would be very helpful to understand those consumer use patterns and reassess the quantitative risk assessments and ultimately, the population impact assessments with these consumer use and exposure patterns in mind.

But, in the end, the IQOS product is very clearly a reduced exposure product, which appears to be, based on the clinical studies, comprehended by consumers. And that further supports their additional use or—not additional use—that further supports their use of IQOS and reduction of cigarettes. So, with that, I would support the reduced exposure claim for IQOS.

Cristine Delnevo:
Thank you. Mr. Murphy.

Patrick Murphy:
So, it seems to me that the FDA was fairly clear in their presentations that at least the third approved reduced exposure claim continues to be supported. I infer that the first two simpler marketing claims are also supported. It also appears that FDA is struggling with how the relative health risks to individuals of the IQOS products, or the toxicological risk profile may have changed based on new data, specifically the data that were used as the basis of the three questions for the committee.

It's an aspect that has to be considered for both the original MRTP application and now the renewal. So, to me, it's a question of does the new information rise to the level whereby the agency would potentially rescind the MRGOs. Again, that would have no effect on the commercialization of these products, only the use of the specific reduced exposure claims. I personally don't believe it does. Thanks.

Cristine Delnevo:
Thank you. Ms. Becenti.

Alberta Becenti:
Okay. Studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces one's body exposure to harmful and potentially harmful chemicals. However, the overall long-term relative health risks of IQOS compared to combustible cigarettes are still largely unknown.

Additionally, the product hasn't been available in the U.S. or international markets long enough to result in long-term studies of human health effects. And then the renewal also identified 36 potentially genotoxic carcinogen compounds found at higher levels in IQOS aerosols. And then, which translates into uncertainty. And then the exposure and the risk consumer misinterpretation of reduced risk to mean—reduced exposure to mean reduced risk.

So, overall, the results suggest that IQOS users in the U.S. tended to be middle-aged with relatively high socioeconomic status who may actually, you know, have a better understanding of the wording. And then but there's others that indicate that people still do not understand. And how is the product going to be marketed? I'm concerned about the youth uptake. And youth like to try new novel products with sleek design and color designs.

And so, that would be my greatest concern is how this market is going to be marketed in the future, and how are we going to protect it from new uptake of this new, you know, tobacco products. Thank you.

Cristine Delnevo:
Thank you. Dr. St. Helen.

Gideon St. Helen:
First of all, thank you for the opportunity to be part of this TPSAC meeting. It was a great learning experience for me. I think I don't have any question in my mind that IQOS is an MRTP. I mean, the evidence clearly shows massive reductions in the exact chemicals that we know causes the diseases and death that are associated with combustible cigarettes, use of combustible cigarettes. So, the volatile organic compounds that we know, acrolein, all of these other VOCs, the carcinogens that we know are associated with cancer, massive reductions in these constituents in IQOS aerosol. So, to me, there is no question that IQOS is an MRTP.

Now, we talked about the new evidence regarding some chemicals that are unique to IQOS. We've known that there are some chemicals that are unique to IQOS from the first application, which was approved. Now, we definitely need a lot more information about the health effects of these chemicals. I don't think the computational toxicological assessment is enough. We need actual toxicology studies to really understand the health impacts or the toxicology of these chemicals, the unique chemicals to IQOS. So, I think the company has to do this kind of toxicology tests to really understand the effects of these unique chemicals.

And then also in terms of dual use, that is definitely a concern whether IQOS will lead to more sustained dual use. Dual use, to me, is complex. Because like I said a while ago, it's not monolithic. There are people who could be dual users who just probably smoke one cigarette a day. There are persons with dual users who might smoke 20 cigarettes a day. So, it's really

complex. FDA already has a solution to that, by reducing the nicotine content of combustible cigarettes. If they would only go ahead with that, make combustible cigarettes less appealing, less addictive. This is a solution to it.

So, I'm thinking of more of, like, the holistic approach to regulation of these products. So, I don't see why IQOS can't be designated again as an MRTP. And then the FDA keeps pushing forward with their proposal to reduce the nicotine content of combustible cigarettes, thereby making it a lot more addictive, making IQOS more attractive to persons who are smokers. So, although the dual use issue is important, I think FDA just has to continue forward with their proposal to make combustible cigarettes much less appealing. Have a more of a holistic approach to tobacco regulation. And that's my contribution.

Cristine Delnevo:
Thank you. Dr. Stepanov.

Irina Stepanov:
Yes. Thank you for this opportunity to be part of this meeting and contribute from my expertise, my point of view. So, I do agree that additional evidence kind of adds strength to the statement that exposure to harmful and potentially harmful constituents related to smoking are significantly reduced when people exclusively use IQOS. However, long-term risks are likely to be different from what can be implied from such reductions.

So, at minimum, I would think that the statement about switching completely from conventional cigarettes to IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals present in cigarette smoke. So, that clarification could potentially be helpful because that is a loophole where consumers can be misled. That it's a blanket statement that overall, there is a reduction in any harmful and potentially harmful chemicals.

Also, I wanted to note that nonclinical evidence—emerging nonclinical evidence in rodents is limited and imperfect. But it cannot be simply dismissed because of relatively consistent red flags that were raised by these studies in terms of potential respiratory and cardiovascular effects. And, lastly, the likelihood of dual use appears to be high.

And in order to take full advantage of this product to be marketed as modified exposure products, there is a need for clarification, the one that I mentioned earlier. But also, potentially adding the context that there are unknowns that these products may pose unique risks that are not known at this time. And that could help add clarity on the current state of knowledge about these products. Thank you again for this opportunity.

Cristine Delnevo:
Thank you. Dr. Zelikoff.

Judith Zelikoff:
Well, I think, the benefits of—the benefits and liabilities of being a Z. One of them is that most of my concerns, most of my thoughts were already expressed, but I'll try to express a few different ones. As far as the warning package, I was—yes, some of the VOCs, some of the semi-

VOCs are reduced. I grant you that. But there are other toxic products that haven't even been—or has not been looked at like particulate matter. Particulate matter is going to be generated, and it's a carcinogen and—a pulmonary carcinogen. And how does that weigh out? Or metals? Are there going to be metals released?

So, for the warning package, I would definitely say it needs to be modified, and maybe what the word of reduce "some toxic agents," or "some toxicants," because not all were measured. And if they were measured, I wasn't aware of that data. But there are many other toxicants, and we know that PM, particulate matter, is going to be released from these products.

Another thing about marketing is that the marketing strategy is the same that has been used over time. And that is especially with the use of menthol. As I pointed out, there are certain, more vulnerable, or there's a target with the menthol to reach certain populations. And, we've seen it, and I think we need to address the importance of menthol in here. And as was pointed out, the FDA in earlier times has banned it. So, I think we can't look at that lightly.

One of the other things, and it was pointed out by the member before me, that you can't, you know, I can't stress enough that the in vitro studies provide some mechanistic evidence for the in vivo studies, despite some of the limitations of the in vivo studies. That gives us pause—that should give us pause, to say, "We have a new market out there. We have people who are not the same as they were 5 years ago." And perhaps we should look more closely at that, and perhaps—and how can we extrapolate from the exposure and say, "Will it be less harmful than combusted cigarettes in the long term?"

And I think from what's there, in terms of the toxicants that have been measured to be low, but again, the ones that are high, and then the ones that have not been measured. How can we say what's going to happen? Intuitively, one would think that you have 7,000 chemicals versus, you know, less than a hundred or whatever, should be. But again, how potent are those chemicals that are being generated in higher amounts?

So, I think overall, that it's a very tough decision. And -- but I think if you're considering the totality of evidence, I think it's very difficult, because I don't think there are sufficient studies that have been brought up to show that totally, it's safer. So, if I had to make a decision right now while understanding some of the users, I would say that without more evidence showing that it's a modified product, I would have to say no. I don't favor renewal.

Cristine Delnevo:
Thank you. And so, for a final comment, I just wanted to kind of weigh in with my thoughts. So, an MRTP authorization should really be for the promotion of public health. And that is about two pieces of a puzzle, the product and the population. And while the product may be a lower exposure product compared to combustible cigarettes, there's a lot of unanswered questions regarding the population itself.

We heard from PMI earlier, the totality of the evidence. We heard that phrase a couple times. The vast majority of IQOS users. Those data are 4 years old. There's no new consumer testing about perception. The data from the PAC study was also collected a number of years ago. And

the tobacco marketplace looks quite different from 5 years ago. And so, the population impacts and the patterns of use are not the same as they used to be.

And so, I'm left with the question of, do today's consumers, those that smoke cigarettes, understand the reduced risk statement? And would they be receptive to using this product? And the simple answer is we don't know. And while the disruption in the sales of product in the U.S. is a valid reason for the gaps in those post-market surveillance studies, the absence of that data is data that TPSAC would normally expect and would want to rely on when renewing and reviewing an MRTP renewal. And so, that's problematic. At the same time, we also know that we need harm reduction opportunities for consumers that use combustible cigarettes.

And so, did I hear anything today that would have me lean towards rescinding the MRTP? No, I didn't. Did I hear any evidence that would make me want to renew the MRTP? No, I didn't. And so, I'm going to leave this almost with this kind of existential question now for FDA is what is possible? And remind FDA that there were 3 years where the product was not for sale in the United States. And if there is any potential way to get this committee the data that we're looking for, I think that would very much be appreciated. And I think the lack of the post-market surveillance studies really made the conversations today very challenging.

And with that, I would like to ask Dr. Ben Apelberg to return and provide his closing remarks.

Ben Apelberg:
Okay. Great. Thanks so much, Dr. Delnevo for leading the committee discussion today. It was really helpful for us to hear. I'd like to close out our meeting today by, once again, thanking the applicant. I know that there's a lot of work that goes into these submissions and presentations before the committee. So, we appreciate the work that went into it.

I'd like to thank the members of the public who submitted comments and spoke today, the many CTP staff members who worked for months to ensure a successful meeting. In particular, I'd like to thank our technical project lead for this application, Dr. Amber Koblitz, and our DFO, Dr. Rachel Jang. Most importantly, thanks to the committee members and our three guest consultants who joined us today.

As Dr. Koplow talked about at the beginning, the referral of all MRTP applications to TPSAC is not only required by the Tobacco Control Act, but also a crucial part of CTP's evaluation of these applications. So, we'll take the committee's scientific advice and recommendations back and consider them as part of the totality of evidence that we evaluate when making determinations about this application.

So, just a big thank you to everyone who helped make CTP's first-ever fully virtual TPSAC meeting a success. And now, I'll turn it back to Rachel to close this out.

Rachel Jang:
Thank you. My picture is not working, I don't think. All right. Thank you, everyone. Thank you, Dr. Apelberg for those wonderful closing comments. In closing, I just want to thank everyone for their hard work and efforts, especially the committee members and Dr. Delnevo, CTP staff, and

AV staff for making this meeting a successful one.

This concludes our meeting today of the Tobacco Products Scientific Advisory Committee. Thank you, everyone. It is now 4:24, and the meeting is officially adjourned. Have a wonderful evening.

[end of transcript]