Script of Philip Morris International's Presentation before the Tobacco Products Scientific Advisory Committee (TPSAC)

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MOIRA GILCHRIST

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Good morning. I'm Moira Gilchrist from Philip Morris International. Thank you, Mr. Chairman; members of the Committee; members of FDA; and everyone here today. We're here to present our Modified Risk Tobacco Product application for IQOS. Mr. Chairman, we have an integrated 90-minute presentation with four different speakers. We'd appreciate the opportunity to deliver the full presentation. After that we'd be happy to answer any questions the committee may have.

To begin, I'll take a few moments to consider the application from the perspective of the 40 million American men and women who currently smoke. For smokers, cigarettes are familiar. They're the most widely used tobacco product in the United States. I'm sure that most people in the room know someone who smokes, it could be a friend, a colleague, or a family member. Smokers live in every region of the United States. They're represented in every ethnicity, every religion, and every socio-economic group. Their best choice would be to quit altogether, but the fact is most don't. This is the status quo.

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To help our discussion, we've illustrated the situation with a very simple diagram. This represents the approximately 40 million Americans who currently smoke. Of course, the picture doesn't remain static. Every year, there's a group of people who start smoking. At the same time, there are a number of smokers who quit. But some of them relapse and return to smoking. There are varying estimates of the rates for each flow in the future. But the key point is that World Health Organization and US

government statistics predict that tens of millions of American men and women will continue to smoke.

This is the situation that the US government has been seeking to address for decades most significantly in 2009 with the Family Smoking Prevention and Tobacco Control Act. The statute aims to deliver real-world solutions to a decades-old problem. It empowers the FDA to change the status quo for 40 million Americans.

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As part of the solution, the Statute and the FDA recognize the continuum of risk for nicotine and tobacco products. On this continuum combustible products are by far the most risky because it's the burning of tobacco that creates the vast majority of the harmful chemicals contained in cigarette smoke that are the primary cause of smoking-related disease. Cessation, of course, is the best way for a smoker to lower their risk. But we know that many don't. We also know from PATH data that more than half of those who continue to smoke are seeking lower risk alternatives. And the Statute mandates that FDA oversee industry's efforts to develop and introduce modified risk products to help move smokers away from cigarettes.

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Under the statute, we're seeking authorization of IQOS as a modified risk tobacco product. IQOS heats tobacco rather than burning it. Because of this, it generates an aerosol that contains on average greater than 90% lower levels of harmful and potentially harmful chemicals compared with cigarette smoke.

Through the course of the presentation we'll show you how IQOS can help change the status quo for millions of American smokers, and lead to significant reductions in harm and the risk of tobacco-related diseases.

To be clear, IQOS is not a perfect solution. It's not risk-free, and it contains nicotine, which is addictive. The best choice for a smoker is to quit altogether. But for those who don't, our evidence shows that IQOS is a much better choice than continuing to smoke.

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As you see, we've added IQOS to this slide. Our data show that it can move millions of those who would otherwise continue smoking away from cigarettes without materially impacting initiation or cessation. It's a real world solution.

I used to be a smoker. I'm a scientist and I work every day on issues related to the health effects of smoking. And yet I continued to smoke. Several years ago I switched completely to IQOS. I found it an acceptable alternative to smoking, and I also knew the reasons to switch. I knew the science that you're going to hear about today. For American men and women who smoke, your friend, your colleague, your family member, shouldn't they have access to and information about a product that's a better choice than smoking?

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The statute gives FDA the authority to change the status quo by verifying that products which claim to reduce harm and risk actually do. And by making those products available and ensuring that smokers are accurately informed about them.

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Beginning with part A, the science in our application is a comprehensive package of both clinical and non-clinical data. Our data demonstrate that smokers who switch completely to IQOS are exposed to much lower levels of toxicants. As you'll see shortly, the ultimate result of this is significantly reduced harm and risk of tobacco-related diseases.

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Part B of the statute requires modified risk tobacco products to benefit the health of the population overall. This requires us to assess intended use – by smokers who would otherwise continue to use cigarettes – and unintended use – by non-smokers and smokers who would otherwise stop. So, the question is, does the likelihood and magnitude of intended use outweigh the likelihood and magnitude of unintended use? We'll show you why there's a high probability that the answer to this question is yes.

Our pre-market data from the United States indicate that when given accurate product information millions of American men and women who would otherwise continue to use cigarettes could switch completely to a much better product. This is in line with our real-world experience in more than 30 countries where the product is already available. More than 3.7 million smokers outside the US have switched exclusively to IQOS in only two years. At the same time, non-smokers and former smokers show very little interest in the product.

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Our application includes three product messages that clearly communicate the results of our scientific assessment:

Message 1: Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

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Message 2: Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes. And,

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Message 3: Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

These messages would appear along with the Surgeon General's warnings.

I acknowledge that many in the public health community are skeptical about our motives.

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The controversial history of the industry is laid out vividly in the statute. But at the same time, the statute created this process and provides for effective oversight of our efforts to develop and introduce less harmful products. And that's exactly why we're here today. We appreciate your expert evaluation of our science based on the

strength of our application and the opportunity that it presents to America's smokers.

If you decide that using IQOS would be a better choice than continuing to smoke then US smokers need to have access to it and information about it. You may ultimately find that we can help change the status quo in a rapid and unprecedented way.

Let's turn to the agenda.

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First, I'll take a few minutes to show you the IQOS system and heating technology. Then Manuel Peitsch, who's our Chief Scientific Officer, will outline the core of our scientific assessment results. After that, we'll look at benefit to the population as a whole: Antonio Ramazzotti, who's our Vice President of Human Insights and Behavioral Research, will share our Perception & Behavior data. Philip Morris USA, our former sister company, will sell IQOS in the United States if authorized by FDA. Sarah Knakmuhs, who's their Vice President of Heated Tobacco Products, will set out our plans for the introduction of IQOS in the United States, including controls to minimize unintended use, as well as plans for post-market surveillance. At the end I'll return to talk about population health impact modelling and conclude the presentation.

Now let's take a closer look at the IQOS system and its underlying heating technology.

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We've been working on the IQOS concept for more than a decade. It's very different from cigarettes and consists of three major elements.

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First, are the HeatSticks - these are designed for use only with IQOS. For the tobacco plug, we use a specific blend of tobacco leaves. They're carefully processed to create a uniform mixture that's formed into a sheet and then crimped. The entire process is designed to produce the highest possible homogeneity of the tobacco.

This in turn ensures that the aerosol is uniform and consistent puff to puff and stick to stick.

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The second important element is the IQOS Holder. It contains a heating blade that heats the tobacco plug from the inside. The blade has a platinum based heating track that's coated with a thin film of glass. The heating blade is connected to a printed circuit board that hosts the firmware for temperature control. When it's in use, the average temperature across the blade is no more than 350 degrees Celsius – that's 662 degrees in Fahrenheit. A cigarette, on the other hand, burns at about twelve hundred degrees Fahrenheit. The heating blade is also a sensor that continually monitors tobacco temperature. The energy supply is automatically cut off if it detects temperatures above the set limit. Every single heating blade is individually calibrated to ensure precision and reliability over and over again during the course of the product's lifecycle. We use infrared cameras to measure the average blade temperature at different set points. Those temperatures are correlated to specific electrical parameters that are unique to each blade and are stored in the permanent memory of the device. Based on these parameters, the device software precisely regulates the energy supplied to the heating blade to achieve the desired temperature profile.

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This slide shows the tobacco temperature at different distances from the surface of the heating blade. As you can see from the uppermost line, the heating blade reaches 350 degrees Celsius but the lines below show that even the tobacco that's closest to the blade never gets to this temperature. In fact, most of the tobacco remains below 250 degrees, well below the temperature required for combustion processes to begin, which is 400.

With combustible cigarettes, each puff introduces oxygen into the system and dramatically increases the tobacco temperature. In contrast, with IQOS, puffing actually decreases tobacco temperature, because fresh air cools the system. You can see this on the graph from the small dips in temperature that appear. This is just one of the many pieces of evidence demonstrating that combustion doesn't occur in IQOS.

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The third element is the IQOS Charger, it's used to recharge the Holder after each use. Both the holder and the charger are manufactured by suppliers who specialize in electronics for medical devices, life sciences equipment, and consumer goods.

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Let me explain how the product operates. First, the user removes the holder from the IQOS charger, then inserts a HeatStick into the Holder, and presses and holds the button. The heating profile begins with a short pre-heat phase, to bring the tobacco up to the correct operating temperature. It then applies a specific and controlled temperature profile for the duration of the experience, which is 6 minutes or fourteen puffs, after which the device shuts off.

The innovative design and engineering that I've just summarized ensures the quality and consistent performance of the IQOS system. It's this performance that leads to the scientific results in our application that Manuel Peitsch will now present. Manuel.

MANUEL PEITSCH

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Thank you Moira, and good morning Mr. Chairman; members of the Committee; members of FDA, and everyone here today.

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I'm going to show how the evidence we have generated through our Scientific Assessment Program supports Part A of the statutory requirement, that IQOS, "as it is actually used by consumers, significantly reduces harm and the risk of tobacco-related disease to individual tobacco users." Implied in this, is the fact that the product should significantly reduce the body's exposure to harmful and potentially harmful chemicals (toxicants for short). Taken together, these objectives represent the three proposed messages in our application.

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The application is extensive and covers 17 non-clinical and 8 clinical studies. In conducting these studies, we followed international quality standards such as ISO, GLP and GCP and used validated analytical methods. In line with the Roadmap of the National Toxicology Program for the 21st Century, we developed and applied an innovative Systems Toxicology-based approach to the non-clinical assessment of IQOS, in addition to employing well established toxicology testing guidelines described by the OECD.

Over the past decade, we published more than 30 peer reviewed publications describing our IQOS assessment studies and over 150 publications describing the approaches and methods we used. All completed studies are included in the application and are available for review. Due to time constraints today, I will focus on the most important study results that support the proposed claims.

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The Framework we developed to assess products with the potential to reduce the risk of smoking-related disease, is informed by what is known from epidemiological evidence. Smoking has been proven to cause a number of severe diseases and population harm. We based our assessment approach on the causal chain of events triggered by exposure to cigarette smoke that ultimately leads to disease. The causal chain of events starts with the burning of tobacco, which leads to the emission of toxicants by cigarettes. Smoking cigarettes exposes the body to these toxicants. This exposure then leads to changes in the abundance of a large number of the body's molecules. These changes then cause the disruption of many biological mechanisms. This in turn causes changes at the cellular and tissue level. Finally, an accumulation of these changes over time leads to the development of disease and by extension population harm.

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It is also accepted that smoking cessation leads to a reduction in the risk of tobacco-related disease. In fact, quitting smoking is the best way to reduce the harm and risk of smoking-related disease.

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Consequently, the epidemiology of smoking and smoking cessation confirms the general principle of toxicology which states that: A reduction in toxic emissions leads to a reduction in exposure, which in turn leads to a reduction in adverse health effects.

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To demonstrate that switching to IQOS reduces harm and the risk of smoking-related disease, our assessment program must demonstrate that: IQOS emits significantly lower levels of toxicants than cigarettes. As a direct consequence of this, switching to IQOS should lead to a significant reduction in exposure to toxicants. And this reduction in exposure should lead to a significant reduction in health effects. In fact, the closer these reductions in exposure are to those observed in smokers who quit, the higher the harm and risk-reduction potential of IQOS.

At each step of the causal chain of events we compared the effects of the IQOS aerosol with those of cigarette smoke and cessation. The data that I am going to present, provides the totality-of-the-evidence that demonstrates that switching to IQOS leads to the reduction of harm and risk of smoking-related disease.

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Since IQOS was designed to heat and not burn tobacco, the IQOS aerosol has a very different composition than cigarette smoke. Cigarette smoke (on the left) has a brown color when captured on a filter pad. It contains 50% water and glycerin, toxicants, and solid carbon-based nanoparticles. In contrast, the aerosol of IQOS shown on the right is visibly different. It essentially contains water and glycerin with significantly reduced levels of toxicants and importantly, no solid carbon-based nanoparticles.

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The solid carbon-based nanoparticles in cigarette smoke are a hallmark of combustion and have been shown to trigger inflammation and demonstrated to cause lung and cardiovascular disease. As you can see from these electron microscopy images, smoke from a burning cigarette contains many solid particles

(left image). In fact one cigarette contains approximately half a trillion solid nanoparticles, which corresponds to approximately (point 7) 0.7 mg/cigarette. In contrast the aerosol from IQOS (on the right) does not contain such particulate matter.

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Our assessment of IQOS continues with the comparison of the level of toxicants contained in the IQOS aerosol with those contained in the smoke of the 3R4F reference cigarette from the University of Kentucky. We selected 54 toxicants for quantification using well established and validated analytical methods. This includes the harmful and potentially harmful constituents described in the lists of Health Canada, the WHO and the FDA-18. Here we present only 48, because 6 were below the limit of quantification in both IQOS aerosol and cigarette smoke. As depicted in this graph, the IQOS aerosol from the three variants contains on average over (>)92% lower levels of toxicants than cigarette smoke. While most toxicants are reduced by more than 90%, 4 are reduced by 80-90%, and 6 are reduced by less than 80%.

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In addition to the quantification of these toxicants, we conducted an in-depth comparative analysis of the composition of the IQOS aerosol and the 3R4F smoke. To be as thorough as possible, we used a combination of liquid and gas chromatography, coupled with high resolution mass spectrometry. We identified 4330 constituents in 3R4F smoke. Of those, 3580 were absent from IQOS aerosol. In comparison, only 750 constituents were identified in IQOS aerosol. Of those, 3 were unique to IQOS, and 50 more abundant than in 3R4F smoke. We conducted a full toxicological evaluation of these 53 constituents. From this, 4 constituents were found to be of toxicological concern because they are potential carcinogens. Our evaluation, based on the published inhalation toxicity literature, indicates that the levels of exposure to these compounds through IQOS are below the level of concern.

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The toxicants presented earlier are known to cause smoking-related disease and have been categorized according to the diseases they cause. Here, we present the average reductions by disease category and see that the carcinogens,

cardiovascular, respiratory, as well as, reproductive and developmental toxicants are all reduced on average by more than 90% in the IQOS aerosol. Nevertheless, it is important to emphasize that toxicants are still present in the IQOS aerosol, and therefore IQOS is not risk-free.

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We have demonstrated that IQOS emits significantly lower levels of toxicants than cigarettes. IQOS does not emit solid particles, and does not present new hazards.

In the causal chain of events linking smoking to disease, a reduction in toxicant emission leads to a reduction in exposure. Let's now look at the effect of switching to IQOS on exposure.

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To assess this, we compared the levels of exposure to toxicants in adult smokers who switched completely to IQOS with the levels of exposure in those who continued to smoke. We conducted 4 clinical exposure studies each with one hundred and sixty smokers. Two were longer-term studies starting with 5 days in confinement followed by an 85-day ambulatory period where the subjects were sent home to use IQOS in a more realistic setting. These 90-day studies were conducted in the U.S. and Japan. Subjects were randomized to either: Continue Smoking, Switching to IQOS, or Smoking Abstinence. We measured 16 biomarkers of exposure, plus nicotine and its metabolites at baseline, on Days 1 through 5, and then on Days 30, 60 and 90. We only present 15, because for toluene, the assessment method was not sensitive enough to detect changes in smoking status, even for smoking abstinence.

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Let's first look at the nicotine exposure, product satisfaction, and product consumption data from the U.S. study.

Delivering nicotine at comparable levels to the adult smoker's own cigarettes is important for product acceptance. After an initial adaptation period, study participants randomized to the IQOS group achieved comparable levels of nicotine uptake. Importantly, nicotine exposure did not increase above levels observed at

Baseline, nor did it exceed the exposure levels in those who continued the smoke their usual cigarettes.

Satisfaction with IQOS, measured with the Modified Cigarette Evaluation Questionnaire converges with that of cigarettes, after an initial adaptation period.

We observe a similar pattern of convergence between IQOS Heatsticks and cigarette consumption over time. Together, these data demonstrate that smoker acceptance of IQOS is similar to that of cigarettes.

Let's now turn to the data on toxicant exposure.

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I will show a couple of examples from the U.S. study to demonstrate how the reduction in emission translates to a reduction in exposure before presenting the full exposure profile.

The IQOS aerosol contains 98% less carbon monoxide than cigarette smoke.

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This leads to a rapid and significant reduction in the levels of carboxyhemoglobin, the biomarker for carbon monoxide, which levels off after only 2 days and is maintained for the full duration of the study.

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When we compare the effect of switching to IQOS to that of smoking abstinence, overlaid in green, we see that the levels of carboxyhemoglobin almost overlaps those of smoking abstinence.

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Although the reduction of acrolein in the IQOS aerosol is less pronounced than that of carbon monoxide, the reduction in exposure is still significant.

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NNK and NNN, 2 carcinogenic tobacco-specific nitrosamines, are reduced by over 95% in IQOS aerosol compared with cigarette smoke. In both cases, the exposure is significantly reduced compared with ongoing smoking and approaches that of smoking abstinence.

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When we look across all the biomarkers of exposure that were measured in the clinical studies, both in the U.S. and Japan the results show that in smokers who switched to IQOS there was a significant reduction in all 15 biomarkers of exposure and

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That these reductions approached those in smokers who abstained from smoking for the duration of the study. In fact,

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Switching to IQOS achieved almost 95% of the overall reduction in exposure achieved by smoking abstinence, where smoking abstinence is the maximum achievable reduction in exposure.

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With this, we have demonstrated that smokers who completely switch to IQOS are exposed to significantly lower levels of toxicants than smokers who continue to smoke cigarettes. In the causal chain of events, a reduced exposure to toxicants leads to a reduction in molecular changes.

Let me show you the effect on molecular changes observed when switching to IQOS.

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We conducted a study in Apoe-/- mice, because this model reproduces the key aspects of atherosclerotic plaque formation and emphysema development, in ways similar to humans, which includes the role of inflammation. The study included: A group exposed to cigarette smoke for 8 months, at a dose corresponding to 30 cigarettes/day. A second group that was first exposed to cigarette smoke for 2 months and then switched to IQOS aerosol for the remaining 6 months, at the equivalent of 30 Heatsticks/day. Similarly the third group of mice was first exposed to cigarette smoke for 2 months and then switched to fresh air for 6 months representing the smoking cessation benchmark.

In addition, we also exposed: a group of mice to IQOS aerosol for the entire 8 months of the study and a group to fresh air for the duration of the study. The number of animals per group and dissection time point was based on the analysis of previous studies and selected to deliver enough statistical power to allow comparisons between groups.

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We measured molecular changes using state-of-the-art technologies that allow for the quantification of both protein abundance and gene expression levels. The results of this study show that exposure to cigarette smoke causes massive changes in protein abundance (here on the left, where the darker colors represent the higher levels of change and asterisks indicate statistically significant values with p-values below (<)0.05) and gene expression levels (here on the right, depicted as volcano plots, where the larger the eruption, the higher the number of significant changes.) The colored dots above the horizontal line indicate differential gene expressions that are statistically significant with False Discovery Rates of 0.05 or better.

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When we look at the data for the group of mice that were switched to IQOS aerosol after 2 months of cigarette smoke exposure, we see that the changes in molecular expression are significantly attenuated,

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And approach the levels seen in the group of mice that were switched to fresh air - the cessation group. As you see on the left, the abundance of inflammatory proteins is strongly reduced following switching and cessation. Similarly, on the right, the high degree of gene expression changes induced by smoke exposure, are strongly attenuated in both switching and cessation groups.

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In the group that was exposed to IQOS aerosol for 8 months, we see only very limited changes in both protein abundance and gene expression.

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This shows that the reduction in exposure to toxicants achieved by switching from cigarette smoke to IQOS aerosol leads to a significant reversal in the molecular changes induced by cigarette smoke. In the causal chain of events, a reduction in molecular changes leads to a reduction in the disruption of biological mechanisms.

Let's now look at the effect of switching to IQOS.

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The molecular changes caused by exposure to cigarette smoke lead to the disruption of a wide range of biological mechanisms, such as cell stress, inflammation and cell death. All of these are known to be associated with smoking-related disease. To walk you through a sample of the data, I am presenting the results for inflammation. In the figure you see that cigarette smoke exposure caused massive lung inflammation.

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Switching to IQOS and cessation both led to significant reductions in inflammation.

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It is also important to note that 8 months of exposure to IQOS aerosol caused only minimal inflammation.

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To confirm these results, we measured the abundance of a number of inflammation markers in the Broncho-alveolar Lavage Fluid (or BALF) of the animals. For example, Interleukin 1-beta, Interleukin-6, KC, and MCP-1 are increased by cigarette smoke exposure (red lines), but not by IQOS aerosol (purple lines), switching to IQOS aerosol (orange lines) reduces the abundance of these markers in a way that is similar to cessation (green lines). Importantly, these inflammation markers have been reported to be more abundant in the BALF of human smokers than non-smokers.

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Results for the other biological mechanisms look very similar and lead to the same conclusions across ALL mechanisms affected by smoke exposure. This includes Cell Stress, Cell Proliferation, Cell Fate & Apoptosis and Tissue Repair & Angiogenesis.

Let's now see how these results are supported by our clinical studies.

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No single clinical risk endpoint, on its own, is predictive of the risk of smoking-related disease. Because of this, we measured a set of endpoints known to be affected by smoking and to reverse upon cessation, in the 90-day clinical studies I presented earlier. To assess the changes upon switching to IQOS, we first have to understand how these endpoints are affected by cessation, because we know that cessation is definitively linked to a reduction in risk for smoking-related disease. The changes in clinical risk endpoints that we measured in smokers who abstained for the duration of the studies are small, which is expected in a healthy study population, yet their direction is consistent with the literature on cessation. Because these changes occurred upon smoking abstinence, which is known to reduce the risk of smoking-related disease, these changes are actually clinically relevant. They are indicative of the positive effects of cessation across a broad range of mechanisms, such as inflammation and oxidative stress, that are linked to multiple smoking-related diseases.

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In both studies, we observed that switching to IQOS also led to positive changes in clinical risk endpoints compared with continued smoking. The changes after switching to IQOS were consistent with the direction of change expected from smoking cessation studies and were of a similar magnitude to the clinically relevant changes observed in participants who abstained from smoking. The consistency of these changes across the disease-relevant mechanisms, are coherent with the multitude of positive changes that we observed in the Apoe switching study.

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Together the results from the in vivo and the clinical studies show that switching to IQOS leads to a reduction in the molecular changes caused by smoke exposure. And reduces the disruption of a broad range of biological mechanisms that are linked to smoking-related diseases. In the causal chain of events, a reduced disruption of biological mechanisms leads to a reduction in cell and tissue changes.

Let’s now look at how switching to IQOS affects these changes.

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The mechanistic disruptions observed in smoke-exposed mice led to several changes at the cellular and tissue level. For instance, the number of inflammatory cells in the lung, in particular neutrophils, is massively increased following smoke exposure, while switching to IQOS rapidly reduces these changes. As does cessation.

8 months of exposure to IQOS aerosol did not induce significant inflammatory cells changes in the lung.

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This slide shows that the results on lung tissue damage followed the same pattern.

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This shows that switching to IQOS leads to a reduction in changes at both the cellular and tissue level. In the causal chain of events, cellular changes and tissue damage caused by smoke exposure eventually lead to the development of disease. Because cessation normalizes these changes and attenuates the progression of tissue damage, cessation will also lead to a reduction in disease manifestations. Switching to IQOS should therefore also lead to a significant reduction in disease risk.

I will now show you what we observed when switching to IQOS.

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The results of our in vivo study show that cigarette smoke exposure leads to an increase in disease endpoints. Here we see that cigarette smoke causes extensive emphysema in the lung, while switching to IQOS led to a significantly reduced progression of the emphysema score. The effects of switching approached those of cessation, and continuous exposure to IQOS aerosol did not cause emphysema. These results were further confirmed in our A/J mouse study.

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This slide shows that cigarette smoke accelerates the growth of atherosclerotic plaque in the aortic arch while switching to IQOS significantly attenuated plaque growth. For this endpoint, the effect of switching also approached that of cessation and continuous exposure to IQOS aerosol had a limited effect on atherosclerotic plaque growth. Adhesion of neutrophils to the vascular endothelium is a critical early step in atherosclerotic plaque formation.

To further support these in vivo results, we used a cell-based assay measuring the adhesion of human monocytic cells to primary human aortic endothelial cells. This study shows that IQOS aerosol causes 10-20 fold less monocytic cell adhesion to endothelial cells than cigarette smoke.

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Let's now consider the totality-of-the-evidence in the context of lung cancer. Several lines of evidence point to the potential of IQOS to reduce the risk of lung cancer compared to cigarettes.

Balkwill and Mantovani postulated that both genetic damage and inflammation are key contributors to cancer. In the context of smoking, this means that: genetic damage and tumor initiation are caused by carcinogens. In parallel, inflammation, which promotes tumor progression and invasiveness, is caused by toxicants as well as carbon-based nanoparticles. Together these mechanisms lead to cancer.

This raises three key questions in the context of IQOS: First: Does switching to IQOS reduce genetic damage? Second: Does switching to IQOS reduce inflammation? Third: Does switching to IQOS therefore lead to a reduction in lung cancer risk?

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Let's first review the evidence related to genetic damage. The emission of carcinogens is reduced by over 90% by IQOS compared with cigarettes. This led to:

- a significant reduction in carcinogen exposure.

- a significant reduction in genotoxicity of the IQOS aerosol in standard cell-based assays… as well as a significant reduction in urinary genotoxicity of the clinical study participants who switched to IQOS compared with those who continued to smoke.

- a significant reduction in DNA damage measured in normal human bronchial epithelial cells. It also led to a significant reduction in the activation of the DNA damage repair mechanism in our animal studies.

- the significant reduction in carcinogen exposure, especially polycyclic aromatic hydrocarbons (or PAHs), also led to a significant reduction in the activation of xenobiotic metabolism as evidenced by gene and protein expression data in cell-based assays, animal studies and our clinical studies.

Taken together, our results demonstrate that IQOS causes less Genetic Damage than cigarette smoke. This indicates that IQOS is likely to cause less tumor initiation than cigarette smoke.

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Before I review the evidence related to lung inflammation, let me come back to the carbon-based nanoparticles that are present in cigarette smoke, but absent in IQOS aerosol. There is a visible color difference when comparing the lungs of mice exposed to cigarette smoke and IQOS aerosol. We believe that this difference is due, at least in part, to the persistent deposition of carbon-based nanoparticles from cigarette smoke. Purified carbon-based nanoparticles, as well as cigarette smoke, have been demonstrated to trigger inflammation, including the production of Interleukin-1beta, Interleukin-6, KC and MCP-1 in non-clinical studies.

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Human data reported in the literature confirm this mechanism: The BALF of smokers contains significantly increased levels of Interleukin-1beta, Interleukin-6, Interleukin-8 and MCP-1 as well as Macrophages and Neutrophils, compared to the BALF of non-smokers.

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This type of inflammation is known to promote tumor progression and invasiveness. In animal models devoid of the Interleukin-1beta gene, tumor progression and invasiveness are reduced.

More recently, in humans, it has been shown that canakinumab, an antibody against Interleukin-1beta, can reduce the incidence and mortality of lung cancer in a dose-dependent manner.

This confirms the role of Interleukin-1beta in tumor progression and invasiveness.

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Let’s now review the evidence from our assessment program related to lung inflammation.

Toxicant emission is reduced by over 90% by IQOS compared with cigarettes. And, the IQOS aerosol does not contain carbon-based nanoparticles. This led to a significant reduction in toxicant exposure and no exposure to carbon-based nanoparticles. These reductions in exposure led to a reduction in lung inflammation. Specifically, our animal study results demonstrated that IQOS aerosol causes significantly less lung inflammation than cigarette smoke. For instance, Interleukin-1beta is not induced by IQOS exposure, while switching and cessation both led to a similar reduction in Interleukin-1beta abundance in the BALF of the Apoe mice.

Taken together, our results demonstrate that IQOS causes less inflammation than cigarette smoke. This indicates that IQOS is likely to cause less tumor progression and invasiveness than cigarette smoke.Because IQOS has a reduced impact on both key mechanisms involved in cancer, as postulated by Balkwill and Mantovani, it can be reasonably inferred that it also reduces the risk of lung cancer compared to cigarettes. We are completing the evaluation of the A/J mouse study, which will provide further evidence for the reduction in lung cancer risk.

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Taken together, these result show that switching to IQOS can reduce the risks of tobacco-related disease.

With that we have covered the evaluation of IQOS along the causal chain of events linking smoking to disease.

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Before I conclude, let's consider the totality-of-the-evidence collected by our multi-step evaluation of IQOS.

First, the IQOS aerosol contains 90-95% lower levels of toxicants than cigarette smoke and no solid carbon-based nanoparticles.

Second, this reduction in emission leads to a reduction in exposure of human study subjects who completely switched to IQOS, and achieves almost 95% of the reduction induced by smoking abstinence, where smoking abstinence is the

maximum achievable reduction in exposure. A similar reduction in exposure is achieved in both animal and cell-based studies, at equivalent nicotine concentrations.

Third, this reduction in exposure leads to a generalized reduction in molecular changes in all animal studies. Importantly, in the Apoe switching study, these reductions approach those induced by cessation and reflect the 90-95% reduction in toxicant exposure. Similar changes were also observed in cell-based studies and in our 90-day clinical studies, clinical risk endpoints affected by smoking showed favorable changes upon switching to IQOS, in a way that is similar to those induced by smoking abstinence.

Fourth, this reduction in molecular changes leads to a generalized reduction in the disruption of biological mechanisms in all animal studies. In the Apoe switching study, these reductions also approach those induced by cessation and reflect the 90-95% reduction in toxicant exposure and molecular changes. In cell-based studies, we also observed a generalized reduction in the disruption of biological mechanisms.

Fifth, this reduction in the disruption of biological mechanisms leads to a reduction in cell and tissue changes in all animal studies. In the Apoe switching study, these reductions also approach those induced by cessation and reflect the 90-95% reduction in the disruption of biological mechanisms from the previous step. In cell-based studies, a generalized reduction in toxicity was also observed.

Lastly, these reductions in cell and tissue changes lead to a reduction in disease endpoints in both the Apoe switching study and the chronic exposure study conducted in A/J mice. The reductions again approach those induced by cessation in the switching study.

In conclusion, IQOS emits toxicants and is not risk free. Nevertheless, IQOS emits significantly lower levels of toxicants than cigarettes. The results of all our studies, across the causal chain of events, are coherent with this reduction in toxicant emission and consistently demonstrate that the IQOS aerosol is less toxic than cigarette smoke. Therefore, the totality-of-the-evidence clearly demonstrates that IQOS presents less risk of harm and tobacco-related disease than cigarettes. This supports the marketing order with the proposed messages.

(Slide 72)

Thank you for your attention. I will now hand over to Antonio Ramazzotti, to show you how the evidence we have collected through our Perception and Behavior Assessment studies supports Part B of the statutory requirement.

ANTONIO RAMAZZOTTI

(Slide 73)

Thank you Manuel. Good morning everyone. To start, I would like to go back to the statute for a moment.

(Slide 74)

Manuel has shown that IQOS presents less risk of harm and tobacco-related disease, as required by Part A of the statute. The assessment then turns to Part B.

As the statute directs, we have examined the likelihood and manner of IQOS use among both smokers and nonsmokers. We seek to maximize the number of adult smokers who switch exclusively to IQOS. At the same time, we want to minimize the likelihood of decreasing cessation among smokers, or increasing initiation among nonsmokers. In short, this is the optimal regulatory outcome, and the opportunity that Moira's diagram depicted earlier.

(Slide 75)

My focus is on our Consumer Perception and Behavior program, or PBA program, as we call it. This work helps us assess who will use IQOS and to what degree.

Our PBA program tracks the FDA's Draft Guidance for modified risk products and reflects advice from experts in the fields of behavioral, regulatory, and tobacco research. We looked to best practices from other product categories that FDA regulates, such as over-the-counter drugs. We carried out 9 U.S. studies involving both qualitative and quantitative research. More than 11,000 people in U.S., including smokers and non-smokers, participated in this research. We have developed a strong evidence base to support the modified risk applications. This

evidence will, of course, be further supported by post-market surveillance and studies should IQOS be authorized.

(Slide 76)

Out of the nine studies, our PBA program included six to develop and assess the IQOS communication. These qualitative and quantitative studies were conducted in 2 phases.

In Phase 1, we explored different product messages conveying the product benefits that our science substantiates, as Manuel just described. We investigated how each element of the different messages contributed to comprehension of the modified risk information, Intent to Use, and Risk Perception.

In Phase 2, we assessed proposed label, labeling, and advertising in terms of consumer understanding, and estimated intent to use among smokers and nonsmokers.

(Slide 77)

As a result of our Phase 1 work, we selected and tested three product messages with either the Surgeon General's warnings or PMI warnings that we developed. The PMI warnings were developed to reflect the characteristics and the risk profile of IQOS and were used in the PBA program for testing purposes. To be clear, we do not propose replacing the Surgeon General's warnings with the PMI warnings.

(Slide 78)

In Phase 2, we conducted three studies to assess communication materials, one for each of the product messages part of our submission. In each study, we enrolled approximately 2,200 participants.

We included smokers, both with and without the intention to quit, former smokers, never smokers, and Legal Age to 25 never smokers. The sample was balanced by smoking status, sex, age and city. Each study was conducted in four cities, one in each of the US Census areas. Each participant was randomized to one of the tested materials, which was given as a physical mockup. The brochure and the HeatSticks

pack carried either one of the four Surgeon General's warnings or the PMI warning. The direct mail was tested only with the PMI warning.

The hypothetical price for IQOS was $79.99 and the price for a pack of 20 HeatSticks was equal to the price of a pack of Marlboro cigarettes in each city where the research took place.

(Slide 79)

Let's look at one of the product messages as actually tested in Phase 2. In the slide you see the product message that "IQOS presents less risk of harm than continuing to smoke cigarettes" on a pack of Heatsticks. The pack on the left includes one of the four Surgeon General's warnings. The pack on the right includes the PMI warning. I will now show you data on comprehension of this product message.

(Slide 80)

This slide shows that the majority of participants, including both adult smokers and adult non-smokers, correctly comprehended the reduced harm message with each warning, 73% with the Surgeon General's warnings, and 78% with the PMI warning.

(Slide 81)

Notably, only 1% and 2% misunderstood the message as stating there to be "no risk of harm."

The results of this study show the majority of participants understood that IQOS presents less risk of harm, but is not risk free. These results are representative of what we observed for the two reduced risk messages, across all tested communication materials.

Now let's turn to likelihood of use.

(Slide 82)

To assess intention to use, we showed communication materials to the study participants.

Here, you can see an example of the results, among adult smokers who reported no intention to quit, when presented with the Heatsticks pack carrying either the Surgeon General's warnings or the PMI warning. 20% of Adult Smokers expressed a "definite" or "very likely" intention to use IQOS with the Surgeon General's warning. And 28% did so for the product bearing the PMI warning.

Across all tested product messages in communication studies, we observed that this group of smokers consistently showed an overall positive intention to use IQOS in the range of 20-39%. The next step was to measure how this level of intention to use translates to actual use. We observed this through our actual use study.

(Slide 83)

Before showing you the key results, let me briefly describe some aspects of the study methodology. The purpose of the Actual Use Study was to investigate how adult smokers might use IQOS in the real world.

The sample included more than one thousand participants in 8 cities, geographically spread across the U.S., and approximated the adult smokers distribution in terms of sex, age, race and income. At enrollment, participants were shown a physical brochure containing the product message that "IQOS can reduce the risks of tobacco-related diseases". Participants were free to consume cigarettes, IQOS and any other product containing nicotine, *ad libitum*, as they would in real life. Daily consumption of IQOS and cigarettes was reported via an electronic diary. The study design included a one-week baseline period, a six-week observational period, and a one-week close out period.

(Slide 84)

At the end of the 6-week observational period, 15% of participants had become exclusive or predominant IQOS users. The proportion of exclusive IQOS users was stable as the majority of participants who switched did so within the first 3 weeks. These are encouraging results considering the pre-market setting, in which the actual use study was conducted. For example, we exposed participants to the product message only once, they did not receive coaching reiterating the benefit of complete switch.

We can look to this study as one way to gauge the magnitude of opportunity in the U.S. The observed 15% switching rate could translate to approximately 6 million smokers switching to IQOS.

(Slide 85)

During the actual use study, we collected data about consumption of IQOS and cigarettes. Across all IQOS use categories there was minimal change in consumption of IQOS and cigarettes taken together, between baseline and observational. Importantly, we observe that the daily cigarette consumption decreased for all IQOS use categories. The largest decrease was observed in participants who were predominantly or exclusively using IQOS at week 6.

Let's now turn to data from countries where IQOS is already commercialized, which can provide useful insights about the acceptance of IQOS and how pre-market information translates to post-market results.

(Slide 86)

We have conducted pre-market Whole Offer Test studies in five countries. The study design was similar to the Actual Use study conducted in the U.S. On this slide you can see that 12% of participants in Italy and 30% in Japan, switched to IQOS at the end of the observational period. These results indicate that there is a meaningful proportion of adult smokers who were likely to switch to IQOS in each country… and this is consistent with what we observed in the U.S., here presented on the right.

(Slide 87)

Let's focus now on post-market results in Japan and Italy. These results come from post-market consumer panels that we have set-up to monitor switching patterns over time. These are composed of adult smokers who have purchased IQOS and agreed to register as a member. We measured switching and pattern of use by categorizing IQOS users according to the same usage categories adopted in the actual use study. These graphs show that exclusive use represents the most common behavior among IQOS purchasers. In August 2017, exclusive use reached 72% in Japan and 61% in Italy, meaning they have successfully switched away from cigarettes

However, this is a static picture taken in August 2017. It is very insightful to look at how the exclusive pattern of use evolved over time by analyzing the switching behavior of different cohorts of IOQS purchasers in the past.

(Slide 88)

The data from Japan show that among those who purchased IQOS in September 2015, at the beginning of the national launch, 35% became exclusive users within the first three weeks from purchase. The proportion of exclusive IQOS users grew over time and reached 61% among the March 2016 purchase cohort. Those data suggest that repeated communication, guided trials, and growing popularity of IQOS are major contributing factors in increasing awareness and encouraging adult smokers to reach exclusive use, during the first weeks following purchase. We believe we would see similar dynamics in the U.S. should IQOS be authorized.

(Slide 89)

Let me now address the likelihood of decreasing cessation among smokers, or increasing initiation among nonsmokers.

I will start with the first - cessation. We do not want to deter smokers from quitting… the best choice to reduce the risk of tobacco-disease is to quit tobacco or nicotine altogether. In our PBA studies, we identified current smokers who had an intention to quit, either in the next 6 months or in the next 30 days. We included them in our communication studies to assess if the exposure to IQOS communication materials would impact their intention to quit.

(Slide 90)

The results of our studies indicate that the exposure to the IQOS communication materials minimally altered the reported intention to quit all tobacco. We believe these results indicate a low likelihood that IQOS will deter adult smokers from quitting. This is an area that will be carefully monitored through post-market studies. Let’s turn to likelihood of increasing initiation among non-smokers.

(Slide 91)

In our IQOS communication studies, we measured Intent to Use IQOS among non-smokers. On this slide you see an example of the results for the message that "IQOS presents less risk of harm than continuing to smoke cigarettes" presented on the HeatSticks Pack. Within adult never smokers, positive intention to try was 0%, and within the Legal Age to 25 never smokers was between 1 and 3%. When we looked across all studies and tested materials, the levels of positive Intention to Try or Use IQOS among adult never smokers were no higher than 2.1%. And for the LA-25 never smokers, these were no more than 3%. This gives us confidence that adult never smokers will have a low interest in IQOS.

One of the main concerns for everyone is to what extent minors will start to use IQOS. We do not do research with anyone below the legal age for smoking. We also confirmed with FDA in advance that this would not be appropriate research for us to do. The results of our IQOS communication studies show that the Intention to Try and Intention to Use among never smokers, including the young adult segment of Legal Age to 25 years old, was low. This… in combination with regulatory and commercial controls, such as age restrictions, advertising restrictions, post-market monitoring and enforcement authority… provide additional safeguards that should minimize this unintended use.

We will discuss with FDA ways to actively monitor this serious issue through post-market surveillance, should IQOS be authorized.

(Slide 92)

We also tested former smokers' intent to use IQOS. On this slide, you see an example of the results from the same study, among adult former smokers. In this case the levels of positive intention to try were 8% and 2%. Again looking at all our studies assessing IQOS communication materials, we observed a low intention to try and use IQOS among adult former smokers between 1% and 9.6%. These levels of Intention to try and use IQOS, indicate that former smokers are likely to have a low interest in IQOS.

From our qualitative studies, we have learned that there were three main reasons for the lack of interest in using IQOS. IQOS contains tobacco, it poses health risks,

and it is addictive. Generally, from never smokers, we heard comments such as that they do not plan on ever smoking cigarettes or using tobacco, of any kind on a regular basis. From former smokers, we heard that they do not want to use IQOS because it would mean going back to tobacco and they do not want to have anything to do with tobacco again.

(Slide 93)

The evidence base I've shared with you today indicates that IQOS will provide a benefit to the health of the population as a whole. Both smokers and non-smokers understood IQOS presents less risk of harm, or that IQOS can reduce the risks of tobacco-related diseases but is not risk free.

A meaningful proportion of American adult smokers will accept IQOS as a replacement for cigarettes and will use IQOS exclusively.
The likelihood of decreasing cessation or increasing initiation is low and can be monitored, measured, and addressed in coordination with FDA's oversight.

Let me now turn it over to Sarah, who will speak about plans to introduce IQOS in the U.S. Thank you.

SARAH KNAKMUHS

(Slide 94)

Thank you, Antonio. Good morning. My name is Sarah Knakmuhs. I am Vice President, Heated Tobacco Products for Philip Morris USA, an Altria company. My role is to lead the commercialization of IQOS in the U.S. I am here today to describe our plans to introduce IQOS to adult smokers in the U.S.

I will address a few key topics, including: how we will educate smokers about IQOS, how we will encourage them to switch completely from cigarettes, and how we will limit our reach to unintended audiences. Under agreements with Philip Morris International, Philip Morris USA is licensed to sell IQOS in the U.S. after PMI receives a marketing order from the FDA. We have been working with PMI since 2013 to support PMI's U.S. research and the preparation of its submissions to the FDA. During that time, we have also had the opportunity to learn from PMI's introduction of IQOS in markets outside the U.S. We are eager to bring IQOS to the United States,

particularly given the scientific evidence supporting its harm reduction claims and the potential for adult smoker conversion demonstrated pre-market in the U.S. and post-market outside the U.S.

(Slide 95)

Today, FDA has the regulatory framework to permit companies to bring modified risk products to the market with accurate risk communications and to provide oversight and safeguards to keep those products out of the hands of youth. In fact, that's one reason Altria supported FDA regulation of tobacco through the Tobacco Control Act.

(Slide 96)

As we bring IQOS to the market, our focus is on the 40 million men and women who smoke in the United States. We believe IQOS could be the product of choice for many U.S. adult smokers, and our goal is to have them convert to IQOS.

(Slide 97)

However, we recognize that IQOS and heat-not-burn technology are novel and unfamiliar to most U.S. cigarette consumers. As PMI has learned internationally, encouraging a consumer to switch from combustible cigarettes to IQOS is not easy. It requires a significant behavior change on multiple levels.

As you might expect, IQOS product use is different and therefore is aided by a hands-on tutorial. Think of the first time you used a smartphone. Any electronic product has a learning curve and can be complicated to use at first. Perhaps even more importantly, the taste of heated tobacco is different than that of burned tobacco. For someone who smokes, the initial taste of IQOS may seem unfamiliar. These changes require altering a behavior with which smokers are comfortable.

(Slide 98)

We have a challenge before us as we sell IQOS. On the one hand, we are committed to maximizing our reach to adult smokers and supporting them so they can switch completely to IQOS. On the other hand, we want to limit our reach to unintended

audiences, such as non-smokers and youth. Our marketing approach is designed with these challenges in mind.

There are three components for the adult smoker: awareness trial and conversion. First, we need to build awareness about IQOS to introduce smokers to the concept of a heated tobacco product and inform them of its reduced risk profile. Second, we need to give them opportunities to try the product. Finally, we need to support IQOS consumers so they can convert, meaning switch completely from cigarettes to IQOS. Let me give you a sense of how this approach might look in practice, along with the safeguards we will employ.

(Slide 99)

To raise awareness about IQOS in our launch market, we will use tools such as print advertising, direct mail and email. Print and digital advertisements will be placed only in publications with predominantly adult readership, following FDA's proposed guidelines. For direct mail and email, we will reach adult smokers by identifying them from our Adult Tobacco Consumer Database, which we have built over many years.

(Slide 100)

We use electronic age verification before we allow a name on that database, so we know that we are reaching our intended audience. Electronic age verification allows us to compare personal information a consumer submits with third-party databases to confirm age and identity, not unlike the identity verification questions used by banks.

(Slide 101)

In comparison to raising awareness about IQOS, trial and conversion require a more involved approach. Every smoker is different so these steps must be personalized to each individual consumer's needs. Trial is more than a simple demonstration of the product. It is a conversation that begins with an accurate overview of the differences between heated versus burned tobacco. We provide a detailed tutorial of the device itself and adult smokers are able to purchase a trial pack of HeatSticks. During this dialogue, we reinforce the importance of using IQOS exclusively to

achieve its full benefits. Finally, should they be interested in buying the device, we encourage them to register for post-purchase support.

This conversation is personal, not transactional, and needs to fit into each adult smoker's busy life. So we will have these conversations with adult smokers through individual interactions, consumer events, and at retail.

(Slide 102)

This face-to-face interaction requires verification of age and identity at the outset. To have a guided trial, consumers must confirm that they are current smokers.

(Slide 103)

This individualized approach continues post-purchase because complete switching is the hardest part of the journey. So we will provide a range of support options to help adult smokers fully switch to IQOS. For example, a new IQOS user may get a friendly reminder email to clean and charge their device. Or a text message from an IQOS expert encouraging them to continue using HeatSticks not conventional cigarettes.

Once again, we will be able to limit our interactions to those who we have age verified, either through a government-issued ID in person or by electronic age verification for those who have registered as IQOS users.

(Slide 104)

This entire approach is unique to IQOS. It requires commitment and patience but we think it is the best way to convince smokers to switch to IQOS. Our approach is to drive awareness and conversion among adult smokers while limiting reach to unintended audiences. Moreover, FDA has the authority to impose additional restrictions on the marketing and sale of tobacco products.

(Slide 105)

Beyond the marketing practices we will use for IQOS, we will also work with PMI to monitor IQOS's impact through post-market surveillance and studies. For

surveillance, we will use our call center to capture reports of adverse events. We will also conduct literature reviews; monitor regulatory reporting systems; and collect reports from the National Poison Data System. The results of this surveillance will be reported to FDA along with a summary of adverse events collected by PMI in its markets outside the U.S.

In addition, we will be conducting studies to assess the impact of IQOS, including cross-sectional surveys and a longitudinal cohort study. These studies will be implemented as IQOS gains traction in the marketplace to assess prevalence, use behaviors, perceptions and self-reported health measures. FDA will provide input into the post-market surveillance program.

(Slide 106)

We look forward to the opportunity to bring IQOS to U.S. cigarette consumers as a modified risk product. This opportunity comes with responsibility – to help adult smokers understand this product as an acceptable less harmful alternative to cigarettes, to encourage them as they switch completely from cigarettes to IQOS, and to implement safeguards to minimize reach to unintended audiences.

We acknowledge FDA's broad oversight and welcome their input as we take on this responsibility and monitor IQOS's post-market impact.

Thank you for your time and attention. Now we'll have Moira return to wrap up the presentation.

MOIRA GILCHRIST

(Slide 107)

Thank you, Sarah. I'll now address the final piece of data related to impact on the population as a whole – Population Health Impact Modeling. FDA acknowledges the difficulties in making premarket assessments for the population as a whole. They encourage manufacturers to develop and apply innovative models to make preliminary estimates.

(Slide 108)

Consistent with FDA's guidance, we developed, validated, and published a Population Health Impact Model using well-established methods in epidemiological modeling and simulation analysis. The model incorporates two main components: the "Prevalence Component" and the "Epidemiological Risk Component." It's a counterfactual model based on the US smoking population between the years 1990 and 2010.

(Slide 109)

The Prevalence Component establishes a hypothetical population of Never, Current, and Former Smokers based on publicly available databases and scientific literature. We applied transition probabilities to this hypothetical population, including initiation, relapse, and cessation. We validated the prevalence component using actual smoking statistics for the corresponding time period. We used data from the studies outlined by Antonio to develop and include IQOS transition probabilities.

(Slide 110)

The "Epidemiological Risk Component" used the tobacco use histories generated by the Prevalence Component, together with estimates of the relative risk of developing ischemic heart disease, lung cancer, stroke, and COPD. Together, these account for more than three quarters of all smoking-related disease.

The model also incorporated the relative risk of IQOS use compared with cigarette smoking based on all of the evidence Manuel presented. We validated the Epidemiological Risk Component by comparing smoking-related deaths predicted by the model, with data from the Surgeon General's Report and other sources.

(Slide 111)

We conducted multiple simulations to estimate the impact of introducing IQOS in the United States. The simulations predicted that introducing the product with its claims would have resulted in a significant reduction in smoking-attributable deaths.

(Slide 112)

For our baseline simulation we assumed that IQOS delivers 90% of the benefits of smoking cessation. This assumption is based on the science in our application, which Manuel summarized earlier. We assumed that 15% of the smoking population would switch to IQOS within ten years, based on Antonio's data. The model predicted that more than 90,000 smoking-related deaths could have been averted within 20-years of introducing of IQOS.

We also ran simulations with more pessimistic assumptions. We wanted to identify events that would have to occur to overwhelm the public health benefit that could be achieved by introducing IQOS. For this to happen, the introduction of IQOS with its product messages would have to cause millions of non-smokers to start using combustible cigarettes, and prevent large numbers of current smokers from quitting. Nothing like this has happened in any country where IQOS is available. In fact, it's quite the reverse.
In Japan we're seeing dramatic decreases in cigarettes sales following the introduction of IQOS. Recently published data from Japan showed that cigarette sales declined by more than 18% in 2017, compared with a historical decline of 3 to 4% per year.
The only major change in the market was significant switching to heated tobacco products – predominantly IQOS.

No model can be perfectly precise, but these results demonstrate the potential for major population benefits over time.

(Slide 113)

The Population Health Impact Model, combined with: our perception and behavior assessment data, commercial and regulatory controls, and post-market surveillance plans for the US demonstrate that the likelihood and magnitude of IQOS benefitting the population as a whole is much greater than the opposite.

If ongoing monitoring suggests that a different outcome is likely, FDA has authority to swiftly modify or withdraw product authorization.

(Slide 114)

With IQOS, meaningful change is possible. It's not a perfect solution, but the statute doesn't require perfection. It calls for change and progress. It enables real-world solutions that are better than the status quo.

(Slide 115)

There's no question that never starting smoking or quitting are the best options. But for those people who would otherwise continue to smoke, your recommendation can help FDA apply the powerful tools given by Congress to change the status quo: millions fewer smokers; millions of changed lives; the potential for significant reductions in tobacco-related diseases; and an important step forward along the harm reduction pathway as called for by Congress and FDA.

Thank you. Mr. Chairman.

(Slide 116)

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