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20 January 2018

Mr. Mitchell Zeller
Director, Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Premarket Tobacco Product Application for IQOS System with Heatsticks

Dear Mr. Zeller:

The attached report from Goldman-Sachs suggests that FDA may make a decision on the Premarket Tobacco Product Application (PMTA) for Philip Morris's IQOS System with Heatsticks as soon as February.

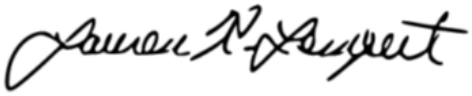
Although FDA has not set a formal procedure for the public to comment on the PMTA, we are submitting for FDA's consideration the ten public comments that we submitted previously to the docket for the MRTP application for IQOS (attached). These comments are as relevant to the PMTA for IQOS as they are to the MRTPA.

As you know, a central requirement for issuing a PMTA order under section 910(c)(4) is a finding by the FDA that issuing a PMTA is "appropriate for the protection of the public health" with respect to the risks and benefits to the population as a whole, considering both users and nonusers. This is the same standard required to issue a Modified Risk Tobacco Product (MRTP) order under section 911(g).
Taken together, these comments based on scientific evidence and analysis reach the conclusion that permitting IQOS to be marketed would not be "appropriate for the protection of the public health" with respect to the risks and benefits to the population as a whole, considering both users and nonusers. Lacking this essential finding, FDA is required to deny the PMTA under section 910(c)(2)(A).

We urge you to carefully review these comments before taking any final action. Additionally, we urge FDA to refer the PMTA to the Tobacco Products Scientific Advisory Committee (TPSAC) (per section 910(b)(2)) and review TPSAC's recommendations on the PMTA before taking final action.

Best wishes,

Stanton A. Glantz, PhD
Professor of Medicine
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education



Lauren Kass Lempert, JD, MPH
Law and Policy Specialist
Center for Tobacco Control Research and Education

Attachments:

1. Public comments submitted by UCSF concerning Philip Morris's MRTP applications for IQOS
2. Goldman-Sachs report on IQOS

Public Comments Submitted on Philip Morris International's MRTP applications for IQOS and Provided to TPSAC

1. Letter Mitchell Zeller protesting the way that the public comment period has been managed dated December 12, 2017

2. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes

3. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes

4. Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application

5. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

6. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims

7. PMI's MRTP application for IQOS does not adequately evaluate potential for liver totoxicity risk

8. PMI's MRTP Application for IQOS Does Not Consider IQOS's Appeal to Youth or Adolescents, or the Likelihood that Youth and Adolescents will Initiate Tobacco Use with IQOS or Use IQOS with Other Tobacco Products

9. The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product

10. Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS

11. Because PMI has not demonstrated that IQOS is associated with lower risks, FDA should not permit modified exposure claims, because such claims are likely to be misunderstood as modified risk claims

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December 12, 2017

Mr. Mitchell Zeller
Director, Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: 82 FR 27487, Docket no. FDA-2017-D-3001-3002 for Modified Risk Tobacco Product Applications: Applications for IQOS System With Marlboro Heatsticks, IQOS System With Marlboro Smooth Menthol Heatsticks, and IQOS System With Marlboro Fresh Menthol Heatsticks Submitted by Philip Morris Products S.A.; Availability

Dear Mr. Zeller:

We are writing to complain about the public comment process for the above-referenced docket on Philip Morris's modified risk tobacco product applications (MRTPA) for IQOS.

The initial June 15, 2017 Notice of Availability for public comment stated that FDA would accept comments on these extremely complex and lengthy applications until today, December 12, 2017 (180 days from the date the Notice was posted). However, FDA failed to make publicly available significant portions of the applications, including the Module 7 Scientific Studies and Analyses. On October 2, 2017, we requested that FDA extend the time period to comment by 180 days from the date that the complete applications have been made public.

On November 21, 2017, FDA issued a notice stating that once all the MRTPA documents – "including amendments" – are posted, FDA intended to issue a notice in the Federal Register announcing when the comment period would close, which would be no earlier than 30 days from the date the last batch of application documents – "including amendments" – is posted. Additional application documents were posted on November 28, 2017.

On December 8, 2017, FDA issued a Special Announcement entitled, "Clarification: No Deadline Set for Public Comments on Philip Morris Products S.A. MRTP Applications" which stated that "at this time, **there is no deadline for public comments** on these applications." However, the deadline set for comments to TPSAC members was not changed (written comments should be received by FDA by 4:00 p.m. on January 4, 2018).

FDA's announcement did little to "clarify" the situation. Instead, this announcement introduced even more confusion for the public and scientists, like us, who seek to carefully analyze the

complete applications and make meaningful comments to help inform FDA's decision on this very important matter.

We understand that FDA is engaged in continual discussions with Philip Morris about its MRTPA, and therefore expect that there will be amendments to the applications. The FDA's decision has created a situation in which the public has no way of knowing what or when amendments, if any, will be made. In addition, by doing so, FDA effectively turned the nominal 180 day comment period (which was reasonable in light of the magnitude and complexity of Philip Morris' application) into a 30-day comment period for the public to analyze new amendments that could be significant.

Given the complexity of the application and how the many parts relate to each other, it might not be easy to determine how changes in one part of the application affect the interpretation of other parts. One could also imagine a situation in which Philip Morris submitted amendments in a way that obscured these important linkages.

This situation puts the public in an even more difficult situation than the FDA did after posting application materials on November 28, 2017 with a 30-day deadline.

In effect the FDA has established short deadlines for the public who wish to comment on the applications, but not for the applicant who submitted the application. The deadline for public comment is not only inadequate to allow thorough examination and thoughtful consideration of the millions of pages of the application materials, but is also fundamentally unfair. Indeed, by permitting Philip Morris to continually amend its application (perhaps in response to comments and analyses we and others have already posted to the docket), FDA effectively accommodates the industry while limiting the ability of the public to participate in the process.

The scientists and experts at UCSF and our colleagues at Stanford and Georgia State University have worked hard and tried the best we could to examine the exceptionally complex application materials, and managed to submit 10 thorough public comments by today, December 12, the original deadline. We identified many serious problems with the applications, including demonstrating that Philip Morris' own data does not support several of its statements.

The FDA has granted Philip Morris an open invitation to amend its applications *ad infinitum*, and we, the public, are simply not in a position to continually track the changes that Philip Morris makes and continually adjust our comments. As a result, the current FDA policy has potentially compromised the value of the 10 comments we have submitted. The other alternative for us or other members of the public who have not yet completed their comments is to wait until the application is posted in full before beginning work on the public comments. The practical effect of doing so would be to cut the effective comment period to 30 days.

To be fair, the public should be given equal consideration to Philip Morris (or any future applicant) and allowed 180 days to submit comments from the date Philip Morris (or any future applicant) has certified that the applications are complete and final and the FDA has posted the compete application.

Also of particular concern, FDA set the deadline for submitting comments to TPSAC for January 4, 2018. This date is almost certainly before all the MRTPA materials (including amendments) will have been posted, and necessarily before the public will have a chance to analyze them and offer

meaningful comments to be considered by TPSAC and FDA at the TPSAC meeting scheduled for January 24-25, 2018.

In addition, to the extent that TPSAC discusses the substance of Philip Morris' still-open application, the FDA will have effectively converted TPSAC into an advisory committee to assist Philip Morris in refining its application prior to TPSAC's formal consideration of the complete application.

These deadlines make a mockery of both the MRTP public comment process as well as the TPSAC process, which are mandated by law in sections 911(e) and (f) of the Family Smoking Prevention and Tobacco Control Act. Neither the public nor TPSAC has been given the *complete* MRTP application materials, and neither the public nor TPSAC has been given enough time to examine the applications and make thoughtful comments or recommendations.

We therefore request that FDA:

1. Set a specific deadline by which all MRTPA materials, including amendments, shall be submitted and made publicly available;

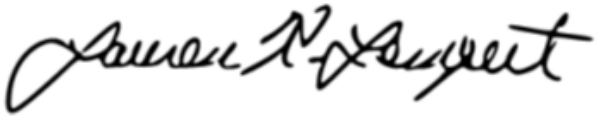
2. Extend the time for public comment to 180 days from the date that the applications are *complete and final* and made publicly available (i.e., all amendments have been posted); and

3. Remove the Philip Morris MRTP applications from the January TPSAC meeting agenda and schedule another TPSAC meeting to a time no sooner than 180 days from the date the applications are final so TPSAC will have a sufficient amount of time to review Philip Morris' application together with the public comments on the complete and final application

Absent such changes, FDA has established a process that is biased against the public interest and in favor of industry.

Respectfully,

Stanton A. Glantz, PhD
Professor of Medicine
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education



Lauren K. Lempert, JD, MPH
Law and Policy Specialist
Center for Tobacco Control Research and Education

attachment: List of public comments submitted by UCSF concerning Philip Morris's MRTP applications for IQOS.

Public Comments Submitted on Philip Morris International MRTP application for IQOS

1. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes

2. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes

3. Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application

4. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

5. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims

6. PMI's MRTP application for IQOS does not adequately evaluate potential for liver totoxicity risk

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8. The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product

9. Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS

10. Because PMI has not demonstrated that IQOS is associated with lower risks, FDA should not permit modified exposure claims, because such claims are likely to be misunderstood as modified risk claims

PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims

Stanton A. Glantz, PhD
Professor of Medicine
Principal Investigator, UCSF Tobacco Center of Regulatory Science
University of California San Francisco

Docket Number: FDA-2017-D-3001
November 13, 2017

In its application PMI presents data that it represents as showing that IQOS produces lower levels of toxic chemicals than conventional cigarettes and lower toxicological effects in animal studies. PMI also presents data on 24 biomarkers of potential harm *in human users* derived from two of their "Reduced Exposure" studies: ZRHR-REXA-07-JP in Japan, and ZRHM-REXA-08-US in the U.S. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function.

These human data are the most important information in the application because they represent direct evidence on how IQOS affects people. As summarized in Table 1 (page 3 of this comment) based on details in section 6.1.4.4 of the PMI MRTP application, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of these 24 biomarkers in Americans in PMI's studies. This is indicated by the fact that 23 of the 95% confidence intervals include zero (i.e., no statistically significant difference).

Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five percent of 24 tests is 1.2 tests, which means that one would expect 1 or 2 false positive results. PMI had one positive result (Soluble ICAM), which is what one would expect by chance.

Overall, PMI's own data supports the conclusion that IQOS is no different from conventional cigarettes in terms of effects on these biomarkers of potential harm in American people.

These results are more important than all the preclinical data (aerosol toxicity and animal studies) because they represent real people smoking the actual IQOS product.

It is also important to note that PMI did not do any of these conventional statistical tests which are routine for such scientific analysis. Rather they simply emphasize the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities. FDA should not tolerate it coming from a tobacco company.

The results reported in PMI's application for Japan are slightly more positive for IQOS, with 3 of 13 biomarkers showing differences from conventional cigarettes (where one would expect 1 false positive by chance). These results are not strong enough to warrant drawing a conclusion of modified risk. More important, the US results are more relevant to Americans because of potential biological differences in response between Japanese and US people.

These conclusions are based on taking PMI's results at face value. Although PMI summarized the results of the ZRHR-REXA-07-JP and XZRHM-REXA-08-US Clinical Risk Endpoint (CRE) studies in Module 6.1.4 CRE, the actual studies themselves have not yet been released. Because the FDA has not yet released these and other PMI clinical studies in Module 7, it is impossible to comment on what pro-IQOS biases may have been built into the study design.

Section 911(g)(1) of the Tobacco Control Act states that FDA may issue an order authorizing marketing of a modified risk product "*only if* … the applicant has demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users." ***PMI has failed to meet this statutory requirement. FDA must deny PMI's application to market IQOS as a modified risk tobacco product because PMI's own data fails to support a modified risk claim in people who are actually using the product.***

Table 1. Summary of Philip Morris Studies of Changes in Biomarkers in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis)		
	Japan	US
Inflammation (6.1.4.4.2*)		
White Blood Cell Count (WBC)	-0.57 GI/L (-1.04, -0.10)	0.17 GI/L (-0.47, 0.81)
C reactive protein (CRP)	6.41% ↓ (-40.75, 37.77)	16.23% ↓ (-21.69, 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓** **(2.05, 14.94)**	**10.59% ↓** **(4.03, 16.71)**
Fibrinogen	5.42% ↓ (-1.80, 12.13)	1.63% ↓ (-6.42, 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓** **(2.55, 21.81)**	13.46% ↓ (-1.95, 23.61)
11-DTX-B2 = 11-dehydro-thromboxane B2 (11-DTX-B2)	5.42% ↓ (-1.80, 12.13)	3.56% ↓ (-23.31, 24.57)
Cholesterol and Triglycerides (6.1.4.4.4)		
High density lipoprotein-cholesterol (HDL-C)	**4.53 mg/dL** **(1.17, 7.88)**	1.4 mg/dL (-2.3, 5.0)
Low density lipoprotein-cholesterol (LDL-C)	0.87 mg/dL (-6.55, 8.30)	-3.3 mg/dL (-12.0, 5.4)
Total cholesterol	2.00 mg/dL (-6.68, 10.67)	-4.0 mg/dL (-13.3, 5.2)
Triglycerides	-6.25 mg/dL (-21.20, 8.69)	0.9 mg/dL (-12.8, 14.6)
Apolipoprotein A1 (Apo A1)	NA	3.1 mg/dL (-4.6, 10. 7)
Apolipoprotein B (Apo B)	NA	-1.6 mg/dL (-7.24, 4.03)
Physiological measures		
Systolic blood pressure	-0.59 mmHg (-3.80, 2.62)	-0.7 mmHg (-4.5, 3.1)
Diastolic blood pressure	-0.68 mmHg (-3.04, 1.69)	0.2 mmHg (-3.7, 4.0)
Lung Function (6.1.4.4.5)		
Forced expiratory volume in 1 second (FEV_1)	1.91 %Pred (-0.14, 3.97)	0.53 % Pred (-2.09, 3.00) 0.05 L (-0.06, 0.15)
FEV_1/FVC (FVC=forced vital capacity)	NA	0.00 (-0.02, 0.02)
Mid expiratory flow (MEF 25-75) (L/s)	NA	-0.67 (-6.33, 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mmHg)	NA	0.31 (-1.09, 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (-0.02, 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (-0.25, 0.43)
Functional residual volume (FRV) (L)	NA	-0.09 (-0.31, 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (-0.08, 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00, 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1
*Section of Philip Morris International's Modified Risk Tobacco Product application. The results are either IQOS:CC or IQOS-CC; CC = conventional cigarettes **Bold** results are statistically significant differences (P<05)		

THE CONVERSATION
Academic rigor, journalistic flair

Philip Morris hides data in plain sight on dangers of new heat-not-burn product

November 28, 2017 9.26pm EST

Sleek IQOS store in Korea. Minji Kim, Ph.D., CC BY-SA

Author

Stanton Glantz

Professor of Medicine, University of California, San Francisco

For as long as smoking has been known to cause cancer and other diseases, Big Tobacco has worked to avoid the truth about its deadly and highly addictive products.

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease.

Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make "safer cigarettes" since the 1960s.

They have also developed products that avoided burning, including products that heat the tobacco

without combustion, e-cigarettes and even nicotine replacement therapy.

Philip Morris International's IQOS is the latest entry into this sweepstakes.

IQOS is a hand-held electric device that generates its nicotine aerosol by heating a stick of ground tobacco and chemicals without setting the tobacco on fire. IQOS does not burn the tobacco, so it produces fewer toxic chemicals than a cigarette.

A man smokes an IQOS. ThamKC/Shutterstock.com

Because IQOS is a new tobacco product, it needs the Food and Drug Administration's approval to sell it in the United States. Philip Morris submitted its massive application to the FDA on May 24, 2017. As required by law, FDA has made most of the application available for the public to review. The FDA will then consider the comments to determine if IQOS "as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users" and to the population as a whole. FDA can approve IQOS only if it meets this standard.

As someone who has worked in tobacco control for decades, I plowed through the application to see what information Philip Morris presented. To my surprise, I found (and told the FDA) that Philip Morris's own application shows that in American people there is no statistical difference in the harm caused by IQOS product and traditional cigarettes.

Bad stuff gets in your lungs either way

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease.

And the adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous. This effect is why smoke-free environments are followed by big drops in heart attacks despite the fact that secondhand smokers breathe in much less smoke that the smokers.

Nevertheless, Philip Morris is aggressively marketing IQOS all over the world on the grounds that it is not as bad as a cigarette because "the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke."

Independent research has found higher levels than Philip Morris claims. Fewer toxic chemicals, however, do not necessarily translate into lower harm.

In the United States, Philip Morris wants to sell IQOS with claims that "Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases" and "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."

To support these claims, Philip Morris's application presents data on toxic chemicals and effects in animals. Most important, Philip Morris reports medical tests that doctors use to assess people's health in people using IQOS.

These 24 medcial tests include blood (cholesterol, inflammation, oxidative stress), blood pressure and lung function. They are the most important information in the application because they represent direct evidence of how IQOS affects people who use them.

A health hazard by any other name

I closely examined Philip Morris's results. They show that there is no statistically detectable difference between IQOS and conventional cigarettes in these medical tests in the Americans Philip Morris studied.

Like all medical tests, there is uncertainty in the results. This range of uncertainty is what statisticians call the 95 percent confidence interval and journalists call "the margin of error."

For 23 of the medical tests, the margin of error in the tests to discern the difference between IQOS and conventional cigarettes included a zero (i.e., no difference). So neither we nor the FDA can be 95 percent confident that IQOS are better for people than conventional cigarettes in those cases.

Moreover, when using the conventional 95 percent confidence standard, one would expect 5 percent

of the tests to yield false positives or 1 out of 24 tests. That is exactly what Philip Morris reported.

In other words, Philip Morris's own data demonstrate that IQOS is no different from conventional cigarettes in terms of effects on these medical tests in American people.

Too hot to cook your turkey

This is not surprising, because IQOS heats the tobacco to 660° Fahrenheit (350° Celsius). That's well below the 1,100°F for combustion, but it is still hot enough to cause chemical reactions known as pyrolysis. Pyrolysis is what turns a turkey baked at 350°F into Thanksgiving dinner. Imagine if you had eaten a turkey cooked at IQOS's 660°F!

These conclusions are based on taking Philip Morris's results at face value, ignoring the fact that the tobacco industry, including Philip Morris, has a long history of manipulating scientific study designs and statistical analysis to get the results they want.

And there is already independent evidence that IQOS compromises functioning of arteries, a key risk factor for heart disease and heart attacks, as badly as a cigarette.

Because Philip Morris's medical tests in humans failed to show that IQOS "as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users," I believe the FDA must deny Philip Morris's application to protect the public health.

Philip Morris's application did include one accurate statement: "The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use." Of course, if people did that, Philip Morris would not make any more money from them.

Smoking **FDA** **Lung cancer** **Big tobacco** **Tobacco control** **Smoking cessation** **Philip Morris**

The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes

Matthew L. Springer, Ph.D., Pooneh Nabavizadeh, M.D., and Leila Mohammadi, M.D., Ph.D.
Department of Medicine, Division of Cardiology
Cardiovascular Research Institute
UCSF Tobacco Center of Regulatory Science
University of California, San Francisco
Docket Number: FDA-2017-D-3001
November 20, 2017

Philip Morris Products S.A. (PMP S.A.) modified risk tobacco product (MRTP) applications[1-3] for its heat-not-burn product IQOS (also designated iQOS and THS2.2) in the United States claim that IQOS does not adversely affect the functioning of the vascular endothelium. The endothelium consists of cells lining arteries that play an important role in controlling normal functioning of arteries (vascular function). Abnormal endothelial function increases the risk of heart disease and heart attacks. ***The evidence that PMI presents is misleading and does not support the conclusion that IQOS will not harm endothelial function. In addition, new independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes.***

This comment focuses on PMI's assertion that IQOS aerosol exposure involves less cardiovascular risk than smoke exposure. PMI researchers have published studies that compare the effects of tobacco smoke and IQOS aerosol on various physiological systems at the cell, animal, and clinical levels (for example, Smith et al.[4]). The conclusions that they draw from these studies all point toward IQOS being substantially less harmful than cigarettes. ***However, some of the criteria used in these studies are incongruous with expected and established physiological assays.***

In addition, PMI's descriptions of their research findings in the MRTP application are worded to imply that IQOS is not harmful to vascular endothelial function known to be caused by tobacco smoke. However, this implication is unsupported because PMI has not performed the most physiologically relevant tests. ***PMI has not shown that IQOS aerosol exposure leads to less vascular endothelial dysfunction than cigarette smoke exposure.***

Endothelial function assessed by arterial flow-mediated dilation (FMD) is a validated measure of cardiovascular health effects. FMD is the process by which arteries dilate (get larger) in response to increased blood flow.[5, 6] The endothelial cells that line the arterial wall mediate blood flow to peripheral tissues and the heart by producing nitric oxide (NO) and other factors that lead to vasodilation. Endothelial cells sense increased blood flow because of increased friction of the liquid against the lining of the artery (shear stress) as blood flow velocity increases, and the cells respond by activating the enzyme endothelial nitric oxide synthase (eNOS), which creates NO, leading to FMD.

FMD is quantified by ultrasound in humans as the percent vasodilation of the arm's brachial artery in response to restoration of blood flow after transient occlusion.[7] FMD is a well-established clinical prognostic indicator of endothelial function that is concordant with other measures of cardiovascular health such as risk of myocardial infarction.[6-9] Brachial artery FMD

correlates with endothelium-dependent vasodilation of the coronary arteries[10] and with a number of adverse cardiovascular outcomes including myocardial infarction and atherosclerosis[11-13] that are increased by cigarette smoke. In a seminal pair of papers in the 1990s, David Celermajer and colleagues showed that both smoking and chronic exposure to secondhand smoke (SHS) impair FMD.[14, 15] Juonala et al.[16] reported that FMD was impaired in young adults whose parents were smokers 19-27 years earlier. Several groups including ours and our collaborators have shown that a 30-minute exposure to SHS at real-world levels impairs FMD in humans.[17-19] In a rat model of FMD, we have shown that exposure to realistic levels of sidestream smoke from tobacco cigarettes, filtered little cigars, and marijuana cigarettes with and without cannabinoids (but not exposure to clean air) impairs FMD, an effect that occurs after as little as one minute of exposure.[20-22] ***In short, measurement of FMD is a common test to determine whether inhalation of aerosols leads to chronic or acute endothelial dysfunction, and FMD measurement is expected to be included in the basis of any claims that a tobacco product does not negatively impact endothelial function.***

PMI's studies of endothelial function are based on isolated cell properties in culture and on biomarkers, and do not directly test for endothelial dysfunction potentially caused by IQOS aerosol inhalation. PMI claims to have studied the relative effects of IQOS aerosol and cigarette smoke on mechanisms involved in endothelial function, with the conclusion that IQOS exposure is more benign than cigarette smoke exposure in this regard. Notably, PMI's studies of endothelial functional properties are on the level of cell culture and address the integrity of endothelial cell monolayers and monocyte efflux as well as molecular changes.[23, 24] Their rodent studies addressed long-term differences in atherosclerotic plaque. Their clinical investigations include measurements of soluble intercellular adhesion molecule-1 (sICAM-1) as a biomarker indicative of endothelial dysfunction.[25] ***Importantly, neither their clinical nor animal studies include measurements of FMD.***

Their published reports have been carefully worded to avoid saying that IQOS does not cause endothelial dysfunction, but the MRTP application makes the claim that the systems toxicology studies reported in the application "cover a variety of human-derived in vitro model systems comparing the impact of THS aerosol with that of cigarette smoke on vascular inflammation, *endothelial dysfunction* and airway epithelium toxicity" (PMP S.A. MRTP application Executive Summary, Section 2.7, page 11). ***The conclusion that IQOS aerosol induces less endothelial dysfunction is not supported by their studies.***

FMD in rats exposed to undiluted IQOS aerosol is impaired to the same extent as in rats exposed to cigarette smoke. Our work[26, 27] demonstrated that ***ten 5-second exposures of rats to IQOS aerosol over a 5 minute period substantially impaired FMD to the same extent as similar exposure to cigarette smoke.*** Our exposure conditions were designed to approximate the use of a single IQOS HeatStick, with identical exposure conditions for the cigarette exposures. To confirm that our exposure conditions were relevant to real-world use, we measured blood levels of nicotine immediately after and 20 minutes after the end of the brief exposure, and determined that the nicotine concentrations after one complete cigarette exposure period were comparable to the blood levels in humans after smoking a single cigarette.

This validated our conditions for inhalation of undiluted cigarette smoke by the rats, and by extension, the relevance of our comparable conditions for inhalation of IQOS aerosol.

These results were presented on November 14, 2017 at the American Heart Association annual Scientific Sessions. Their press release containing a more detailed description of these findings (attachment #1), as well as the poster presentation itself (attachment #2), are appended at the end of this comment after the references.

Conclusion. Unless PMI is able to provide results from humans or living animals showing that IQOS aerosol exposure leads to less vascular endothelial dysfunction than cigarette smoke exposure, PMI's MRTP application should not claim nor imply that IQOS carries reduced risk for vascular endothelial function.

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ATTACHMENT #1: AHA PRESS RELEASE

Heat-not-burn tobacco products may be 'not so hot' at protecting blood vessel function

Tuesday News Tip Poster Presentation T1051 Session: AT.APS.28.

Embargoed until time 12 p.m. PT/ 3 p.m. ET, Tuesday, Nov. 14, 2017

This news tip contains updated study information not reflected in the abstract.

ANAHEIM, California, Nov. 14, 2017 — Heat-not-burn devices may eliminate users' exposure to tobacco smoke, but the vapor they produce has the same negative impact on blood vessel function as smoking, according to a preliminary animal study presented at the American Heart Association's Scientific Sessions 2017, a premier global exchange of the latest advances in cardiovascular science for researchers and clinicians.

Heat-not-burn products are not new, but have been recently updated and test marketed in several countries outside the United States with greater success. Despite tobacco industry claims of heat-not-burn products being less harmful than regular cigarettes, the health effects of the devices are still unproven, according to researchers.

Heat-not-burn devices raise the temperature of tobacco enough to release nicotine-containing vapor but not enough to burn, avoiding smoke exposure. To test the devices' ability to reduce harm, researchers assessed whether exposure to the vapor affects the ability of rats' blood vessels to widen when there is increased blood flow – a measure of blood vessel health that is impaired with exposure to smoke from cigarettes, small cigars and marijuana.

Researchers found:

- After ten 15-second exposures over five minutes to the vapor from iQOS, a heat-not-burn device that has been test-marketed in several countries, blood vessel function decreased by 58 percent.
- Similarly, after ten 5-second exposures over five minutes to iQOS vapor, blood vessel function decreased by a similar amount, 60 percent.
- The reduction was comparable to that induced by cigarette smoke (57 percent for the 15-second exposures, 62 percent for the 5-second exposures).
- Exposure to clean air had no impact on blood vessel dilation.
- The amount of nicotine in the rats' blood after exposure to cigarette smoke was similar to the amount in blood after humans have smoked one cigarette, confirming that the

exposure conditions were relevant to the real world. However, the amount of nicotine in the blood after exposure to iQOS vapor was substantially higher (70.3 nanogram/milliliter for iQOS, 15.0 nanogram/milliliter for cigarettes).

Using heat-not-burn products may not avoid the adverse cardiovascular effects of smoking cigarettes.

The research was conducted by Pooneh Nabavizadeh, M.D. in a group led by Matthew L. Springer, Ph.D. Other contributors were Jiangtao Liu, M.D., Sharina Ibrahim, B.Sc. and Ronak Derakhshandeh, M.S.

The study was funded by the National Heart, Lung, and Blood Institute at the National Institutes of Health and the U.S. Food and Drug Administration Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA.

Presentation Location: Basic Science Section, Science and Technology Hall

ATTACHMENT #2: AHA POSTER PRESENTATION

Inhalation of Heat-Not-Burn Tobacco Aerosol Impairs Vascular Endothelial Function

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Introduction: "Heat-not-burn" (HNB) tobacco devices heat tobacco at temperatures that avoid combustion but cause the nicotine to aerosolize, leaving the leaf material intact but depleted of volatile substances. A new HNB product, iQOS, from Philip Morris, has been test marketed in several non-US countries and has been considerably more successful than previously introduced HNB products[1]. Despite harm reduction claims by the tobacco industry[2], the health effects of HNB products are incompletely understood. Notably, industry-supported studies of potential cardiovascular consequences of HNB aerosol exposure published to date[3] have not included some common measures of adverse effects of smoke exposure, such as vascular endothelial function tested in vivo[4].

Figure 1. iQOS. *iQOS is composed of three main parts: HeatStick, holder, and pocket charger. HeatSticks are inserted in the holder, which contains an electronic heating blade to heat tobacco and release aerosol. HeatSticks contain strips of processed and reformed tobacco. (Photo: M. Springer)*

Methods: We exposed rats (n=8/group) via nose cone to iQOS aerosol, Marlboro cigarette mainstream smoke, or clean air as a control, ten times over 5 min to approximate the consumption of a single iQOS HeatStick. Exposure conditions were 15 seconds and 5 seconds twice per minute. To generate the aerosol and mainstream smoke, we used a manual system for the 15-second and an analytical vaping machine for the 5-second exposure (Figure 2). Arterial flow-mediated dilation (FMD) was quantitated pre- and post-exposure by measuring femoral artery diameter with micro-ultrasound before and after 5 min of transient surgically induced ischemia, and expressed as the percent vasodilation[5,6] (Figure 3). Serum samples were collected after the exposure and assessed for nicotine and cotinine levels.

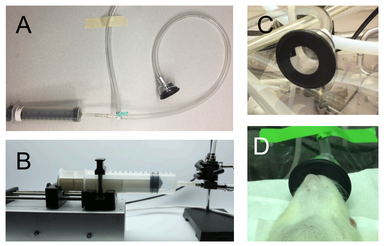

Figure 2. Aerosol generator and exposure systems. *A. Manual exposure system; B. Analytical vaping machine made by Gram Research Technology; C. iQOS aerosol coming out of nose cone; D. Rat's nose placed in the nose cone.*

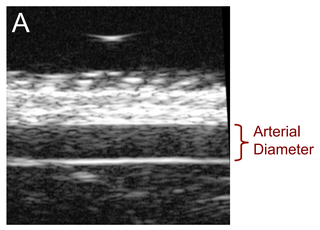

Figure 3. Arterial Flow-Mediated Dilation. *A. Ultrasound imaging of rat femoral artery; B. FMD experimental design.*

Results: FMD was impaired comparably by 5-second exposures to iQOS aerosol (9.6±1.0(SD)% pre-exposure vs. 3.8±2.6% post-exposure, p=.0001 by 2-tailed paired t-test) and cigarette smoke (11.2±2.6% pre-exposure vs. 4.2±2.3% post-exposure, p=.0005). 15-second exposures to iQOS aerosol and cigarette smoke impaired FMD to a similar extent (10.6±2.9% pre-exposure vs. 4.5±1.9% post-exposure, p=.0008; and 10.6±2.0% pre-exposure vs. 4.6±1.3% post-exposure, p=.0004, respectively). FMD was not affected in the clean air control group (8.3±1.9% vs. 8.8±4.5%, p=.82) (Figure 4). The percent FMD impairment was not significantly different in groups exposed for 5 seconds compared to 15 seconds (p=.27).

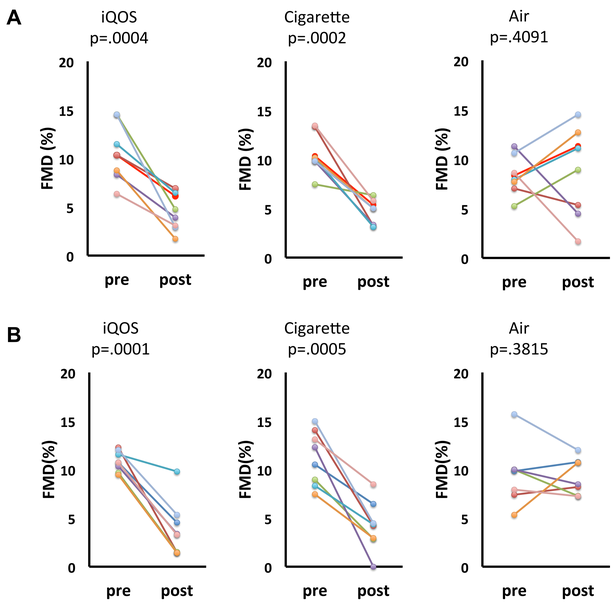

Figure 4. FMD was impaired by mainstream cigarette smoke and iQOS aerosol. *A. Ten 15-second exposures. B. Ten 5-second exposures.*

Results (continued): Nicotine levels in the 5-second cigarette group were similar to the amount in blood after humans have smoked one cigarette, confirming that the exposure conditions were relevant to real-world smoking. Serum nicotine and cotinine levels were significantly higher in the iQOS-exposed group compared to the cigarette-exposed group (Figure 5).

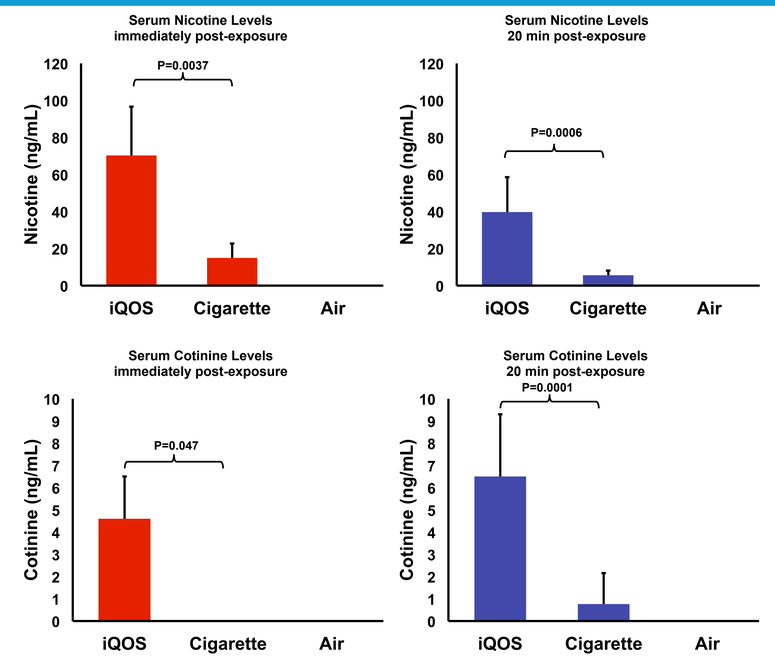

Figure 5. Serum nicotine and cotinine levels immediately and 20 min post-exposure.

Conclusion: We conclude that acute exposure to iQOS aerosol at doses relevant to real world use can substantially impair endothelial function in rats comparably to cigarette smoke despite the absence of combustion. Use of HNB tobacco products does not necessarily avoid the adverse cardiovascular effects of smoking cigarettes.

Funding: This work was supported by grant R01HL120062 from the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA.
Disclosures: none

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Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application

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UCSF TCORS

Docket Number: FDA-2017-D-3001

November 22, 2017

To be granted an MRTP order under section 911(g) of the Family Smoking Prevention and Tobacco Control Act, Philip Morris (PM) must demonstrate that the marketing of its IQOS product will or 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." For its modified exposure claim, PM must further demonstrate that issuance of an exposure modification order would be "appropriate to promote the public health." Therefore, FDA recommends that an MRTP application should contain *"an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole."* In particular, FDA recommends that applicants submit "quantitative estimates of the effect the marketing of the product, as proposed, may have on the health of the population as a whole." (Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, page 21). In an effort to meet this requirement, PM created its "Population Health Impact Model" (PHIM), a computational model that purports to estimate the potential impact on public health of marketing its IQOS as an MRTP.

However, PM has not met its burden to demonstrate that a MRTP order would "benefit the health of the population as a whole" or "promote the public health" because its PHIM makes several questionable assumptions, leaves out some important measures of health impact, and relies heavily on research funded by the tobacco industry. It ignores risks to individuals other than the product user, compares risks only to those of cigarettes, focuses on deaths from only 4 diseases, ignores nonfatal disease incidence, ignores healthcare costs, and makes a number of other questionable assumptions. Our detailed comments on each of these issues follow.

Risk to others is ignored. The PHIM model uses individual risk times prevalence to derive population harms. It ignores risk to others, such as secondhand exposure from IQOS products. PM alleges that "we [PM] do not account for environmental tobacco smoke exposure, where we showed earlier (Weitkunat 2015)[1] that, whether or not the MRTP reduces the risk from ETS exposure would have little effect on the estimated drop in mortality associated with MRTP introduction" (Module 6, Section 6.5.5, page 41). The work cited was funded by the tobacco industry, and needs to be verified in independent work. It is also unclear what the authors mean, given that it is known that secondhand smoke exposure from cigarettes results in over 42,000 deaths a year in the US alone.[2] It seems likely that IQOS products would also cause mortality in non-users who are exposed.

Reduced risk compared to what? The PHIM considers only 5 tobacco use behaviors – never smoking, current cigarette smoking, current MRTP use, current dual use (MRTP and cigarettes), and former use (of cigarettes or MRTP or dual use of cigarettes and MRTP). The model ignores other tobacco products, such as e-cigarettes, which PM and other tobacco interests consistently argue have substantially lower risk of illness and death than cigarettes. Thus, the comparison in PM's analysis is only between a higher risk product (cigarettes) and what PM claims is a lower risk product (its IQOS Tobacco Heating System or "THS"). The results would be very different if the comparison were with a lower risk product (e-cigarettes), and it is likely that some e-cig users would be lured to heat-not-burn (HNB) products, suggesting that such a comparison is reasonable. PM acknowledges that

> "the Prevalence Component only accounts for the use of cigarettes and an MRTP, and does not consider other tobacco products, such as cigars, pipes or smokeless tobacco. Failure to do so might cause some bias in estimating the reduction in deaths attributable to an MRTP if CC smokers switching to an MRTP tend to change their use of these other products. However, unless evidence emerges that this occurs to any material extent, no attempt will be made to account for this possibility, as this would make the estimation process extremely complex and highly unreliable due to the number of assumptions required and the interactions between the smoking statuses."

While we acknowledge that data on the risks of products such as e-cigarettes are only now becoming available, there have been studies on the risks associated with cigar use and smokeless tobacco use. PM is willing to assume that the relative risks of death from use of IQOS is a fraction of the risks of death from cigarette smoking. They could easily conduct a sensitivity analysis by assuming the relative risk of death from e-cigarette smoking is a fraction of the risk from cigarette smoking, using reasonable estimates of the risk ratio.

It is not acceptable for PM to say that there is no evidence that switching from products other than cigarettes might occur. Evidence is available from other countries and for products that may be similar to IQOS. In Japan, where IQOS products are now available, over one-third of IQOS users are poly-users, most of whom also smoke cigarettes.[3] Our analyses of the 2012-2014 National Adult Tobacco Surveys indicate that 80.9% of e-cigarette users are poly-users, most of whom also smoke cigarettes. Thus, the behavior of IQOS users, including poly-use with conventional cigarettes and other tobacco products, can be included in modeling the impact of this new product on health.

The PHIM assumes cigarette users will switch to IQOS use exclusively. The model assumes zero probability that the user will switch to cigarettes or become a dual user of cigarettes and IQOS (Module 6, Section 6.5.3.4, page 25). This is not a reasonable assumption. As described above, we already have contrary evidence from IQOS use in Japan and from e-cigarette use in the U.S. Poly-tobacco use, the use of 2 or more tobacco products, is common, and was reported by 3.9% of the adult population in 2015.[4] There is a growing and substantial literature showing that those who initiate tobacco use with e-cigarettes may go on to smoke cigarettes,[5] and that those who use e-cigarettes remain dual users rather than quitting conventional cigarettes.[6] IQOS is likely to have a similar impact.

The PHIM includes only deaths, ignoring disease incidence. However, to be granted an MRTP order, section 911(g)(2)(B)(ii) requires PM to demonstrate that the "reasonably likely overall impact of use of [IQOS] remains a *substantial and measurable reduction in overall **morbidity*** and mortality among individual tobacco users." While smoking causes nearly 500,000 deaths a year in the US,[7] the morbidity burden is much larger, with 6.9 million US adults reporting smoking-related diseases in 2009.[8] Asthma, for example, a disease known to be exacerbated by smoking, impacted 18.4 million US adults in 2014 and caused 3,651 deaths.[9] Ignoring disease morbidity resulting from IQOS use grossly underestimates its impact on health.

Only 4 diseases are included in the PHIM. The model considers only 4 diseases caused by smoking – lung cancer, ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD). PM acknowledges that "overall estimates of deaths saved due to the introduction of IQOS would have to be increased about 50% to give an estimate for all smoking-related diseases combined" (Module 6, Section 6.5.5, p. 41). This makes it clear that the estimate provided of deaths is a gross underestimate. At least 22 causes of death for adults[10] and 4 causes of death for infants[11] have been causally linked to cigarette smoking. Studies need to be conducted to investigate whether there are other diseases that may be associated with IQOS products.

Relative risk estimates are all derived from studies funded by Philip Morris, but better estimates are available. All the studies cited for the excess relative risk estimates are conducted by Peter N Lee and colleagues, British researchers at a private consulting firm (P N Lee Statistics and Computing Ltd) that is funded by Phillip Morris. Many of these studies are published in the journal *Regulatory Toxicology and Pharmacology*, a journal recently found to show bias in favor of the tobacco industry, publishing mostly work funded by the industry and reaching conclusions that favor the industry in 96% of papers.[12] The PHIM uses relative risk (RR) of death for cigarette smokers relative to never cigarette smokers from 4 smoking-related diseases (lung cancer, IHD, stroke, and COPD). However, rather than use the estimates published by the Surgeon General of the US,[7] they rely on estimates from a published meta-analysis by Forey and colleagues[13] involving 39 North American studies (see Module 6, Section 6.5.3.5, page 28) while the 2014 US Surgeon General Report's[7] RR estimates were based on US cohorts (See Module 6, Section 6.5.3.5, Table 7, and Module 6, Section 6.5.6, page 44). PM claims that their RR estimates are better. However, the PM estimates come from a study funded by Philip Morris and conducted by Lee and colleagues. The PHIM model needs to be based on findings from independent research that is not funded by the tobacco industry. ***The Surgeon General estimates, which are larger and independently vetted through a more thorough process of independent peer review than the Forey estimates, are more appropriate and should be used in all analyses.***

The PHIM assumes that the Relative Risk (RR) of death from IQOS is a fraction of the RR of death from cigarette smoking. Because the RR of death caused by the 4 smoking-related diseases for users is not known, the authors replied upon a "fraction" measure called "the relative exposure of IQOS compared to smoking cigarettes", denoted by "*f*" (see page 6, Table 5 on page 19, and pages 22-23). They developed some clinical and non-clinical models, and estimated that the mean value of "*f*" is 0.35 and the median value is 0.30. Afterwards, in their simulations, they used *f* -values between 0.1 and 0.3. ***This is a KEY assumption used in their***

approach: whatever the RR value of cigarette smoking for death, they multiplied that RR value by the f -value (0.1 to 0.3). As a result, the use of the MRTP yields far fewer attributable deaths compared to cigarette smoking. The validity of this assumption needs to be investigated by independent researchers. PM also cites an industry funded study by Weitkunat[1] (Module 6, Section 6.5.1, page 6).

Moreover, with a single exception, the clinical results included in the MRTP application do not show statistically significant improvements in the biomarkers of harm that PM assessed in actual people. Thus, even when taken uncritically at face value, PM's own application does not support assertions of reduced harm, much less the 70% to 90% reductions in risk that their model assumes.[14]

The RR of death for dual use is arbitrarily assumed to be the mean of the risk of cigarette smoking plus the risk of IQOS use (see Module 6, Section 6.5.3.2, page 19, Table 5). The basis for this assumption seems unclear and this approach is highly simplified. There is some evidence that dual users have greater risks of negative health outcomes than sole cigarette users,[15, 16] which suggests that the PHIM model would lead to an underestimate in the number of deaths attributable to use of cigarettes and IQOS.

The PHIM model doesn't consider the impact that IQOS product use might have on people with pre-existing conditions. Cigarette smoking and e-cigarette use among people with cardiovascular disease (CVD) or respiratory diseases have been shown to worsen their health outcomes and increase their healthcare costs.[7, 17] One study reported that ongoing tobacco use was associated with worsened ischemic conditions.[18] Another study found that patients with peripheral artery disease who smoked were more likely to be hospitalized, and had higher annual healthcare costs, than those who didn't smoke.[19] It is likely that IQOS use would have a similar negative impact on those whose health is already compromised.

E-cigarettes, a product with lower disease risks than cigarettes, have been found to have additional independent negative health impacts even among cigarette smokers. We compared the prevalence of symptoms among adult users and nonusers of e-cigarette users. Even after controlling for cigarettes smoked per day, e-cigarette users had greater odds of symptoms including wheezing and shortness of breath.[15] PM needs to present data that the IQOS aerosol is different enough from e-cigarettes to avoid these effects or include them in its models. And PM also needs to determine whether there are other health effects associated with IQOS use.

The PHIM completely ignores healthcare costs. One way of quantifying the impact of illness is through healthcare costs. Cost measures incorporate the severity and time course of illness. There are many published studies that document methods for estimating healthcare costs attributable to tobacco use.[20-25] ***Ignoring healthcare costs is a major flaw in the PHIM and a major omission in this MRTP application.***

The PHIM completely ignores possible health impacts of IQOS use on young adults. Related to the point above (omission of health care effects not related to fatal diseases), the model ignores health effects of increased use of e-cigarettes and cigarette smoking among young adults. Research has found substantial increase in utilization of hospital services (for

reasons other than pregnancy or injury) in young adult smokers, including those in their 20s.[26] The MRTP application assumes there are no health effects in the population under 30. Youth and young adults who use products may suffer health effects, experience premature mortality, and incur healthcare costs. ***Leaving young people out of the model will lead to an underestimate of the impact of IQOS use on health.***

The PHIM completely ignores any health impact of use on children. Children are likely to be impacted by the product in several ways. First, children are likely to suffer negative health effects when exposed to their parents' secondhand smoke.[27-29] A recent literature review identified a number of toxic compounds in e-cigarette aerosol in addition to particulate matter, indicating that the aerosol can be harmful to human health.[30] Thus, the vapor from IQOS is likely to be harmful as well and should be investigated. Second, women who use IQOS while pregnant may cause lifelong health impacts for their children, as is known to be the case for women who smoke cigarettes or use snuff while pregnant.[31-33] Other risks to children from IQOS use include fires and explosions, such as those that occur with e-cigarettes, and nicotine poisoning from the product such as the poisoning that has occurred from e-liquids.

The PHIM completely ignores any impact of IQOS use on uptake of cigarette smoking by youth and young adults. If IQOS products are marketed as a MRTP, this may impact tobacco use initiation among youth and young adults who would never initiate tobacco use if the IQOS product is never allowed in the market. Youth have initiated tobacco use with e-cigarettes at unprecedented rates,[34] and may find the IQOS product to be similarly appealing. The PHIM application assumes that uptake of the MRTP will be limited among youth because of the relatively high cost. However, this assumption ignores shared use among users, as occurs with cigarettes and hookah. There is consistent and strong evidence that e-cigarette use among adolescents and young adults increases subsequent uptake of cigarette smoking.[5] One of the claims about IQOS in this application is that IQOS mimics cigarette smoking better than e-cigarettes or vaping because of more rapid nicotine delivery. Therefore, even if the rate of purchase of the IQOS is lower among youth than cheaper cigarettes, e-cigarettes or vaping devices, IQOS may be much more effective at addicting youth and young adults to nicotine as well as increasing transition to cigarette smoking among youth who experiment with shared devices. A net increase in nicotine addiction and cigarette uptake among adolescents and young adults is a realistic possibility that this application ignores.

Conclusion: The Population Health Impact Model underestimates the health impact of IQOS products and the model predictions do not justify the MRTP claim. The model does not meet the FDA's recommendation for MRTP applications that they contain *"an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole"* (Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, page 21). In Philip Morris' own words, the "PHIM has been developed to estimate the reduction in mortality from the four major smoking-related diseases (lung cancer, IHD, stroke and COPD) that would occur over a period following the introduction of a MRTP" (Module 7, Section 7.4, page 1). This is contrary to the requirement that the application consider morbidity and mortality and the population as a whole. The model omits many important factors, including morbidity impacts, healthcare

costs, risks to nonusers, impact on children, mortality from diseases other than the 4 considered, impacts on people with pre-existing conditions, and likely dual- and poly-use patterns. The analyses presented compare IQOS to cigarette smoking, while many users are likely to be e-cigarette and other tobacco product users, resulting in a very different change in risk.

PM's so-called Population Health Impact Model greatly underestimates the impact of IQOS products on the market and does not show a positive impact on the health of the population as a whole. The application should be denied.

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Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

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Docket Number: FDA-2017-D-3001

November 29, 2017

Philip Morris Products SA, a subsidiary of Philip Morris International (collectively referred to as PMI hereafter), has recently submitted a "modified risk tobacco product" (MRTP) application to the FDA for review and approval of IQOS. (We refer to the product as IQOS in this comment in place of tobacco heating system, THS 2.2.) According to FDA's draft guidance, an MRTP is "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."[1] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (1) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and, (2) benefits 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.

[1] Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance. <https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM297751.pdf>

We recognize the possible benefit to individuals and public health of marketing tobacco products with substantially reduced risks profiles compared to currently marketed products such as combustible cigarettes, cigars, and some smokeless tobacco products. Given FDA's mission to protect Americans from tobacco-related diseases and death by regulating tobacco, it is critically important that FDA undergo a thorough science-based review of PMI's application to market IQOS as an MRTP. ***The PMI MRTP application lacks important information needed for the FDA to determine that IQOS should be marketed as an MRTP, so should deny the application until PMI presents the information necessary to demonstrate that any product permitted to be marketed as an MRTP actually reduces risk.***

1. Aerosol Chemistry (Module 6.1.1.):

a. ***PMI should report emission levels of all 93 HPHCs in IQOS aerosol*.** According to the FDA, harmful and potentially harmful constituents (HPHCs) are "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers."[2] The FDA has an established list of 93 HPHCs.[3] Quantifying levels of HPHCs in aerosol/smoke of tobacco products that deliver nicotine through the pulmonary route is critical to understanding the potential health risks associated with these products. PMI measured the levels of 58 HPHCs, which they referred to as PMI-58, in mainstream IQOS aerosol. PMI claims that this list contains "chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke," (Module 6.1.1 Aerosol Chemistry p. 6). They also claim that it contains the 18 HPHCs subject to

[2] https://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponents/ucm20035927.htm
[3] https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm297786.htm

reporting on FDA's abbreviated list. No rationale for leaving out the other 35 HPHCs on the FDA's established list was given. The public (and the FDA) cannot assume that these 35 HPHCs are not important or that they are at much lower levels in IQOS emissions compared to other tobacco products. Since PMI is attempting to market IQOS as a reduced risk product, a more extensive rather than limited analysis of HPHCs is needed.

b. ***PMI should report levels of HPHCs in IQOS sidestream emissions*.** PMI's analysis of the PMI-58 HPHCs was done in mainstream IQOS aerosol. The implicit assumption is that IQOS has no sidestream emissions. However, research on IQOS by Imperial Tobacco Ltd. found "a large number of different VOC [volatile organic compound] species across a range of masses were released into the airspace" when IQOS was activated but not puffed on.[4] In order to protect non-users of tobacco products, FDA must insist that PMI fully characterizes HPHC levels in sidestream emissions from IQOS.

c. ***PMI should report results of non-targeted analyses of constituents in mainstream and sidestream IQOS emissions, in addition to their current targeted analysis.***

The MRTP application reports the results of analyses comparing the emissions of HPHCs from IQOS and a reference cigarette (Module 6.1.1 pp 13-19). The analyses reported by PMI show significant reductions in most of the HPHCs that were measured compared to emissions from a reference 3R4F cigarette.

Significantly, the reported studies fail to address the important question "does the aerosol generation process for IQOS produce substances not found in the smoke of

[4] O'Connell G, Wilkinson P, Burseg K, Stotesbury S, Pritchard J. Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation. J Environ Anal Chem. 2015;2(163):2380-2391.10001.

conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?" The main rationale for the development of IQOS and other heat-not-burn products is that combustion, meaning incomplete combustion of many organic materials, including tobacco, produces highly toxic substances such as some on the HPHC lists. The heat-not-burn products generate an inhalable aerosol without combustion, thereby purportedly eliminating or reducing the levels of substances that are generally formed as combustion by-products. ***Nevertheless, the heat required to generate the aerosol in IQOS will likely produce substances not detected in cigarette smoke. Substances in the IQOS (from tobacco or the numerous additives) could undergo heat-induced reactions to form new substances that might not survive in the higher temperature and strong oxidizing conditions in a combusted tobacco product.***

There are reasons to suspect that the temperatures produced in IQOS are sufficient to cause chemical reactions to occur, as have been demonstrated with e-cigarettes.[5] In other words, substances in the aerosol may not be limited to those present in the tobacco prior to aerosol generation. E-cigarettes use heat to generate an inhalable aerosol without combustion, in a fashion similar to aerosol generation in a heat-not-burn product, and it is well known that numerous chemical reactions occur during the "vaping" process. For example, formation of toxic aldehydes, including formaldehyde, acetaldehyde, and acrolein, via dehydration and oxidation of the vehicles propylene

[5] Sleiman, M., J. M. Logue, V. N. Montesinos, M. L. Russell, M. I. Litter, L. A. Gundel, and H. Destaillats. 2016. "Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals." Environmental Science & Technology 50(17): 9644-51.

glycol and glycerin is of particular concern.[6,7] In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[8]

Similarly, one would expect chemical reactions to occur during aerosol generation in IQOS, and ***there is no reason to expect that all of the substances formed, or that survive during aerosol generation, would be the same as those found in cigarette smoke.*** In fact, even among combusted tobacco products, the composition of the aerosols may differ. A recent study by Klupinski and colleagues reported that unique substances, such as ambrox, 3-methylbutanenitrile, and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke.[9] The study describes methodology for "non-targeted" analysis of tobacco smoke aerosol, and the authors suggest that "the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest. Such analyses are critical in identifying tobacco-related exposures that may affect public health." ***PMI should undertake such studies and report the full results.***

In addition to the "targeted" analyses for specific HPHCs that were carried out, PMI should carry out "non-targeted" analyses comparing IQOS aerosol with smoke from

[6] Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, Kurek J, Goniewicz ML. Carbonyl compounds in electronic cigarette vapors—effects of nicotine solvent and battery output voltage. Nicotine & Tobacco Research. 2014;16(10):1319-1326.
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[9] Klupinski TP, Strozier ED, Friedenberg DA, Brinkman MC, Gordon SM, Clark PI. Identification of New and Distinctive Exposures from Little Cigars. Chem Res Toxicol. 2016 Feb 15;29(2):162-8. doi: 10.1021/acs.chemrestox.5b00371. Epub 2016 Jan 21. PMCID: PMC4933306 DOI: 10.1021/acs.chemrestox.5b00371

combustible tobacco products in an attempt to identify potentially toxic chemicals in IQOS aerosol that may not be present in tobacco smoke. The aforementioned study by Klupinski et al. constitutes "proof of concept" for the feasibility of such chemical analyses.

d. ***PMI should compare aerosol constituents of IQOS to that of other combustible tobacco products and e-cigarettes.*** While PMI's application focuses primarily on comparisons between IQOS emissions and combustible cigarette smoke, it is unlikely that IQOS will only be used by combustible cigarette smokers. Instead, the likely scenario is that at least some users of other combustible and non-combustible tobacco products will switch to IQOS. Unless PMI can guarantee that their product be marketed and sold to current combustible cigarette smokers only, it makes no sense that their comparison is limited to cigarettes. FDA should at least insist that PMI reports comparisons of HPHC emissions between IQOS and all combustible products and electronic nicotine delivery products. This set of data is critical for an accurate assessment of the relative safety/risks of IQOS ***as actually used*** compared to and in conjunction with (i.e., dual use) other tobacco products.

e. ***PMI should characterize free radical emissions in IQOS aerosol.*** Free radicals are associated with oxidative stress, an underlying mechanism of many disease outcomes, including cardiovascular disease and cancer. Previous research has demonstrated high free radical emissions from e-cigarettes.[10] FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

[10] Goel R, Durand E, Trushin N, Prokopczyk B, Foulds J, Elias RJ, Richie Jr JP. Highly reactive free radicals in electronic cigarette aerosols. Chemical Research in Toxicology. 2015;28(9):1675-1677.

2. Justification of selection of biomarkers of exposure (Module 6.1.3.1):

a. ***PMI should expand the list of HPHCs for which systemic exposure was assessed.***

PMI used 1-hydroxypyrene, a metabolite of pyrene (a polycyclic aromatic hydrocarbon, PAH) as a biomarker of PAHs. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is not highly related to nicotine intake and tobacco-specific nitrosamine exposure.[11] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. Given the link between PAH exposure and cancer, it is important that PMI reports PAH biomarkers that are more selective of tobacco smoke than 1-hydroxypyrene.

Further, PMI's list of 17 HPHCs, for which systemic exposure were assessed, do not include any inorganic compounds, phenols, and metals. Systemic exposure to these chemicals, especially metals, should be included in PMI's MRTP. One risk assessment model estimated that metals, such as cadmium, chromium (hexavalent), and arsenic, accounted for a significant fraction of the cancer and non-cancer disease risk indices of tobacco smoking.[12] For this reason, FDA should insist that PMI report exposure to metals from IQOS use.

3. Summary of biomarkers of exposure assessments (Module 6.1.3.2.):

[11] St.Helen, G., M. L. Goniewicz, D. Dempsey, M. Wilson, P. Jacob, 3rd, and N. L. Benowitz. 2012. "Exposure and kinetics of polycyclic aromatic hydrocarbons (PAHs) in cigarette smokers." Chemical Research in Toxicology 25(4): 952-64.

[12] Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tobacco Control. 2003;12(4):424-430.

PMI conducted four clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced," based on FDA MRTP draft guidance. Two of the studies were 5-day studies in confinement, where smokers of combustible tobacco cigarettes were randomly assigned to either switch to IQOS, continue their own brand of cigarettes, or abstain from using tobacco products. The two other studies were 3-month studies consisting of 5 days of confinement followed by up to 3 months in their naturalistic environments (Module 6.1.3.2. p. 9). The first two studies were done in Poland and Japan and the latter two in Japan and the U.S. All studies contained 160 subjects, each. All four studies are of acceptable design, and included biomarker analysis in 24-hour urine (a strength).

However, there are some concerns:

a. ***PMI should present results of statistical tests.*** In figures such as Figure 1, 3, and 5 (Module 6.1.3.2. pp. 15, 20, and 25) comparisons of reduction in biomarkers of exposure to HPHCs are given for smokers who switch to IQOS and those who were in the abstinence arm. Simply stating the percentage reduction in exposure when a smoker moves from cigarettes to IQOS or from cigarettes to abstinence is not sufficient. Important to our understanding of the relative safety/risks of IQOS is information on the magnitude of the exposure to toxicants when using IQOS compared to during abstinence. FDA should insist that results of statistical tests be presented for comparisons of reductions with IQOS compared to abstinence.

b. ***Clinical studies lacked racial diversity. PMI should investigate the effect of race on use patterns and biomarkers of exposure.*** The studies were conducted with either Japanese or Caucasians. As such, these studies are most likely not representative of the U.S.

population, which is diverse racially. Metabolism of and reaction to the absorbed constituents of tobacco products,[13,14] as well as attitudes, perceptions, preferences, and tobacco use patterns may differ across racial/ethnic groups. For example, we have observed racial differences in the manner in which combustible tobacco cigarettes are smoked and how cigarettes per day related to exposure biomarkers.[15] African Americans tend to smoke each cigarette much more intensely than Caucasian smokers do. African Americans and Native Indians have been shown to be more susceptible to lung cancer than Caucasians.[16] These previous observations underscore the need to include a racially diverse sample in assessing tobacco use patterns and toxicant exposures, and to conduct clinical studies with a sample that is representative of the U.S. population.

c. ***Noncompliance during outpatient (ambulatory) product use reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS.*** The two 3-month studies included 5 days in a controlled setting and 85 or 86 days in their naturalistic environment. They compared the use of IQOS with combustible cigarette smoking and smoking abstinence. PMI implied that both studies showed significant reductions in HPHC biomarkers with use of IQOS, but did not present any associated P values to compare reductions in HPHC biomarkers during IQOS use and smoking abstinence. The results are presented together in Figure 5 (Module 6.1.3.2. p. 25) and Figure 8 (Module

[13] Benowitz NL, Perez-Stable EJ, Fong I, Modin G, Herrera B, Jacob P. Ethnic differences in N-glucuronidation of nicotine and cotinine. Journal of Pharmacology and Experimental Therapeutics. 1999;291(3):1196-1203.
[14] Benowitz NL, Pérez-Stable EJ, Herrera B, Jacob III P. Slower metabolism and reduced intake of nicotine from cigarette smoking in Chinese-Americans. Journal of the National Cancer Institute. 2002;94(2):108-115.
[15] Benowitz NL, Dains KM, Dempsey D, Wilson M, Jacob P. Racial differences in the relationship between number of cigarettes smoked and nicotine and carcinogen exposure. Nicotine & Tobacco Research. 2011;13(9):772-783.
[16] Haiman, C. A., D. O. Stram, L. R. Wilkens, M. C. Pike, L. N. Kolonel, B. E. Henderson, and L. Le Marchand. 2006. "Ethnic and racial differences in the smoking-related risk of lung cancer." New England Journal of Medicine 354(4): 333-42.

6.1.3.2. p. 32), and are most likely meant to convey the message that IQOS use results in reductions in HPHCs comparable to smoking abstinence. To be a valid comparison, it is important that study participants complied with the assigned product/regime allocation, particularly those of the smoking abstinence arm. If participants in the abstinence arm smoked cigarettes (going against the study regime), percentage reductions in biomarkers of HPHCs would be lower, and most likely be comparable to that of reductions among participants in the IQOS arm, i.e. the study would show comparable reductions in HPHC exposure with IQOS and abstinence. It is not clear from the application how compliance was determined. Compliance was said to be "particularly high" for the first study. This is a relative term and needs to be quantified in the application. For the second study, PMI reports "good" compliance of subjects in the IQOS arm but "poor" compliance in the abstinence arm. With only 7-9 out of 41 subjects from the smoking abstinence arm being included in the "PP set" (it was not clear what PP set meant), comparisons of HPHC exposure reduction between IQOS use and smoking abstinence are not valid. PMI noted that "in light of the limited number of subjects in the [smoking abstinence] arm and the increased variability, the results obtained using the [smoking abstinence] arm should be interpreted with caution." ***FDA has to ensure that PMI follows its own advice in interpreting the findings with caution. Until it does, FDA cannot rely on the data presented in the application.***

d. ***PMI should describe exposure biomarkers among dual use groups.*** Most e-cigarette users also smoke combustible cigarettes.[17] The most likely scenario if IQOS is allowed

[17] Liu G, Wasserman E, Kong L, Foulds J. A comparison of nicotine dependence among exclusive E-cigarette and cigarette users in the PATH study. Preventive Medicine. 2017.

into the U.S. market is high prevalence of dual use of IQOS and tobacco cigarettes or other tobacco products. It is unknown if dual use would result in decreased exposure to tobacco smoke toxicants in the context of nicotine titration (harm reduction), or additive exposure to toxicants from cigarettes and IQOS. It is therefore imperative that FDA insist that PMI conducts studies to assess exposure to toxicants during periods of dual IQOS-tobacco cigarette use.

Conclusion

In summary, to ensure that IQOS is truly a modified risk tobacco product with net benefits to individual users and the population as a whole, before acting favorably on an MRTP application for ICOS, FDA should require that: (1) PMI expands the list of reported HPHCs tested in IQOS emissions and those included in biomarker analysis; (2) characterize HPHC emissions in sidestream aerosol from IQOS; (3) conduct non-targeted analysis to identify other potentially toxic constituents of IQOS emissions that may be unique to IQOS (in addition to reported targeted analysis); (4) compare aerosol constituents from IQOS with that of other combustible tobacco products such as cigars in addition to cigarettes; (5) characterize free radical emissions in IQOS aerosol; (6) conduct clinical studies with samples that are representative of the U.S. population (e.g. racial diversity); and, (7) conduct studies to describe exposure biomarkers during periods of dual use. Section 911(g) of the Family Smoking Prevention and Tobacco Control Act is clear and unambiguous: **FDA may issue an MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) 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." Since PMI has failed to make this required showing, FDA is not authorized to issue an MRTP order.

IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims

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Docket Number: FDA-2017-D-3001
November 30, 2017

Section 911 of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) requires the FDA to enforce rigorous standards that tobacco companies must meet before marketing a product as a "modified risk tobacco product" (MRTP). Section 911(g) mandates that FDA may issue an MRTP order *only if* the applicant has demonstrated by substantial and objective scientific evidence that its product, *as it is actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) 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."[1] Recently, Philip Morris International (PMI) submitted an MRTP application for their new IQOS system. The IQOS, which stands for ("I-Quit-Ordinary-Smoking,") is part of the growing class of "heat-not-burn" (HNB) tobacco products. Based on claims from Philip Morris International Science, the research arm of PMI, HNB products are meant to reduce or eliminate the formation of the compounds that

[1]Family Smoking Prevention and Tobacco Control Act, 21 U.S.C. §387k, Pub. L. 111-31, 123 Stat. 1776 (2009).

make traditional cigarettes lethal while retaining the sensory experience of cigarettes for "current adult smokers."[2]

Within their MRTP application, PMI presents the results of extensive experiments comparing IQOS emissions to those of conventional cigarettes (CCs). Many established cigarette smoke toxicants were measured and shown to be present at lower levels with IQOS than with CCs. Most of the toxicological studies focus on endpoints informed by the known toxicity of CCs. In aggregate, the *in vivo* data presented suggest that IQOS induces significant lung inflammation in comparison to sham controls, but with less lung inflammation than CCs. While these decreases in pulmonary inflammation might appear promising, it remains uncertain whether they would lead to clinically meaningful differences in long-term effects for regular users of HNB products.

Herein we comment on concerns of toxicity of IQOS in relation to immune and pulmonary function. Both of these represent potential health risks for consumers. In light of these concerns, ***PMI has failed to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals, and failed to prove that IQOS will benefit the health of the population as a whole as required by section 911(g); therefore, FDA should deny PMI's MRTP application***.

[2] International, P. M. (2017). "Heat-Not-Burn." Retrieved October 18, 2017, 2017, from https://www.pmiscience.com/platform-development/platform-portfolio/heat-not-burn.

Potential for immunosuppressive effects

On November 28, 2017, FDA posted voluminous amounts of data and studies that had not previously been made available to the public. It is not possible for scientists or the public to sufficiently analyze all of this additional data in the time allowed for public comment.

Nevertheless, Module 7 of PMI's MRTP application includes detailed *in vivo* studies in which rats were exposed to 3R4F cigarette smoke, IQOS emissions, or air for 90 days. Female rats exposed to IQOS were shown to have elevated levels of blood neutrophils, signaling possible acute inflammation.[3] Additionally, there were signs of thymic atrophy in male and female animals exposed to IQOS emissions.[4] Thymic atrophy is related to decreases in host memory T cell populations,[5] which in turn decreases the response time and sensitivity of immune function.[6] It will thus be important to examine the impacts of IQOS emissions on host defense in models of viral and bacterial infection. ***Based on these results, IQOS emissions may have novel effects on host immune defenses not observed with CC that could be important for human users.***

IQOS emissions pose risk for pulmonary toxicity

Emissions from the IQOS appear to have significantly decreased effects on lung weight in comparison to 3R4F cigarette smoke in *in vivo* exposure studies. However, there are

[3] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 8
[4] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 10
[5] Aspinall, R. and D. Andrew (2000). "Thymic atrophy in the mouse is a soluble problem of the thymic environment." Vaccine **18**(16): 1629-1637.
[6] Berard, M. and D. F. Tough (2002). "Qualitative differences between naive and memory T cells." Immunology **106**(2): 127-138.

differences between IQOS and sham groups for bronchoalveolar lavage (BAL) cell counts and some histopathological findings, which suggest that IQOS causes pulmonary inflammation in female rats.[7] While the comparison between sham and IQOS treated rats is not statistically significant, it is entirely possible that slight differences detected after just 90-days of *in vivo* exposure could translate to clinically significant outcomes in humans after prolonged use of HNB products.

Despite some pre-clinical data that may suggest reductions in pulmonary health effects, PMI fails to show reductions in pulmonary inflammation and function in its human clinical studies. First, no biomarkers of inflammation, such as white blood cell count (WBC) with differential from lavage fluid[8] or induced sputum[9] are measured. Rather, the inflammatory biomarkers presented are measured in plasma and are nonspecific for pulmonary inflammation. Furthermore, among the inflammatory biomarkers measured, PMI shows no statistically significant difference between IQOS users and conventional cigarette smokers in plasma WBC, plasma CRP (C-reactive protein) or plasma fibrinogen. The only human data presented that specifically relate to pulmonary health effects are pulmonary function tests. Notably, there was no statistically significant difference between IQOS users and conventional cigarette smokers for any of the pulmonary function measures tested. ***Thus, PMI fails to show any reduction in pulmonary toxicity in people who used IQOS compared to conventional cigarettes.***

[7] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 8

[8] Hunninghake, G. W., J. E. Gadek, O. Kawanami, V. J. Ferrans and R. G. Crystal (1979). "Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage." Am J Pathol **97**(1): 149-206.

[9] Pavord, I. D., M. M. Pizzichini, E. Pizzichini and F. E. Hargreave (1997). "The use of induced sputum to investigate airway inflammation." Thorax **52**(6): 498-501.

Additional concerns

Section 911(g)(1) requires PMI to demonstrate that IQOS ***"as it is actually used by consumers"*** would significantly reduce harm and the risk of disease to individuals. Further, section 911(g)(4) requires FDA in making an MRTP determination to consider ***the increased or decreased likelihood that existing users who would otherwise quit smoking will switch to the applicant's product.*** However, despite significant evidence that many tobacco consumers use two or more kinds of tobacco products currently and are unable to switch completely from one product to another, in both their *in vitro* and *in vivo* experiments, ***PMI has failed to simulate poly-tobacco use – that is, exposure to IQOS aerosols in combination with other tobacco prevalent products.***

Based on data from PMI Science, over one third of IQOS users in Japan, where HNB products have been heavily commercialized, use HNB products in addition to other tobacco products (primarily traditional cigarettes).[10] While HNB products are not yet commercially available in the United States, it seems reasonable that similar dual or poly use patterns would develop here. This is certainly the case for electronic cigarettes, another recent product that was promoted for "smoking cessation" that has a dual use rate of at least 60% in the United States[11] (one 2017 study reported a rate of 87%[12]).

[10] A van der Plas, L. P., D Skiada, M Dobrynina, G Baker, F Ludicke (2017). Prevalence and patterns of tobacco use in Japan after the commercialization of a heat-not-burn alternative (IQOS) to cigarettes. P. Science. www.pmiscience.com, Philip Morris International.

[11] (2016). "QuickStats: Cigarette Smoking Status* Among Current Adult E-cigarette Users,dagger by Age Group - National Health Interview Survey, section sign United States, 2015." MMWR Morb Mortal Wkly Rep **65**(42): 1177.

[12] Liu, G., E. Wasserman, L. Kong and J. Foulds (2017). "A comparison of nicotine dependence among exclusive E-cigarette and cigarette users in the PATH study." Prev Med.

Despite being touted as a smoking cessation product, electronic cigarettes have been associated with reduced cigarette quit-rates among current smokers.[13] A similar effect could certainly be seen with the IQOS. Dual-use has not been studied at all and it is possible that dual-use has differential, and possibly worse, effects in comparison to cigarette smoke or e-cigarette vapor alone. Thus, ***dual-use is an essential issue to address in the context of HNB systems like IQOS; because PMI failed to present sufficient evidence on dual use, FDA should not permit PMI to market IQOS as a modified risk tobacco product.***

Conclusion: FDA should deny the IQOS MRTP application

Through marketing the IQOS, PMI stands to retain their old user base and supply chains, while also possibly gaining new customers under the guise of being a "healthier" alternative to combustible cigarettes. Based on internal PMI documents from 2014, it is clear the IQOS was developed as a way to create an artificial paradigm shift in the tobacco product landscape that would allow PMI to maintain their market share.[14] This is a particular concern because PMI plans to cobrand IQOS with Marlboro conventional cigarettes.

Within the text of their MRTP application, PMI implies that switching to IQOS is equivalent to complete smoking cessation. Given the results described above, it is clear this is not the case. ***Although IQOS might be less harmful than CCs based on in vivo and in vitro measures of pulmonary and cardiovascular effects, the data clearly suggests that IQOS***

[13] Kalkhoran, S. and S. A. Glantz (2016). "E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis." Lancet Respir Med **4**(2): 116-128.
[14] Aditya Kalra, P. B., Duff Wilson, Tom Lasseter (2017). The Philip Morris Files, Part 1. Reuters Investigates. www.reuters.com, Reuters.

exposure still entails significant pulmonary toxicity relative to complete cessation and PMI fails to show any reduction in harm in its human clinical studies.

Furthermore, there is evidence that IQOS may have major effects on host immunity. Given that dual use of IQOS with other tobacco products seems likely, it is possible that users would be exposed to pulmonary and cardiovascular toxicity from CCs, and experience immunologic effects from IQOS. Despite these concerns, ***PMI has failed to include any studies on the effects of IQOS in the context of bacterial or viral infection, or any studies modeling dual or poly-tobacco product use within their application.***

Because PMI has not presented evidence that it analyzed these matters, it would be dangerous and a violation of the section 911 mandates for FDA to allow PMI to label and advertise IQOS as a reduced or modified risk product. For these reasons, ***we strongly recommend that FDA deny PMI's MRTP application.***

PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk

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Docket Number: FDA-2017-D-3001

November 30, 2017

Philip Morris International (PMI) has recently submitted an application to market the IQOS as a "modified risk tobacco product" (MRTP). The IQOS, PMI's addition to a growing class of "heat-not-burn" (HNB) tobacco products, is designed to allow users to maintain the sensory feel of smoking while decreasing exposure to the harmful toxicants found in conventional cigarette smoke. The *in vivo* toxicology data from Module 7 of PMI's MRTP application includes extensive studies focusing on pulmonary and cardiovascular endpoints. In this regard, PMI has presented evidence that it represents as showing decreased pulmonary and cardiovascular toxicity of the IQOS, relative to conventional cigarettes. PMI's representations ignore the fact that in clinical studies of American people for 23 of 24 biomarkers of potential harm, including several related to pulmonary and cardiovascular toxicity are not significantly different between IQOS and conventional cigarettes.[1] In addition, having reviewed the in vivo

[1] PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims. Public comment submitted by SA Glantz to FDA on PMI's Modified Risk Tobacco Product application for IQOS. Tracking number 1k1-8zrx-juh9. Available at https://tobacco.ucsf.edu/pmi%E2%80%99s-own-data-biomarkers-potential-harm-americans-show-iqos-not-detectably-different-conventional-cigs

toxicological profile in detail, we are concerned ***that IQOS may have unanticipated qualities of toxicity that merit further studies of long-term product safety.***

By focusing solely on endpoints informed by the established toxicity of cigarettes, PMI has failed to consider the potentially unique toxicities of IQOS. In particular, we are concerned by multiple instances of data indicating that ***exposure to IQOS emissions might have hepatotoxic effects.*** Based on toxicology data from Module 7 of the application, rats exposed for several months to IQOS show significant increases in liver transaminases (AST and ALT).[2] Furthermore, liver weights are increased[3] and hepatocellular vacuolization[4] is observed, suggesting the possibility of metabolic enzyme induction. ***Notably, hepatotoxicity was not observed even with the highest levels of CC smoke exposure tested,***[5] ***which suggests that, on this dimension, IQOS may be more dangerous than conventional cigarettes.***

The clinical data provides further cause for concern. In PMI's clinical studies of 22 healthy volunteers, 5% of subjects had increased levels of bilirubin.[6] Given the findings of hepatotoxicity in rats, it is possible these conditions are in fact related to IQOS exposure. ***For the sake of consumer safety, it is critical that this unanticipated hepatotoxicity be explored in greater detail prior to allowing PMI to market this technology as a reduced or modified risk tobacco product.***

It is possible that IQOS exposure would further increase risks of hepatotoxicity for users ingesting common medications like acetaminophen (and other cytochrome P450 altering

[2] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 6
[3] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 10
[4] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 14
[5] Module 7.2, Preclinical In Vivo 90dReg Report Manuscript, Table 6
[6] Appendix A6.1.5.4

drugs), and substances such as alcohol. Given the high rates of alcohol use among smokers,[7, 8] this is an area of particular concern.

Section 911(g) of the Family Smoking Prevention and Tobacco Control Act provides that FDA may issue a MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) 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." ***Since PMI's studies failed to adequately evaluate the hepatotoxicity of IQOS, and failed to consider how the product might be "actually used by consumers," including significant evidence that smokers have high rates of alcohol use, FDA must deny PMI's MRTP application.***

Section 911(d) is clear and unambiguous about the evidence an applicant must provide before FDA can issue an MRTP, including all research findings and scientific information "relating to the effect of the product on tobacco-related diseases and health-related conditions, including information both favorable and unfavorable to the ability of the product to reduce risk or exposure and relating to human health." However, despite the signals contained within their *in vivo* and clinical data, ***discussion of potential hepatotoxicity is notably absent from the many executive summaries and manuscripts that comprise PMI's MRTP application***.

[7] Drobes, 2002 Drobes, D. J. (2002). "Cue reactivity in alcohol and tobacco dependence." Alcohol Clin Exp Res **26**(12): 1928-1929.

[8] Batel, 1995 Batel, P., F. Pessione, C. Maitre and B. Rueff (1995). "Relationship between alcohol and tobacco dependencies among alcoholics who smoke." Addiction **90**(7): 977-980.

Until this matter has been thoroughly examined, it would be dangerous to allow PMI to label or market IQOS as a reduced or modified risk product. For this reason, ***we strongly recommend that FDA denies PMI's MRTP application.***

PMI's MRTP Application for IQOS Does Not Consider IQOS's Appeal to Youth or Adolescents, or the Likelihood that Youth and Adolescents will Initiate Tobacco Use with IQOS or Use IQOS with Other Tobacco Products

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Docket Number: FDA-2017-D-3001

December 7, 2017

Philip Morris International's (PMI) Modified Risk Tobacco Product (MRTP) application for IQOS does not adequately consider IQOS's appeal to or impact on youth or adolescents, and does not provide the necessary scientific evidence to support its MRTP claims of reduced risk or reduced exposure, especially as these claims affect youth and adolescents. Therefore, FDA should deny PMI's MRTP application for IQOS.

1. Background

PMI is seeking FDA authorization to market their IQOS heating system with three flavors of their "HeatSticks" as a MRTP with three claims:

(1) Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases;
(2) Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes; and
(3) Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

Section 911 of the Family Smoking Prevention and Tobacco Control Act[1] and FDA's Guidance for Industry on Modified Risk Tobacco Product (MRTP) Applications[2] spell out the rigorous requirements that MRTP applicants must meet before a product can be deemed a "modified risk tobacco product" and can be marketed with MRTP claims. In particular, to market IQOS with the MRTP claims stated above, PMI must prove using substantial and objective scientific evidence that the new product, *as it is actually used by consumers*, will:

[1] Family Smoking Prevention and Tobacco Control Act, 21 U.S.C. §387k, Pub. L. 111-31, 123 Stat. 1776 (2009).
[2] Food and Drug Administration, Modified Risk Tobacco Product Applications, Draft Guidance (March 2012). Available at https://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf

(1) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
(2) 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.

In fulfilling the MRTP application requirements specified in section 911(g), FDA recommends in its MRTP Guidance that applicants submit, among other things, the following data and information:

1) Scientific evidence regarding the effect that IQOS and its marketing will have on increasing the likelihood that *non-users* (including never users and former users) will start using the product (Guidance, p. 20);
2) Data and information on how consumers *actually use* IQOS, including data and information addressing concurrent use of multiple products containing nicotine or tobacco (Guidance, p. 15), and scientific evidence demonstrating that consumers actually use the product in a way that exposes them to the claimed reduced level of substances or harm (Guidance, p. 17);
3) Human studies that evaluate consumer understanding and perceptions of the product, including its labeling, marketing, and advertising, including:
    a. The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
    b. Consumers' beliefs about the health risks of using the product relative to other tobacco products;
    c. Consumer beliefs about the health risks of using the product relative to cessation aids; and
    d. Consumer beliefs about the risks of using the product relative to quitting all tobacco use (Guidance, pp. 20-21)

Despite the requirements of the law and these explicitly stated FDA guidelines, PMI has met none of them with respect to the use of IQOS among adolescents. In addition, the discussion of the effects of IQOS on young adults is cursory at best. For these reasons, explained more fully below, FDA should deny PMI's MRTP application for IQOS.

2. Because PMI's MRTP application did not consider the impact of IQOS on adolescent use, it did not demonstrate that the product, as actually used by consumers, will benefit the health of the population as a whole, including current non-users; in particular, it did not provide any scientific evidence regarding the effect that IQOS and its marketing would have on increasing the likelihood that adolescents who are currently not tobacco users will start using IQOS.

Despite section 911(g)'s requirement, PMI failed to provide adequate scientific evidence demonstrating that IQOS would "benefit the health of the population as a whole," in particular non-users (including adolescents and young adults) as well as current users of other tobacco products.

PMI merely claimed that in a pre-market setting, the effect of IQOS on initiation among non-users could not be assessed. For that reason, PMI used "behavioral intention," which it

defined as a person's perceived likelihood or subjective probability that he or she will engage in a given behavior as a proxy to predict the behavior of using an MRTP (Chapter 6.3.1). ***. Other factors that PMI did not consider, including willingness to use tobacco, perceived social norms, peer influences, and perceptions and attitudes towards the specific tobacco product is more predictive of use than intentions alone.***[3] As detailed below, ***it is incorrect to assume that intentions are the primary drivers of behavior, especially for adolescents***

a. **Intentions are not a proxy for actual behavior, especially for adolescents**

According to older decision-making theories such as the Social Cognitive Theory,[4] the Health Belief Model,[5] the Theory of Reasoned Action,[6] and the Theory of Planned Behavior,[7] people's behaviors are largely shaped by their intentions to engage in that behavior. These intentions are, in turn, shaped by their perceptions of behavior-related risks and benefits. While these theories have some merit, they are largely relying on cognitive processes, whereby one is expected to have a deliberate, planned decision to or not to engage in a behavior. In these cases, intentions are more likely to lead to behavior. However, as discussed in detail below, studies show that these cognitive models do not accurately or fully predict how adolescents decide whether or not to engage in a behavior, including tobacco use.

In contrast, current research demonstrates that decision-making does not only involve a deliberate, analytic process. Instead, many decisions, including adolescents' decisions to use tobacco, are based more on heuristic, reactive, and affective processes.[8] While adolescents may not have an active plan in mind to smoke, they often find themselves in situations in which they would consider smoking even though they were originally committed to avoiding it. Willingness to smoke is shaped by perceptions, including perceived peer norms and peer acceptance of smoking as well as images associated with smoking. For example, adolescents are less likely to smoke if they hold negative images that smokers are dirty, wrinkled, and have yellow teeth. In contrast, adolescents who are exposed to positive images of smokers are more likely to view smoking favorably and therefore try smoking.[9] Indeed, willingness is a better predictor of

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[3] Gerrard, M., Gibbons, F.X., Benthin, A.C., & Hessling, R.M. (1996). A longitudinal study of the reciprocal nature of risk behaviors and cognitions in adolescents: What you do shapes what you think and vice-versa. *Health Psychology, 15,* 344-354.

[4] Bandura, A. (1994). Social cognitive theory and exercise of control over HIV infection. In R.J. DiClemente & J.L. Peterson (Eds.), *Preventing AIDS: Theories and methods of behavioral interventions*. New York: Plenum Press

[5] Rosenstock, I.M. (1974). Historical origins of the health belief model. In M.H. Becker (Ed.), *The Health Belief Model and Personal Health Behavior* (pp. 1-8). Thorofare, NJ: Charles B. Sclack.

[6] Fishbein M, Ajzen I. Belief, attitude and behavior. *Reading, MA: Addison-Welsey Publishing Co*. 1975.

[7] Ajzen I. From intentions to actions: A theory of planned behavior. In: *Action control.* Springer; 1985:11-39.

[8] Meg Gerrard et al., A Dual-Process Approach to Health Risk Decision Making: The Prototype Willingness Model, 28(1) Developmental Review 29 (2008).

[9] McKelvey, K., Popova, L., Pepper, J., Brewer, N., Halpern-Felsher, B. Adolescents Have Unfavorable Opinions of Adolescents Who Use E-cigarettes. In Review.

tobacco use than intentions and should be used in studies examining whether and why an adolescent would use any tobacco product.[10,11]

b. PMI's application did not include information from studies with adolescents younger than 18

In addition to inappropriately relying on intentions as a proxy for actual behavior and behavior change, none of PMI's cited studies were conducted with adolescents younger than 18. PMI does not provide any reliable information in its application on whether adolescents would be interested in using IQOS, if adolescents would initiate nicotine use with IQOS, if adolescents would switch from another tobacco product to IQOS, or if adolescents would use IQOS along with other tobacco products.

One way to obtain information on adolescents' interests and behavior is to conduct studies with adolescents. However, neither PMI nor any other tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21, to be conservative) because they could use such information to design marketing campaigns to attract youth to their products. A different way to get at adolescents' interest and behavior is relying on research on other, similar products, such as electronic cigarettes, conducted with no direct or indirect involvement of tobacco companies or their agents.[12] There is a rich literature on adolescents conducted independent of the industry that PMI could have, but did not, present on current, former and non-users of cigarettes to understand their intentions as well as their willingness to use IQOS. This research also provides insights on the extent to which warning messages and ads influence youth perceptions and willingness to use IQOS.

In particular, it is important to consider IQOS and PMI's MRTP application in the context of recent experience with e-cigarettes and other novel tobacco products. Since e-cigarettes were first introduced in the U.S. less than a decade ago, there has been a rapid rise in the use of e-cigarettes,[13] a nicotine product that has been marketed with claims of reduced harm similar to PMI's claims about its IQOS product. E-cigarette use is especially common among adolescents and young adults. On the U.S. market since 2007, past 30-day use of e-cigarettes has

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[10] Gerrard, M., Gibbons, F.X., Benthin, A.C., & Hessling, R.M. (1996). A longitudinal study of the reciprocal nature of risk behaviors and cognitions in adolescents: What you do shapes what you think and vice-versa. *Health Psychology, 15,* 344-354; Meg Gerrard et al., A Dual-Process Approach to Health Risk Decision Making: The Prototype Willingness Model, 28(1) Developmental Review 29 (2008).

[11] Gerrard M, Gibbons FX, Stock ML, Lune LS, Cleveland MJ. Images of smokers and willingness to smoke among African American pre-adolescents: An application of the prototype/willingness model of adolescent health risk behavior to smoking initiation. Journal of Pediatric Psychology. 2005 Feb 23;30(4):305-18.

[12] Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.

[13] McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. Nicotine Tob Res. 2015 Oct;17(10):1195-202

surpassed use of conventional cigarettes, with use prevalence of 11.3% among high school students (8.0% for cigarettes).[14] Among young adults 18-24 years old, 23.5% have ever used an e-cigarette.[15] Youth are also most likely to use flavored e-cigarette and other tobacco products.[16]

The available evidence reported in scientific studies on currently marketed novel tobacco products (including e-cigarettes) conducted independent of the tobacco industry suggest that the introduction of novel IQOS products will attract adolescent non-users into initiating tobacco use with IQOS. Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them, the product's flavors, smell and taste, the product's perceived harm reduction, and the ease and location of use.[17] The marketing of IQOS with harm reduction claims and the claim that they are "smokeless" makes it likely that these products will appeal to youth.

The experience with e-cigarettes, which have also been promoted with harm reduction and "smokeless" messages, is directly relevant to adolescents' likely reaction to IQOS. In addition, both have a modern hi-tech image, another common characteristic that raises concerns that IQOS will attract youth. Many adolescents at low risk of initiating nicotine use with conventional

[14] Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. MMWR Morb Mortal Weekly Rep 2017; 66:597–603. DOI: http://dx.doi.org/10.15585/mmwr.mm6623a1; Syamlal G, King BA, Mazurek JM. Tobacco Use Among Working Adults — United States, 2014–2016. MMWR Morb Mortal Weekly Rep 2017;66:1130–1135. DOI: http://dx.doi.org/10.15585/mmwr.mm6642a2; see also Centers for Disease Control and Prevention. "National Youth Tobacco Survey (NYTS)." 2015. Web. 22 Aug. 2016; Centers for Disease Control and Prevention "Youth and Tobacco Use." 2016. Web. 22 Aug. 2016; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Gilreath TD, Leventhal A, Barrington-Trimis JL, et al. Patterns of alternative tobacco product use: Emergence of hookah and E-cigarettes as preferred products amongst youth. *Journal of Adolescent Health*. 2016;58(2):181-185; NIDA. Tobacco/nicotine and E-cigs. https://www.drugabuse.gov/drugs-abuse/tobacconicotine-e-cigs. Updated 2017. Accessed 09/12, 2017.

[15] QuickStats: Percentage of adults who ever used an e-cigarette and percentage who currently use e-cigarettes, by age group. National Health Interview Survey, United States, 2016. MMWR Morb Mortal Weekly Report, 2017;66:892. DOI: http://dx.doi.org/10.15585/mmwr.mm6633a6

[16] Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. JAMA. 2015;314(17):1871-1873; Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252; Feirman SP, Lock D, Cohen JE, Holtgrave DR, Li T. Flavored tobacco products in the united states: A systematic review assessing use and attitudes. Nicotine Tob Res. 2016;18(5):739-749; Wagoner KG, Cornacchione J, Wiseman KD, Teal R, Moracco KE, Sutfin EL. E-cigarettes, hookah pens and vapes: Adolescent and young adult perceptions of electronic nicotine delivery systems. Nicotine Tob Res. 2016.

[17] McKelvey, K., Ramos, M., Roditis, M., Ramamurthi, D., Halpern-Felsher, B. A Qualitative Analysis of Adolescents' Appeal of Various Tobacco Products. In preparation.

cigarettes initiate with e-cigarettes.[18] Adolescents who initiate nicotine use with e-cigarettes are more susceptible to smoking combustible cigarettes.[19] This experience with e-cigarettes raises the concern that adolescents will use both IQOS and other tobacco products concurrently, just as adolescents are dual and poly-users of e-cigarettes along with other tobacco products.[20]

3. PMI's application does not consider the impact of poly-use of novel tobacco products among adolescents

PMI ignores evidence that adolescent and young adult smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently. [21] Although PMI's own studies show that IQOS is often/sometimes actually used with conventional cigarettes, they fail to analyze the impact of this dual use. In particular, PMI reports (section 3.5.3 and 6.2.2) that 22.4% of US study participants still were using both regular combustible cigarettes and IQOS after 6 weeks. In other countries, dual use of IQOS and combustible cigarettes ranged from 27% (Germany) to 39% (Switzerland) after 4 weeks (section 3.5.3, Table 5). According to

[18] Dutra, LM, Glantz, SA. E-cigarettes and national adolescent cigarette use: 2004-2014. Pediatrics. 1239(2), 2017; Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. Tob Control. 2016 Apr;25(e1):e52-9; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

[19] Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD.JAMA Pediatr. 2017 Aug 01;171(8):788-797; Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med*. 2015;49(2):199-206; Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res*. 2016;18(5):654-659; 16. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700-707; E-cigarette use and willingness to smoke: a sample of adolescent non-smokers.Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. Tob Control. 2016 Apr;25(e1):e52-9.

[20] Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use:. *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

[21] Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, et al. Tobacco use among middle and high school students - United States, 2011-2016. MMWR Morb Mortal Wkly Rep. 2017;66(23):597-603.

PMI's 2016 full-year report,[22] 21-31% of users across multiple countries are dual-users with substantial portion of their tobacco use (>30%) from products other than IQOS, including regular combustible cigarettes. Another 7-15% are "Predominant (70-95% IQOS)" users, meaning they still use regular cigarettes along with IQOS up to 30% of the time. While this information is based on adults there is no reason to expect that youth would not behave similarly. Indeed, dual and poly-use of tobacco products is more common among youth than adults.[23]

PMI should have used the available experience with e-cigarettes collected independent of the tobacco industry to draw reasonable inferences about how IQOS would affect youth, but did not. The fact that PMI did not address these issues at all is a major shortcoming of the application that should lead FDA to deny the application. Indeed, section 911(d) of the Tobacco Control Act requires every MRTP application to include "(5) all documents (including underlying scientific information) relating to research findings conducted, supported, or possessed by the tobacco product manufacturer relating to the effect of the product on tobacco-related diseases and health-related conditions, *including information both favorable and unfavorable* to the ability of the product to reduce risk or exposure and relating to human health; (6) data and information on how consumers actually use the tobacco product… [emphasis added]." In its Guidance on MRTP applications, FDA explains that the term "possessed" includes research "findings from studies not conducted or supported by the manufacturer, but which it has received or has reviewed…" Further, FDA's Guidance states: "*FDA expects that the applicant will include*, among other things, as part of its submission of relevant documents, study reports, study protocols, and raw data… [emphasis added]." It is not credible for PMI to argue that it does not know about or has not reviewed the literature on the experience of e-cigarettes and adolescents, even if it did not conduct its own studies.

4. The actual marketing of IQOS to date in other countries demonstrates that PMI has not adequately protected against use by nonsmokers and suggests that the product's name, physical appearance, and retail environment will appeal to young people.

The IQOS product, packaging, name, and store designs imitate Apple's iPhone and other i-products that are exceptionally popular with young people.

Piper Jaffray's October 11, 2017 "Taking Stock with Teens" survey of 6,100 U.S. teens showed that Apple's iPhone continues to rise in popularity among teens, with 78% of U.S. teens saying they owned an iPhone, and 82% of teens saying their next smartphone will be an iPhone.[24] An April 2017 Fortune Magazine article led with the statement: "Teenagers are

22 https://www.pmi.com/investor-relations/overview/event-details/?eventId=5246224, Slide p. 19

[23] Kowitt, SD, Patel, T., Ranney, LM, Huang, LL, Sutfin, EL, Goldstein, AO. Poly-tobacco use among high school students. Int J Environ Res Public Health. 2015 Nov; 12(11): 14477–14489. Published online 2015 Nov 13. doi: 10.3390/ijerph121114477. PMCID: PMC4661661; Soneji, S., Sargent, J, Tanski, S Multiple tobacco product use maong US adolescents and young adults. Tobacco control, 25(2), 2016.

[24] [Piper Jaffray, Taking Stock with Teens – Fall 2017, October 11, 2017. Available at www.piperjaffray.com/3col.aspx?id=4610]

obsessed with Apple's iPhone," based on the Spring 2017 edition of Piper Jaffray's teen survey in which 76% of U.S. teenagers said they had an iPhone, and 81% said their next smartphone will be an iPhone.[25] ***Considering IQOS's similar design to iPhone (and the fact that PMI also calls it iQOS), it is reasonable to assume that adolescents will find IQOS's design appealing, and will begin to use IQOS either alone or coupled with other tobacco products.***

Indeed, one of the common reasons young adults try e-cigarettes was novelty/technological appeal.[26] Therefore, it is especially concerning that the IQOS product design closely mimics Apple's iPhone and other savvy, high-tech electronic products. The packaging resembles iPhones and other high-end smartphones, where the device and parts are neatly placed on molded plastic trays inside a glossy white box (Figure 1). Such marketing tactics are likely to appeal to adolescent and young adult never-smokers, making them more likely to try IQOS like many adolescents and young adults were attracted to try e-cigarettes.

Adding to these concerns, the IQOS flagship stores in Seoul, Korea, visited in June 2017, look remarkably similar to high-end technology brand stores such as Apple or Microsoft stores in the U.S.[27] (Figure 2). The design of the store and the way the products are displayed on the table in a spacious store contrasts sharply from a normal corner store where cigarette packs are tightly stacked, and gives a clean and refined look and feel to IQOS. Stores located in other countries have similar tech-savvy atmosphere, such as the IQOS store in Amsterdam, Netherlands (Figure 3).

5. PMI's MRTP application failed to consider the likelihood that IQOS's two menthol flavors would appeal to youth and adolescents and encourage initiation among non-users

The IQOS heatsticks currently come in three flavors, Marlboro HeatSticks, Marlboro Smooth Menthol HeatSticks, and Marlboro Fresh Menthol HeatSticks. (PMI's application is silent on whether or not there will be more flavors of IQOS in the future.) Flavor or "taste" is one of the most commonly used marketing techniques to entice young people to use a product; in particular, sweet and salty flavors are used to promote food (mostly candy and snacks[28]) to children.[29] ***PMI completely ignored all the evidence that menthol products would attract youth***

[25] .[Reisinger, D., Fortune. Apple's iPhone is the Dominant Smartphone Among Teenagers, April 11, 2017. Available at fortune.com/2017/04/11/apple-iphone-teenagers/]

[26] Choi K., Fabian L., Mottey N., & Corbett A.(2012). Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: Findings from a focus group study. *American Journal of Public Health, 102*, 2088–2093; Pokhrel P, Herzog TA, Muranaka N, Fagan P. Young Adult E-Cigarette Users' Reasons for Liking and Not Liking E-Cigarettes: A Qualitative Study. Psychol Health. 2015;30(12):1450-1469.

[27] Kim M. Philip Morris International Introduces New Heat-Not-Burn Product, IQOS, in South Korea. Tobacco Control. 2017.

[28] Jenkin G, Madhvani N, Signal L, Bowers S. A systematic review of persuasive marketing techniques to promote food to children on television. *Obesity reviews*. 2014;15(4):281-293.

[29] Jenkin G, Madhvani N, Signal L, Bowers S. A systematic review of persuasive marketing techniques to promote food to children on television. *Obesity reviews*. 2014;15(4):281-293.

and that adolescents will find these flavors appealing and therefore more likely to be used by them.

Figure 1. Packaging of IQOS (top: picture taken by Minji Kim) resembles that of high-end smartphone (bottom: Apple iPhone 7; source: phonearena.com[30]).

[30] https://www.phonearena.com/news/Apple-iPhone-7-unboxing-hands-on-with-the-speedy-new-water-resistant-iPhone_id85512

Figure 2. IQOS Flagship store in Seoul, Korea, June 2017. Photos by Minji Kim, PhD.

Figure 3. IQOS Flagship store in Amsterdam, Netherlands, September 2017. Photo by Minji Kim, PhD.

Exposure to flavored products and ads for such products is positively associated with youth consumption.[31] Research on newer tobacco products, including e-cigarettes, comports with these findings. Flavored tobacco products play an important role for online e-cigarette marketing and boosts user interaction and positive emotion.[32] Further, compared to ads for unflavored tobacco products, flavored e-cigarette advertisements elicit greater appeal and interest in buying and trying e-cigarettes.[33] The appeal of ads for flavors has been linked to rapid and persistent adoption of e-cigarettes among youth;[34] and 75% of US youth stated they would not use e-cigarettes without flavors.[35] Ads depicting flavors using colorful images make e-liquids attractive to youth,[36] and a 2014 content analysis of e-cigarette retail websites, which showed ads were appealing to youth.[37] Questions remain including whether the flavors will be attractive to adolescents who have never used a tobacco product or to adolescents who currently use at least one product. PMI did not present any information or studies on the IQOS advertisements for these flavored tobacco products that would permit an assessment of whether the ads will be appealing and misleading to youth, as we have seen in studies on e-cigarettes.[38]

6. PMI's arguments that modified risk claims will not attract never-smokers are illogical and inconsistent with the available evidence.

PMI's application states that adult never-smokers in their study reported greater perceptions of risk for IQOS than current or former smokers (section 6.4.4.1-3), and argues that IQOS will not cause or motivate "non-users to be interested in the product because it is still considered a risky product" (section 6.4, p. 70). PMI's reasoning and interpretation of their results is not logical. Many studies have shown that non-tobacco users report greater perceptions

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[31] Cairns G, Angus K, Hastings G, Caraher M. Systematic reviews of the evidence on the nature, extent and effects of food marketing to children. A retrospective summary. *Appetite*. 2013;62:209-215

[32] Liang Y, Zheng X, Zeng DD, Zhou X. Impact of flavor on electronic cigarette marketing in social media. 2015:278-283

[33] Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112.

[34] Liang Y, Zheng X, Zeng DD, Zhou X. Impact of flavor on electronic cigarette marketing in social media. 2015:278-283l Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: An experimental study. *Tob Control*. 2016;25(e2):e107-e112.

[35] Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob Control*. 2014;23 Suppl 3:iii3-9

[36] Sterling KL, Fryer CS, Nix M1, Fagan P. Appeal and Impact of Characterizing Flavors on Young Adult Small Cigar Use.
Tob Regul Sci. 2015 Apr;1:42-53. Epub 2015 Mar 1.

[37] Grana RA, Ling PM. "Smoking revolution": A content analysis of electronic cigarette retail websites. *Am J Prev Med*. 2014;46(4):395-403

[38] (Choi, Fabian, Mottey, Corbett, & Forster, 2012; Feirman et al., 2016; Kong, Morean, Cavallo, Camenga, & Krishnan-Sarin, 2015; Wagoner et al., 2016).

of tobacco-related risk, compared to tobacco users.[39] However, you cannot then extend these findings to mean that non-users will never go on to use tobacco. Perceptions can change over time, and across products. ***Instead, the relevant question is how non-tobacco users perceive IQOS compared to other tobacco products, and whether the marketing and appeal of this new tobacco product will result in lower perceptions of risk of IQOS compared to other tobacco products, which then will result in use.***

In addition, PMI ignores the fact that most tobacco use begins before age 18. There is no reason to expect that IQOS would be any different, particularly in light of the fact that e-cigarettes, a similar product, have been more popular with youth than adults.

The question PMI should have asked (and that the FDA should ask) is whether IQOS, with lower perceived risks, encourages never-smokers -- including adolescents and young adults -- who would otherwise not use any tobacco products to be more likely to try the IQOS product. Indeed, exposure to e-cigarette advertisements causes increases in smoking urge among adult former and current smokers[40] and reduces adolescent never-smokers' perceived risks of regular cigarettes.[41] Indeed, the fact that e-cigarettes are perceived as less harmful than regular cigarettes by adolescents and young adult never-smokers[42] is one reason that they are often the first tobacco product adolescents and young adults use, which also predicts future cigarette use.[43] According to PMI's application, while non-smokers' perceived risk score for IQOS are higher than current and former smokers in PMI's studies after seeing the modified risk claims (section 6.4.4.1-3), the scores are significantly lower than the non-smokers' perception of risks for

[39] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66.

[40] Durkin SJ, Bayly M, Wakefield MA. Can E-Cigarette Ads Undermine Former Smokers? An Experimental Study. Tob Regul Sci. 2016;2(3):263-277; Maloney EK, Cappella JN. Does Vaping in E-Cigarette Advertisements Affect Tobacco Smoking Urge, Intentions, and Perceptions in Daily, Intermittent, and Former Smokers? Health Communication. 2016;31(1):129-138.

[41] Kim M, Popova L, Halpern-Felsher BL, Ling PM. Effects of E-Cigarette Advertisements on Adolescents' Perceptions of Cigarettes. *Health communication.* In Press; Petrescu DC, Vasiljevic M, Pepper JK, Ribisl KM, Marteau TM. What Is the Impact of E-Cigarette Adverts on Children's Perceptions of Tobacco Smoking? An Experimental Study. *Tob Control.* 2016.

[42] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

[43] Kalkhoran S, Glantz SA. E-Cigarettes and Smoking Cessation in Real-World and Clinical Settings: A Systematic Review and Meta-Analysis. The Lancet Respiratory Medicine. 2016;4(2):116-128; Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence. JAMA. 2015;314(7):700-707; Miech R, Patrick ME, O'Malley PM, Johnston LD. E-Cigarette Use as a Predictor of Cigarette Smoking: Results from a 1-Year Follow-up of a National Sample of 12th Grade Students. Tob Control. 2017.

regular cigarettes. ***Like e-cigarettes, PMI's results show that nonsmokers (which would include adolescents and young adults) are more likely to try IQOS than regular cigarettes.***

In considering PMI's claims about the impact of reduced risk perceptions on behavior of non-users, it is important to consider parallels with e-cigarettes when they first entered the market. Many e-cigarette users started using e-cigarettes because they perceive these e-cigarettes as less harmful (i.e., "reduced risk") than cigarettes and to be effective as smoking cessation aids.[44] An analysis of e-cigarettes retail websites showed that 95% of the 59 included websites made explicit claims that e-cigarettes can aid in smoking cessation or improve health.[45] Websites that compared cigarettes with e-cigarettes stated that e-cigarettes were cleaner (95% of the websites), cheaper (93% of the websites), could be used to circumvent indoor clear air policies (71% of the websites), and could aid in smoking cessation (64% of the websites). A study of the content of websites of e-cigarette manufacturers in China showed similar claims of health-related benefits, reduced secondhand smoke exposure, and utility for smoking cessation.[46] These explicit claims were made in the absence of consistent evidence pointing to benefits in health or smoking cessation.

Furthermore, these claims often led to a belief among both cigarette smokers and nonsmokers (including adolescents) that e-cigarettes are therefore a less harmful choice for any user (that is, not just in comparison to cigarettes), which in turn resulted in e-cigarette initiation among non-smokers.[47] In particular, adolescents believe that e-cigarettes are less harmful than cigarettes and all other tobacco products,[48] that e-cigarettes are acceptable and socially normative (with sizeable proportions (20-28%) agreeing that it is ok to use e-cigarettes indoors and

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[44] Roditis M, Delucchi K, Cash D, Halpern-Felsher B. Adolescents' perceptions of health risks, social risks, and benefits differ across tobacco products. *Journal of Adolescent Health*. 2016;58(5):558-566; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res*. 2015;17(7):847-854; El-Toukhy S, Choi K. A risk-continuum categorization of product use among US youth tobacco users. *Nicotine Tob Res*. 2016.

[45] Grana, RA and Ling P. Smoking revolution: a content analysis of electronic cigarette retail websites. Am J Prev Med. 2014; 46(4): 395-403; Klein EG, Berman M, Hemmerich N, Carlson C, Htut S, Slater M. Online E-cigarette marketing claims: A systematic content and legal analysis. *Tobacco Regulatory Science*. 2016;2(3):252-262.

[46] Yao T, Jiang N, Grana R et al., A content analysis of electronic cigarette manufacturer websites in China. Tob Control. 2016; 25(2):188-94

[47] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

[48] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

outdoors),[49] and that such perceptions and attitudes are directly related to initiation and use of e-cigarettes.[50] Despite studies showing negative health effects of e-cigarettes, adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes, and contain none or just limited amounts of nicotine. Adolescents also consider e-cigarettes to be trendier, more prevalent, and more acceptable than conventional cigarettes.[51] The lowest perceptions of harm and the most positive attitudes regarding e-cigarettes have been reported among adolescents who have used e-cigarettes.[52] Given the similarities between IQOS and e-cigarettes (electronic, hi-tech, and claims of reduced harm, a better alternative to cigarettes, no "smoke") it is reasonable to expect that IQOS will be popular with youth, because they will make similar assumptions about the risks associated with IQOS, and will be willing to initiate and use IQOS.

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[49] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20.

[50] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Pepper, JK, Emergy, SL, Ribisl, KM, Rini, CM, Brewer, NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. J Behav Med. 2015 Apr;38(2):318-26.

[51] Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Hammal F, Finegan BA. 2016. Exploring Attitudes of Children 12–17 Years of Age Toward Electronic Cigarettes. *Journal of Community Health.* 1-7; Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. 2013. *J Am Coll Health.* 61(3):149-155.Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

[52] Ambrose BK, Rostron BL, Johnson SE, et al. 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. *Am J Prev Med.* 47(2 Suppl 1):S53-60; Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436) ; Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *American Journal of Health Behaviors*; 2015 May; 39(3):421-432; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85. Trumbo & Harper, 2013)

Thus, exposure to the marketing of IQOS focusing on claims of reduced risks is likely to cause similar harmful effects on never- and former-smokers, and could cause youth and adolescent never-smokers to initiate nicotine use with IQOS. PMI's application is silent on these important issues.

7. Conclusion

When evaluating whether PMI should be allowed to market IQOS as a MRTP, FDA must consider that adolescents who otherwise would not have used any tobacco product might find IQOS appealing and will initiate using IQOS as their first tobacco product. This is especially likely given adolescents' attraction to flavored tobacco products, the appeal of novel and technology-centric products among adolescents, and the tendency for the public at large, including adolescents, to misinterpret reduced harm claims.

Further, FDA must consider whether the evidence submitted by PMI were *independent studies*, and not studies that were conducted by PMI or influenced or paid by PMI.[53] In particular, FDA must review independent studies of adolescents' perceptions of IQOS and the marketing claims made about IQOS, as well as independent studies that examine whether in the real world adolescents are more or less likely to initiate with IQOS compared to other tobacco products. FDA should review studies that examine adolescent consumers,' potential consumers,' and non-consumers' perceptions of IQOS products, and their use in the real world. FDA must evaluate whether and to what extent adolescents initiate with IQOS, whether they are likely to use both IQOS and other tobacco products, and whether adolescents initiating with IQOS will be more likely to subsequently initiate cigarette use. ***Because PMI's did not submit with its MRTP application such rigorous, independent studies and because the application made no consideration of potential impact on adolescents, FDA does not have sufficient evidence on which to determine the public health impact of IQOS on the population as a whole as required by section 911(g), and should deny PMI's application.***

[53] Institute of Medicine. 2012. *Scientific Standards for Studies on Modified Risk Tobacco Products*. Washington, DC: The National Academies Press. https://doi.org/10.17226/13294.

The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product

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Docket Number: FDA-2017-D-3001

December 8, 2017

An essential condition that FDA is required to consider before permitting the marketing of any modified risk or exposure product (MRTP) is the effect that the MRTP and its marketing will have on consumer understanding and perceptions. According to the FDA Guidance, "All MRTPAs [MRTP applications] must contain evidence to show that the advertising and labeling concerning modified risk 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 of the diseases and health-related conditions associated with the use of tobacco products [emphasis added]." [1]

For exposure modification orders, "any aspect of the product's label, labeling, and advertising that would make it a modified risk tobacco product must be limited to an explicit or implicit representation that the product or its smoke does not contain or is free of a substance or contains or presents a reduced level of exposure to a substance."[2] Importantly, "***applicants seeking an exposure modification order must demonstrate through testing of actual consumer perception that the proposed labeling and marketing of the product does not mislead consumers into believing that the product is or has been demonstrated to be less harmful, or mislead consumers into believing that the product presents less of a risk of disease than one or more other commercially marketed tobacco products***." [3]

To address the effect of marketing on consumer understanding and perception, FDA recommends that applicants submit human studies regarding consumer understanding of the product, including its labeling, marketing and advertising. To inform FDA's evaluation of the proposed MRTP's marketing on consumer perception and understanding, the scientific studies submitted by the applicant should include:

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[1] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(h)(1) of the Family Smoking Prevention and Tobacco Control Act.
[2] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(g)(2)(A)(ii) of the Family Smoking Prevention and Tobacco Control Act.
[3] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012; Section 911(g)(2)(B)(iii) of the Family Smoking Prevention and Tobacco Control Act.

1. The ability of consumers to understand the modified risk claims and the significance of the information in the context of one's health;
2. Consumers' beliefs about the health risks of using the product relative to other tobacco products, including those within the same class of products;
3. Consumer beliefs about the health risks of using the product relative to cessation aids; and
4. Consumer beliefs about the risks of using the product relative to quitting all tobacco use.[4]

As described in detail below, Philip Morris International (PMI) failed to meet this burden, failed to provide compelling scientific evidence on consumer perception and understanding of the labeling and marketing of its proposed IQOS product, and failed to demonstrate that the labeling and marketing of the product will not mislead consumers. Therefore, FDA should deny PMI's MRTP application for IQOS.

PMI's own data do not support the conclusion that IQOS is less dangerous than conventional cigarettes in terms of effects on these biomarkers of potential harm in American people; any marketing claims of modified risk are fundamentally misleading and should not be permitted.

As a preliminary matter, we have shown in another public comment[5] that PMI's MRTP application does not support any claim of modified risk in human users. PMI presents data on 24 biomarkers of potential harm in American human users, including measures of inflammation,

[4] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012.

[5] Glantz S. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims. Docket Number: FDA-2017-D-300. November 13, 2017. Tracking number: 1k1-8zrx-juh9. See also the other public comments submitted by UCSF: Springer ML, Nabavizadeh P, Mohammadi L. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes. Docket Number: FDA-2017-D-3001. November 20, 2017. Tracking number 1k1-8zxa-mq9v. Chun LF, Moazed F, Matthay MA, Calfee CS, Gotts JE. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims. Docket Number: FDA-2017-D-3001. November 30, 2017. Chun LF, Moazed F, Matthay MA, Calfee CS, Gotts JE. PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk. Docket Number: FDA-2017-D-3001. November 30, 2017. Tracking number 1k1-9039-d91g. St.Helen G, Jacob P III, Nardone N, Benowitz NL. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application. Docket Number: FDA-2017-D-3001. November 29, 2017. Tracking number is 1k1-902j-m8kv.

oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. These human data are the most important information in the application because they represent direct evidence on how IQOS affects people. Based on details in section 6.1.4.4 of the PMI MRTP application, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of these 24 biomarkers in Americans in PMI's studies. This is indicated by the fact that 23 of the 95% confidence intervals include zero (i.e., no statistically significant difference).

Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five percent of 24 tests is 1.2 tests, which means that one would expect 1 or 2 false positive results. PMI had one positive result, which is what one would expect by chance.

PMI's entire analysis is based on comparisons with conventional cigarettes, which ignores a wide range of other tobacco products, including e-cigarettes, which are often represented as less dangerous than cigarettes.

PMI's analysis of relative harm is based on comparison of IQOS with conventional cigarettes, and does not compare IQOS to any other tobacco products, including e-cigarettes, which the tobacco industy represents as less dangeous than cigarettes. The Perception and Behavioral Assessment studies did assess how adults perceive risks from IQOS as compared to combustible cigarettes, e-cigarettes, and NRT. However, clinical studies only compared IQOS emissions to combustible cigarettes. It is therefore unclear on what information consumers based their comparative perceptions, and it is likely that those perceptions are incorrect. There are numerous studies showing that people perceive lower harm from all tobacco products, compared to cigarettes; however, what is important is to examine how perceptions of IQOS compare to newer, and arguably more popular, products on the market, such as e-cigarettes.

Since e-cigarettes were first introduced in the U.S. less than a decade ago, there has been a rapid rise in the use of e-cigarettes,[6] a nicotine product that has been marketed with claims of reduced harm similar to PMI's claims about its IQOS product. E-cigarette use is especially common among adolescents and young adults. On the U.S. market since 2007, past 30-day use of e-cigarettes has surpassed use of conventional cigarettes, with use prevalence of 11.3% among high school students (8.0% for cigarettes).[7] Among young adults 18-24 years old, 23.5% have

[6] McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. Nicotine Tob Res. 2015 Oct;17(10):1195-202

[7] Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. MMWR Morb Mortal Weekly Rep 2017; 66:597–603. DOI: http://dx.doi.org/10.15585/mmwr.mm6623a1; Syamlal G, King BA, Mazurek JM. Tobacco Use Among Working Adults — United States, 2014–2016. MMWR Morb Mortal Weekly Rep 2017;66:1130–1135. DOI: http://dx.doi.org/10.15585/mmwr.mm6642a2; see also Centers for Disease Control and Prevention. "National Youth Tobacco Survey (NYTS)." 2015. Web. 22 Aug. 2016; Centers for Disease Control and Prevention "Youth and Tobacco Use." 2016. Web. 22 Aug. 2016; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Gilreath TD, Leventhal A, Barrington-Trimis JL, et al. Patterns of alternative tobacco product use: Emergence of hookah and E-cigarettes as preferred products amongst

ever used an e-cigarette.[8] Youth are also most likely to use flavored e-cigarette and other tobacco products.[9] As such, there is reasonable concern that adolescents will compare IQOS to e-cigarettes when assessing risk reduction, and will be more likely to try IQOS products.

PMI's arguments that modified risk claims will not attract nonsmokers are illogical and inconsistent with the available evidence.

PMI's application states that adult never-smokers in their study reported greater perceptions of risk for IQOS than current or former smokers (section 6.4.4.1-3), and argues that IQOS will not cause or motivate "non-users to be interested in the product because it is still considered a risky product" (section 6.4, p. 70). PMI's reasoning and interpretation of their results is not logical. Many studies have shown that non-tobacco users report greater perceptions of tobacco-related risk, compared to tobacco users.[10] However, you cannot then extend these findings to mean that non-users will never go on to use tobacco. Perceptions can change over time, and across products. Instead, the question is how non-tobacco users perceive IQOS compared to other tobacco products, and whether the marketing and appeal of this new tobacco product will result in lower perceptions of risk of IQOS compared to other tobacco products, which then will result in use.

In addition, PMI ignores the fact that most tobacco use begins before age 18. There is no reason to expect that IQOS would be any different, particularly in light of the fact that e-cigarettes, a similar product, have been more popular with youth than adults.

The question PMI should have asked (and that the FDA should ask) is whether IQOS, with lower perceived risks, encourages never-smokers -- including adolescents and young adults -- who would otherwise not use any tobacco products to be more likely to try the IQOS product.

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youth. *Journal of Adolescent Health*. 2016;58(2):181-185; NIDA. Tobacco/nicotine and E-cigs. https://www.drugabuse.gov/drugs-abuse/tobacconicotine-e-cigs. Updated 2017. Accessed 09/12, 2017.

[8] QuickStats: Percentage of adults who ever used an e-cigarette and percentage who currently use e-cigarettes, by age group. National Health Interview Survey, United States, 2016. MMWR Morb Mortal Weekly Report, 2017;66:892. DOI: http://dx.doi.org/10.15585/mmwr.mm6633a6

[9] Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. JAMA. 2015;314(17):1871-1873; Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. N Engl J Med. 2014;370(23):2250-2252; Feirman SP, Lock D, Cohen JE, Holtgrave DR, Li T. Flavored tobacco products in the United States: A systematic review assessing use and attitudes. *Nicotine Tob Res*. 2016;18(5):739-749; Wagoner KG, Cornacchione J, Wiseman KD, Teal R, Moracco KE, Sutfin EL. E-cigarettes, hookah pens and vapes: Adolescent and young adult perceptions of electronic nicotine delivery systems. *Nicotine Tob Res.* 2016.

[10] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66.

In making its determination on whether to issue an MRTP order, FDA is required to take into account "the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application."[11] To help inform its decision, FDA should consider the recent and well-documented experience with e-cigarettes. In particular, exposure to e-cigarette advertisements causes increases in smoking urge among adult former and current smokers,[12] reduces adolescent never-smokers' perceived risks of regular cigarettes,[13] and has been shown to be associated with increased chances of use in cross-sectional[14] and longitudinal studies. [15]

In addition, the fact that e-cigarettes are perceived as less harmful than regular cigarettes by adolescents and young adult never-smokers[16] is one reason that they are often the first tobacco product adolescents and young adults use, which also predicts future cigarette use.[17] According to PMI's application, while non-smokers' perceived risk score for IQOS are higher than current and former smokers in PMI's studies after seeing the modified risk claims (section 6.4.4.1-3), the scores are significantly lower than the non-smokers' perception of risks for

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[11] Section 911(g)(4)(C) of the Family Smoking Prevention and Tobacco Control Act.

[12] Durkin SJ, Bayly M, Wakefield MA. Can E-Cigarette Ads Undermine Former Smokers? An Experimental Study. Tob Regul Sci. 2016;2(3):263-277; Maloney EK, Cappella JN. Does Vaping in E-Cigarette Advertisements Affect Tobacco Smoking Urge, Intentions, and Perceptions in Daily, Intermittent, and Former Smokers? Health Communication. 2016;31(1):129-138.

[13] Kim M, Popova L, Halpern-Felsher BL, Ling PM. Effects of E-Cigarette Advertisements on Adolescents' Perceptions of Cigarettes. *Health communication.* In Press; Petrescu DC, Vasiljevic M, Pepper JK, Ribisl KM, Marteau TM. What Is the Impact of E-Cigarette Adverts on Children's Perceptions of Tobacco Smoking? An Experimental Study. *Tob Control.* 2016.

[14] Dai, H., & Hao, J. (2016). Exposure to advertisements and susceptibility to electronic cigarette use among youth. Journal of Adolescent Health, 59(6), 620-626; Mantey, D. S., Cooper, M. R., Clendennen, S. L., Pasch, K. E., & Perry, C. L. (2016). E-cigarette marketing exposure is associated with e-cigarette use among US youth. Journal of Adolescent Health, 58(6), 686-690; Giovenco, D. P., Casseus, M., Duncan, D. T., Coups, E. J., Lewis, M. J., & Delnevo, C. D. (2016). Association between electronic cigarette marketing near schools and e-cigarette use among youth. Journal of Adolescent Health, 59(6), 627-634.

[15] Nicksic, N. E., Harrell, M. B., Pérez, A., Pasch, K. E., & Perry, C. L. (2017). Recall of E-cigarette Advertisements and Adolescent E-cigarette Use. Tobacco Regulatory Science, 3(2), 210-221.

[16] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

[17] Kalkhoran S, Glantz SA. E-Cigarettes and Smoking Cessation in Real-World and Clinical Settings: A Systematic Review and Meta-Analysis. The Lancet Respiratory Medicine. 2016;4(2):116-128; Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence. JAMA. 2015;314(7):700-707; Miech R, Patrick ME, O'Malley PM, Johnston LD. E-Cigarette Use as a Predictor of Cigarette Smoking: Results from a 1-Year Follow-up of a National Sample of 12th Grade Students. Tob Control. 2017.

regular cigarettes. ***Like e-cigarettes, PMI's results show that non-smokers (which would include adolescents, young adults, and former smokers) are more likely to try IQOS than regular cigarettes.***

A larger concern about PMI's modified risk claim is that IQOS's labeling and marketing can mislead non-smokers and former-smokers into initiating or re-initiating tobacco use. While some marketing materials mention that IQOS is "not for non-smokers" (e.g. Module 4, A4.1.1, "Brochure Reduced Risk Claim (Important Warning)", p.3), this statement is not predominantly displayed and thus can easily be overlooked by consumers or misunderstood.

Thus, exposure to modified risk claims in IQOS marketing may lead to an increase in exposure to harmful and potentially harmful chemicals in e-cigarettes among never- and former-smokers, including adolescent never-smokers who initiate nicotine use with IQOS.

PMI's application failed to analyze how IQOS labeling and marketing would affect former smokers. The evidence cited in PMI's MRTP application (Section 6.3.2.2.4.2.1) states that relapse to smoking is common among former smokers.. For youth, the cut-off level for susceptibility to cigarettes indicate that only those who choose "Definitely not" are classified as not susceptible, but every other answer (maybe not, maybe yes, definitely yes) qualifies an individual as susceptible. If the same criteria are used, around 66% of former smokers would be susceptible to trying IQOS if offered by a friend (study PBA05). These results should address whether the IQOS product will be viewed as a way to evade smokefree policies or might reframe nicotine use as socially normative, both of which are perceptions associated with e-cigarette marketing, particularly among older adults and former cigarette smokers.[18] ***PMI's own premarket perception studies to address the appeal of IQOS to former smokers indicate that a large proportion would be interested in trying it, depending on the cut-off level for susceptibility.***

The law is crystal clear: FDA may only issue a MRTP order if "the applicant has demonstrated that such product, as it is actually used by consumers, will (A) ***significantly reduce harm*** and the risk of tobacco-related disease to individual tobacco users; and (B) ***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 [emphasis added]."[19] However, PMI has failed to demonstrate that its IQOS product will significantly *reduce* harm or benefit the population as a whole, not solely among current adult cigarette smokers. ***Indeed, the labeling and marketing of IQOS would likely increase harm, especially among adolescent non-users who initiate with IQOS, and would thus not benefit the health of the population as a whole, especially "persons who do not currently use tobacco products."***

PMI did not submit evidence showing that IQOS *as actually used by consumers* would expose them to the claimed reduced level of exposure or risk, and did not submit data and

[18] Cataldo JK, Petersen AB, Hunter M, Wang J, Sheon N. E-cigarette marketing and older smokers: road to renormalization. *Am J Health Behav* 2015;39(3):361-71 (PMC PMC4351761)
[19] Section 911(g)(1) of the Family Smoking Prevention and Tobacco Control Act.

information demonstrating that consumers actually would switch completely to IQOS, rather than use IQOS concurrently with other tobacco products.

Section 911(d)(6) requires that MRTP applicants must submit "data and information on how consumers actually use the tobacco product," and the Guidance recommends that applicants submit data and information specifically addressing "concurrent use of multiple products containing nicotine or tobacco."

Rather than presenting the needed evidence, PMI's MRTP application is based on the premise that smokers who completely switch to IQOS would realize health benefits and reduced harm. PMI's application merely assumes that people who switch to IQOS will not use other tobacco or nicotine products. PMI ignores evidence that adolescent and young adult smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently.[20] PMI's MRTP application also ignores the fact that most smokers who use e-cigarettes do not switch completely from cigarettes to other tobacco products.[21]

The experience with e-cigarettes, which have also been promoted with harm reduction and "smokeless" messages, is directly relevant to adolescents' likely reaction to IQOS. In addition, both have a modern hi-tech image, another common characteristic that raises concerns that IQOS will attract youth. Many adolescents at low risk of initiating nicotine use with conventional cigarettes initiate with e-cigarettes.[22] Adolescents who initiate nicotine use with e-cigarettes are more susceptible to smoking combustible cigarettes.[23] This experience with e-cigarettes raises

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[20] Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, et al. Tobacco use among middle and high school students - United States, 2011-2016. MMWR Morb Mortal Wkly Rep. 2017;66(23):597-603.

[21] Messer K, Vijayaraghavan M, White MM, Shi Y, Chang C, Conway KP, Hartman A, Schroeder MJ, Compton WM, Pierce JP. Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. Addict Behav. 2015 Dec;51:113-9. doi: 10.1016/j.addbeh.2015.06.045. Epub 2015 Jul 4.

[22] Dutra, LM, Glantz, SA. E-cigarettes and national adolescent cigarette use: 2004-2014. Pediatrics. 1239(2), 2017; Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. Tob Control. 2016 Apr;25(e1):e52-9; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

[23] Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD.JAMA Pediatr. 2017 Aug 01;171(8):788-797; Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med*. 2015;49(2):199-206; Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res*. 2016;18(5):654-659; 16. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of

the concern that adolescents and young adults will use both IQOS and other tobacco products concurrently, just as adolescents and young adults are dual and poly-users of e-cigarettes along with other tobacco products.[24]

Indeed, PMI's application indicates substantial dual use of IQOS and conventional cigarettes as actually used. PMI reports (section 3.5.3 and 6.2.2) that 22.4% of US study participants still were using both regular combustible cigarettes and IQOS after 6 weeks. In other countries, dual use of IQOS and combustible cigarettes ranged from 27% (Germany) to 39% (Switzerland) after 4 weeks (section 3.5.3, Table 5). According to PMI's 2016 full-year report,[25] 21-31% of users across multiple countries are dual-users with substantial portion of their tobacco use (>30%) from products other than IQOS, including regular combustible cigarettes. Another 7-15% are "Predominant (70-95% IQOS)" users, meaning they still use regular cigarettes along with IQOS up to 30% of the time. ***The reality of these high levels of dual use contradict the qualifying language included in the proposed IQOS labeling that users must "switch completely" from regular cigarettes to IQOS to get the claimed benefit that underlies all the assessments of the modified risk health effects in other parts of the PMI application.***

PMI does not present compelling evidence that their marketing messages will lead current smokers to switch completely from conventional cigarettes to IQOS.

Tobacco companies have a long history of testing the concept of reduced risk and reduced smoke products similar to IQOS, and consumers in these studies have been uniformly enthusiastic about the concept. However, the actual products have done poorly on the market because they did not deliver on the promises of the concept testing.[26]

PMI did conduct some studies on consumers' comprehension of the modified risk claims (Section 6.4.4.1). The results showed that out of 2,255 adult participants in the US, 62% to 78% of study participants in different study arms identified the "correct" statement ("the risk of tobacco-related diseases can be reduced by completely switching from CC [conventional cigarettes) to IQOS"; section 6.4.4.1, Table 11). However, it is not clear whether the participants fully understood both of the important concepts included in the statement: "reduced" risks (vs. being risk-free) as well as "completely switching" (vs. dual- or poly-use with regular cigarettes). (In addition, as discussed at the beginning of this comment, PMI's own data do not support the conclusion that IQOS is less dangerous than conventional cigarettes.) ***Thus, PMI did not and***

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electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700-707; E-cigarette use and willingness to smoke: a sample of adolescent non-smokers.Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. Tob Control. 2016 Apr;25(e1):e52-9.

[24] Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use:. *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

[25] https://www.pmi.com/investor-relations/overview/event-details/?eventId=5246224, Slide p. 19

[26] Ling PM, Glantz SA. Tobacco industry consumer research on socially acceptable cigarettes. *Tob Control.* 2005 Oct;14(5):e3. Review. PubMed PMID: 16183968; PubMed Central PMCID: PMC1748101.

cannot substantiate their claim that "scientific studies have shown that switching completely from conventional cigarettes to the IQOS system reduces the risks of tobacco-related diseases" and they did not and cannot provide evidence that U.S. adults or adolescents (who are likely users of IQOS) understand the modified risk claims made in their labeling and marketing.

According to PMI's application (7.3.2; PBA05RRC - 2 csr-app-16_1_1-protocol.PDF), PMI's research question looked at whether "…completely switching from conventional cigarettes to IQOS: a) can increase the risk of tobacco-related disease, b) can reduce the risk of …, c) has the same risk of tobacco-related diseases, d) can eliminate the risk of …, e) don't know." (#44, p.89) However, as presented, this question cannot measure whether the participants understood the phrase "completely switching" and therefore fails to demonstrate at least two important factors that FDA deemed critically important to its review of MRTP applications: (1) whether consumers fully "understand the modified risk claims and the significance of the information in the context of ones health," or (2) whether consumers truly understand "the health risks of using the product."[27] Rather, this question can only test the recognition of the terms "reduced" vs" "eliminates," since all response options included the phrase "completely switch." According to the results, less than 6% of participants selected the response that IQOS "eliminates" the risks, which PMI interpreted to indicate that participants did understand the "reduced" risks of IQOS compared to regular cigarettes. ***However, given the response options available to study participants, the question whether consumers fully understood "switching completely" remains untested.***

Given that PMI's research attempted to test understanding of "switching completely" but embedding the concept within the response option for "reduced" risks ("the risk of tobacco-related diseases can be reduced by completely switching…"), we do not have a way to tell whether the participants chose that response because they noticed or understood what was meant by the words "completely switching" from regular cigarettes to IQOS or whether they were interpreting the response differently. Participants were not asked to compare risks of using IQOS vs. using IQOS and regular cigarettes vs. only using cigarettes. The question of whether people truly understand "switching completely" also remains unaddressed in the second quantitative study (Section 6.4.4.2 where PMI tested the effect of a different claim "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes" on 2,247 adults' perceptions of IQOS in the US) and the third quantitative study (Section 6.4.4.3 where PMI tested the effects of reduced exposure claim "Switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals" on 2,272 adults' perceptions of IQOS in the US). ***The fact that more than 25% of actual users of IQOS are using regular combustible cigarettes may be due to the insufficient communication and comprehension of the need to switch completely.***

To support their reduced risk marketing claim, PMI also conducted focus groups and in-depth interviews with adult participants to assess risk perceptions related to IQOS (THS 6.4 Consumer Understanding and Perceptions). Participants were presented with different types of claims (e.g., reduced exposure versus reduced risk) and varying levels of specificity (e.g., general health claims versus specific health claims). For instance, participants were presented

[27] FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, March 2012.

with general claims such as "switching to THS 2.2 can lower several risk factors that could lead to smoking-related diseases," and specific claims such as "switching to THS 2.2 can lower your cardiovascular risk."[28] ***None of the scenarios discussed the potential general or specific risk of dual and/or poly-use among current smokers who are unable to switch completely to IQOS.***

The tested claims inappropriately assumed cardiovascular benefit despite the fact that PMI's own data presented in the application show no significant differences in biomarkers of potential harm for cardiovascular disease in their human studies.[29] Participants' quotes were generally positive toward the use of IQOS, but it is unclear whether the opinions stemmed from a consensus among participants or whether only a minority of participants expressed those views. It was unclear how much, if any, evidence was provided to support the claims of reduce tobacco-related disease or reduced harm. Thus, claims by PMI that participants "correctly" comprehended the inherent risks related to IQOS are incomplete without understanding the context in which focus group discussions were conducted.

Furthermore, the two qualitative studies only used 10 non-smokers. For example, in the study THS-PBA-02-US, only 6 non-smokers participated in individual interviews. Of these six non-smokers, only two were 21-36 years old (which could be considered as young adult) – one male and one female. The conclusion that never smokers are not interested in these products that the report makes is based on only 6 never smokers, most of whom were beyond the age of tobacco initiation.

In quantitative studies, PMI reported creating a new risk perception instrument that included an 18-item perceived health risk scale, a 7-item perceived addiction risk scale, and a 2-item perceived harm to others scale. PMI reported that THS was on average "8 and 22 points lower than CC on the 0 to 100 perceived health risk scale" (THS 6.4 Consumer Understanding and Perceptions). PMI claims that their development and assessment studies demonstrated that the majority of smoking and non-smoking participants consistently ranked THS as lower risk compared to combustible cigarettes but higher risk compared to e-cigarettes and nicotine replacement therapy. Nonsmokers had a higher risk perception compared to smokers. These findings need to be interpreted in the context of the measurement instrument used in the study.

Questions in the PMI's "Perceived Risk Instrument" provided conditional scenarios, for example, "What do you think is the risk, if any, to you personally of getting the following (sometime during your lifetime) because you smoke cigarettes…" However, these scenarios were very generic. Compare, for example, to specific scenarios used by Halpern-Felsher et al[30].„ "Imagine that you just began smoking. You smoke about 2 or 3 cigarettes each day. Sometimes you smoke alone, and sometimes you smoke with friends. What are the chances of…?" PMI's questions also did not specify the amount of use (i.e., how much a person smokes), presence of

[28] THS Messages tested in THS-PBA-02-US, Table 3, MRTPA section 6.4, page 14.

[29] Glantz S. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims. Docket Number: FDA-2017-D-300. November 13, 2017.. Tracking is 1k1-8zrx-juh9.

[30] Halpern-Felsher, B. L., Biehl, M., Kropp, R. Y., & Rubinstein, M. L. (2004). Perceived risks and benefits of smoking: differences among adolescents with different smoking experiences and intentions. *Preventive Medicine, 39*(3), 559-567. doi:DOI 10.1016/j.ypmed.2004.02.017

dual use (using cigarettes in addition to another tobacco product), and age of quitting for cessation questions. The use of the different measurement instrument makes comparison with other studies difficult.

In their Perceived Risk Instrument, PMI is measuring absolute perceptions of risk for each product (separately for cigarettes and IQOS), rather than asking direct comparative questions (e.g., "Are (IQOS products) less harmful/equally as harmful/more harmful than (cigarettes)?" Past research has found that when risks are measured for products separately, greater proportion of people perceive alternative tobacco products as less harmful.[31] When comparative risk is measured with a direct question, a greater portion of participants responds that alternative tobacco products are equally as harmful as cigarettes. ***The choice of indirect and direct questions seems to be guided by tobacco companies' goals rather than measures of validity***.

For example, in its 2011 Citizen's Petition to the FDA, RJ Reynolds argued that US consumers overestimate risk of smokeless tobacco because the studies they cited reported that a large portion of the public perceived smokeless tobacco as equally harmful to cigarettes. However, most of the studies cited in that petition used direct way (single question) of measuring perceived harm. When the goal of the tobacco company was to show that the public believes alternative tobacco products are as harmful as cigarettes, direct way of measuring relative risk has been used. In the PMI's MRTP application, the goal seems to be to demonstrate greater difference in perceptions of risk between various products, so they used indirect way of measuring relative risk. While we have argued for the use of indirect measures,[32] some research indicates that direct measures might have closer relationship to people's behavior.[33] ***Thus, both indirect and direct measures should have been, but were not, used to support the conclusions made in the PMI's study are not the artifact of their carefully selected measurement tool.***

PMI's claims of reduced exposure and reduced harm from IQOS do not account for how their product is likely to be actually used, and in particular do not account for the tobacco use behaviors that accompany the introduction of a new tobacco or nicotine product into the market, as was the observed concern with e-cigarettes.

Section 911(g) mandates that FDA may issue a MRTP order *only if* the applicant has demonstrated that the proposed product, *as it is actually used by consumers*, will significantly reduce harm to individual tobacco users and benefit the health of the population as a whole. ***Since PMI's MRTP application for IQOS fails to take into account how IQOS is likely to be***

[31] Popova, L., & Ling, P. M. (2013). Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health, 103*(11), e21-e23; Wackowski OA, Bover Mandersiki MT, Delnevo C. Comparison of Direct and Indirect Measures of E-cigarette Risk Perceptions. Tob Regul Sci. 2016; 2(1): 38-43; Persoskie, A., Nguyen, A. B., Kaufman, A. R., & Tworek, C. (2017). Criterion validity of measures of perceived relative harm of e-cigarettes and smokeless tobacco compared to cigarettes. *Addictive Behaviors, 67*, 100-105.

[32] Popova, L., & Ling, P. M. (2013). Perceptions of Relative Risk of Snus and Cigarettes Among US Smokers. *American Journal of Public Health, 103*(11), e21-e23.

[33] Persoskie, A., Nguyen, A. B., Kaufman, A. R., & Tworek, C. (2017). Criterion validity of measures of perceived relative harm of e-cigarettes and smokeless tobacco compared to cigarettes. *Addictive Behaviors, 67*, 100-105.

actually used, PMI has failed to make the required showing and FDA must not issue a MRTP marketing order.

Although some current smokers may switch completely to IQOS and be successful at smoking cessation, some users of IQOS will become dual and/or poly-users, as is the case e-cigarettes, and to some degree, smokeless tobacco. Indeed, as discussed above, PMI's own data show substantial levels of dual use in their test populations. If this were to happen, IQOS could cause significant increased population level harm by increasing nicotine dependence and tobacco-related diseases from the use of more than one tobacco product, as we are seeing with dual-use of e-cigarettes and cigarettes.[34]

E-cigarettes, like IQOS, are marketed as non-combustible alternatives to conventional cigarettes. PMI does not address the evidence that adolescents believe that e-cigarettes are less harmful than cigarettes and all other tobacco products,[35] that e-cigarettes are acceptable and socially normative,[36] and that these perceptions and attitudes are directly related to initiation and use of e-cigarettes.[37] Despite studies showing negative health effects of e-cigarettes, adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes, and contain none or just limited amounts of nicotine. Adolescents also consider e-cigarettes to be trendier, more prevalent, and more acceptable than conventional cigarettes.[38] Adolescents who have used e-cigarettes have reported the lowest perceptions of

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[34] Kalkhoran S, Glantz SA. Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis. JAMA Intern Med. 2015 Oct; 175 (10): 1671-80. doi: 10.1001/jamainternmed.2015.4209.
Mejia AB, Ling PM, Glantz SA. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. Tob Control. 2010 Aug;19(4):297-305. doi: 10.1136/tc.2009.031427. Epub 2010 Jun 27.

[35] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

[36] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20.

[37] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Pepper, JK, Emergy, SL, Ribisl, KM, Rini, CM, Brewer, NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. J Behav Med. 2015 Apr;38(2):318-26.

[38] Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Hammal F, Finegan BA. 2016. Exploring Attitudes of Children 12–17 Years of Age Toward

harm and more positive attitudes regarding e-cigarettes.[39] ***Given that there are no current studies on adolescents' perceptions of IQOS, PMI should have addressed (and the FDA should address) the analogous evidence from e-cigarettes to estimate the effects that IQOS will have on adolescents' willingness to make similar assumptions about the risks associated with IQOS, and will be willing to initiate and use IQOS.***

There are other important parallels with the entry of e-cigarettes into the market that can be used to assess the likely effects of IQOS in the marketplace. Studies on risk perceptions of electronic cigarettes have shown that many users of e-cigarettes perceive these products to be less harmful than cigarettes and to be effective as smoking cessation aids.[40] An analysis of e-cigarettes retail websites showed that 95% of the 59 included websites made explicit claims that e-cigarettes can aid in smoking cessation or improve health.[41] Websites that compared cigarettes with e-cigarettes stated that e-cigarettes were cleaner (95% of the websites), cheaper (93% of the websites), could be used to circumvent indoor clear air policies (71% of websites), and could aid in smoking cessation (64%). Other studies that evaluated the content of websites of e-cigarette manufacturers in China showed similar claims of health-related benefits, reduced secondhand

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Electronic Cigarettes. *Journal of Community Health.* 1-7; Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. 2013. *J Am Coll Health.* 61(3):149-155.Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

[39] Ambrose BK, Rostron BL, Johnson SE, et al. 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. *Am J Prev Med.* 47(2 Suppl 1):S53-60; Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436); Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *American Journal of Health Behaviors*; 2015 May; 39(3):421-432; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85. Trumbo & Harper, 2013)

[40] Roditis M, Delucchi K, Cash D, Halpern-Felsher B. Adolescents' perceptions of health risks, social risks, and benefits differ across tobacco products. *Journal of Adolescent Health.* 2016;58(5):558-566; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res*. 2015;17(7):847-854; El-Toukhy S, Choi K. A risk-continuum categorization of product use among US youth tobacco users. *Nicotine Tob Res*. 2016.

[41] Grana, RA and Ling P. Smoking revolution: a content analysis of electronic cigarette retail websites. Am J Prev Med. 2014; 46(4): 395-403; Klein EG, Berman M, Hemmerich N, Carlson C, Htut S, Slater M. Online E-cigarette marketing claims: A systematic content and legal analysis. *Tobacco Regulatory Science*. 2016;2(3):252-262.

smoke exposure, and utility for smoking cessation.[42] These explicit claims were made in the absence of consistent evidence pointing to benefits in health or smoking cessation. Furthermore, these claims are often communicated to cigarette smokers and non-smokers alike, including adolescents, leading to the belief that e-cigarettes are a less harmful choice for any user (that is, not just in comparison to cigarette use), which in turn resulted in e-cigarette initiation among non-users.[43] In particular, adolescents believe that e-cigarettes are less harmful than cigarettes and all other tobacco products[44] and that e-cigarettes are acceptable and socially normative (with a sizeable proportion (20-28%) agreeing that it is ok to use e-cigarettes indoors and outdoors).[45] Such perceptions and attitudes are directly related to initiation and use of e-cigarettes.[46] Despite studies showing negative health effects of e-cigarettes, adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes, and contain none or just limited amounts of nicotine. Adolescents also consider e-cigarettes to be trendier, more prevalent, and more acceptable than conventional cigarettes.[47] The lowest

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[42] Yao T, Jiang N, Grana R et al., A content analysis of electronic cigarette manufacturer websites in China. Tob Control. 2016; 25(2):188-94

[43] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66

[44] Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

[45] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20.

[46] Gorukanti, A. Delucchi, K., Ling, P.P, Fisher-Travis, R. Halpern-Felsher, B. Adolescents' Attitudes towards E-cigarette Ingredients, Safety, Addictive Properties, Social Norms, and Regulation. *Preventive Medicine*. 2016 Oct 20; Roditis, M., Delucchi, K., Cash, D., & Halpern-Felsher, B. Adolescents' Perceptions of Health Risks, Social Risks, and Benefits Differ across Tobacco Products. *Journal of Adolescent Health*. 2016 May, 58(5):5558-66 ; Pepper, JK, Emergy, SL, Ribisl, KM, Rini, CM, Brewer, NT. How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products. J Behav Med. 2015 Apr;38(2):318-26.

[47] Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 57(1):46-51; Hammal F, Finegan BA. 2016. Exploring Attitudes of Children 12–17 Years of Age Toward Electronic Cigarettes. *Journal of Community Health.* 1-7; Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. 2013. *J Am Coll Health.* 61(3):149-155.Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85.

perceptions of harm and more positive attitudes regarding e-cigarettes have been reported by adolescents who have used e-cigarettes.[48]

Given the similarities between IQOS and e-cigarettes (both products are electronic and hi-tech, and are marketed with reduced harm claims, as better alternatives to cigarettes, and with claims of no "smoke"), it is reasonable to expect that IQOS, like e-cigarettes, will be popular with youth. This is particularly likely because youth will make similar assumptions about the risks associated with IQOS as they make about the risks of e-cigarettes, and will be willing to initiate and use IQOS.

Thus, a major gap in PMI's application is the absence of any comparisons with e-cigarettes. PMI must show that the proposed marketing of IQOS will not result in perceptions and behaviors that have been concerning for e-cigarettes: namely, that youth and non-smokers are likely to initiate based on faulty perceptions of the product's harms, and are likely to dual-use the product with other forms of tobacco. **While PMI asserts in its application that IQOS products will be marketed exclusively to current cigarette smokers, there is no practical way to restrict sales and use among non-smokers.**

In Korea, PMI stresses that IQOS is meant to be used only by established smokers as an alternative to conventional cigarettes (see Figure 1). Nevertheless, a postdoctoral fellow, who is part of the UCSF TCORS and who is a never-smoker, easily purchased IQOS at one of the Korean IQOS stores in June 2017. At one store, a clerk asked the researcher's smoking status and refused to let her in the store because she was not a smoker. ***In another store, however, the staff did not ask the researcher's smoking status, and she easily purchased IQOS in that store***.

Moreover, checking for smoking status in the first store relied on self-report. Unlike checking the consumer's age using government-issued photo ID, smoking status is hard to validate. ***While there was a 15-minute "information session" provided by the staff inside the Korean flagship store before purchase, it focused on how to use the device, and none of the warnings for nonsmokers or former smokers, or emphasis on complete switching (vs. dual use), were provided***.[49]

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[48] Ambrose BK, Rostron BL, Johnson SE, et al. 2014. Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth. *Am J Prev Med.* 47(2 Suppl 1):S53-60; Anand V, McGinty KL, O'Brien K, Guenthner G, Hahn E, Martin CA. 2015. E-cigarette Use and Beliefs Among Urban Public High School Students in North Carolina. *The Journal of adolescent health: official publication of the Society for Adolescent Medicine.* 57(1):46-51; Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436) ; Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *American Journal of Health Behaviors*; 2015 May; 39(3):421-432; Roditis, M.L., & Halpern-Felsher, B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes and marijuana: A Qualitative Analysis. *Journal of Adolescent Health*. 2015 Aug; 57(2); 179-85. Trumbo & Harper, 2013)

[49] Kim M. Philip Morris International Introduces New Heat-Not-Burn Product, IQOS, in South Korea. *Tob Control.* In press.

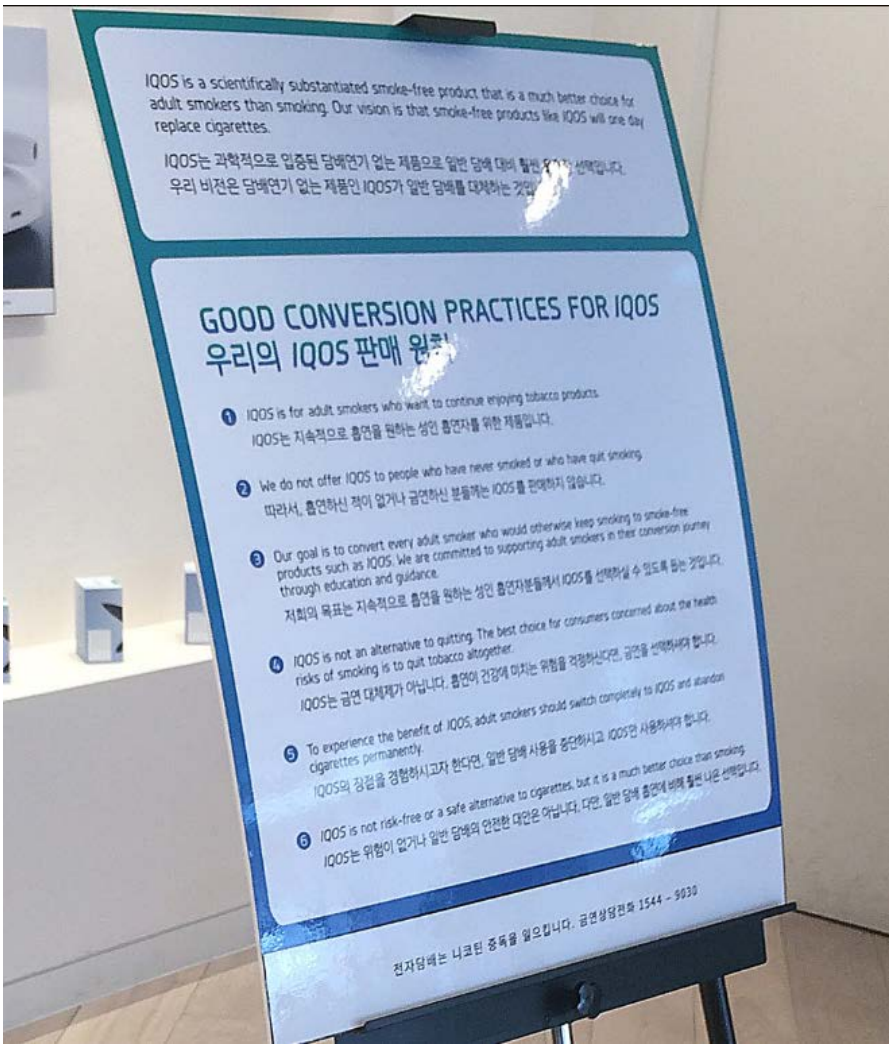

Figure 1. IQOS marketing material in the flagship store in Seoul, Korea. Bullet point #1 asserts that "IQOS is for adult smokers who want to continue enjoying tobacco products. Bullet point #2 asserts that "We [PMI] do not offer IQOS to people who have never smoked or who have quit smoking." However, although this poster was displayed inside the store, the store staff did not discuss these contents or verify if potential purchasers were current adult smokers or current never smokers. (Picture taken by Minji Kim.)

In addition, limiting purchases by youth and non-smokers online is nearly impossible.[50] The PMI application does not address this problem at all.

There is sufficient evidence demonstrating that youth under age 18 purchase tobacco products on the Internet. Indeed, the Internet serves as a significant means of acquiring tobacco

[50] Halpern-Felsher, B. FDA Should Restrict Internet Sales of All Tobacco Products Including E-Cigarettes, Docket No. FDA-2014-N-0189. https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/FDA-Comment-BHF-Submitted%20in%20Response%20to%20FDA%20Deeming%20Rule_Internet%20Sales_FINAL.pdf

for youth, with Internet sales serving as a way to circumvent the age restrictions and face-to-face age verification requirements, given that age verification is virtually non-existent and meaningless.[51] In 2004-2005, youth were 2.6 times more likely to purchase cigarettes over the Internet than were similar students just 4-5 years earlier. The rates went from 1.6% in 2001 to 5.2% in 2005. Moreover, 9% reported that they intended to purchase cigarettes through the Internet.[52] Furthermore, age restrictions over the Internet are extremely difficult to enforce.[47]

The effects on youth and adolescents are also important, but neither PMI nor any other company should conduct research on youth because this information, collected under the guise of harm reduction or "youth smoking prevention" could easily be used to improve marketing to youth. Rather, as discussed above, the analysis should be done based on current patterns of use of similar products that are already in the market, most notably e-cigarettes.

PMI's application does not provide compelling evidence that users will understand the need to "switch completely" from cigarettes to obtain the alleged benefit of using IQOS

The following comments should not be interpreted as accepting PMI's assertion that "switching completely" from conventional cigarettes to IQOS will reduce risk. As discussed at the beginning of this comment, PMI's own clinical biomarker studies do support the reduced risk claim in humans.

While adults often report a desire to quit smoking as a motivator for e-cigarette use,[53] youth most commonly report curiosity as a reason to try e-cigarettes.[54] It is very plausible that youth would find IQOS to be appealing, similar to how youth attraction to e-cigarettes is enhanced due to curiosity about new technology,[55] menthol flavor,[56] and ability to use in places where smoking is prohibited.[57] It has been consistently reported in multiple, well-controlled

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[51] Fix, BV, Zambon M, Higbee C, Cummings KM, Alford T, Hyland A. 2006. Internet cigarette purchasing among 9th grade students in western New York.: 2000-2001. Preventive Medicine, 43(3), 191-195, 2006.

[52] Abrams SM, Hyland A, Cummings KM (2003). Internet cigarette purchasing among ninth-grade students in Western New York. Preventive Medicine, 36(6): 731-733.

[53] Rutten LJ, Blake KD, Agunwamba AA, Grana RA, Wilson PM, Ebbert JO, Okamoto J, Leischow SJ. Use of e-cigarettes among current smokers: Associations among reasons for use, quit intentions, and current tobacco use. *Nicotine Tob Res* 2015;17(10):1228-34 (PMC PMC4592339)

[54] Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436)

[55] Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res* 2015;17(7):847-54 (PMC PMC4674436)

[56] Krishnan-Sarin S, Green BG, Kong G, Cavallo DA, Jatlow P, Gueorguieva R, Buta E, O'Malley SS. Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes. *Drug Alcohol Depend* 2017;180:193-9 (PMC PMC5659733)

[57] Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Trying E-cigarettes and Risk of Continued Use. *Pediatrics* 2016;138(3) (PMC PMC5005025 conflicts of interest to disclose.)

prospective studies, that youth who experiment with e-cigarettes are at substantially elevated risk of subsequent initiation of cigarette smoking.[58] ***PMI's MRTP application ignores the fact that based on the public health experience with e-cigarettes, it likely that IQOS would be appealing to these groups, and therefore lead to an increase in tobacco-related harm among youth and current non-smokers.***

Importantly, PMI's proposed claims introduce language ("switching completely," "significantly reduces," and "potentially harmful chemicals") that is unlikely to be familiar to the average tobacco consumer, especially adolescents and youth. It is essential that PMI demonstrate that such claims will be understood by the general public and that consumers' (or potential consumers') interpretations of these claims are aligned with the actual risks of IQOS and HeatSticks. The language used in these claims must be tested thoroughly among the entire population for salience, credibility, readability, and accuracy of consumers' interpretations.

There is reason to believe that potential IQOS consumers will misunderstand the concept of "switching completely." For example, many individuals who engage in smoking do not consider themselves to be smokers,[59] including large numbers of young adult smokers and >12% of all adult smokers in California.[60] Smoking cigarettes but not identifying as a smoker is common among non-daily smokers who were formerly daily smokers,[61] opening the likelihood that THS users may consider themselves to have "switched completely" even if they continue to smoke combustible cigarettes.

The law requires PMI to demonstrate that the proposed marketing of IQOS as a MRTP will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes, and will not lead to substantial product appeal (and subsequent use) among youth, adolescents, and young adults. Until such evidence is available, FDA should reject PMI's MRTP application.

PMI has not provided sufficient evidence that the proposed disclaimers associated with their modified risk or modified exposure claims (i.e., the "PMI IMPORTANT WARNINGS" in Section 6.4.5.1) will assure accurate perceptions of product risk.

PMI proposed the following "important warning" for its modified risk Claim #1:

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[58] Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: A systematic review and meta-analysis. *JAMA Pediatr* 2017;171(8):788-97

[59] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3 ; Guillory J, Lisha N, Lee YO, Ling PM. Phantom smoking among young adult bar patrons. *Tob Control* 2017;26(2):153-7 (PMC PMC5067225)

[60] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3

[61] Leas EC, Zablocki RW, Edland SD, Al-Delaimy WK. Smokers who report smoking but do not consider themselves smokers: a phenomenon in need of further attention. *Tob Control* 2015;24(4):400-3

- Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

PMI proposed the following "important warning" for its reduced harm Claim #2:

- Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- *HeatSticks* contain nicotine, which is addictive.

PMI proposed the following "important warning" for its reduced exposure Claim #3:

- It has not been demonstrated that switching to the *iQOS* system reduced the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

PMI compared their own proposed disclaimers to existing Surgeon General warnings; however, new Surgeon General warnings specific to heat-not-burn tobacco have yet to be designed, limiting the relevance of this comparison. Furthermore, disclaimers are often insufficient to correct consumer misperceptions. For example, disclaimers intended to inform consumers that "natural" or "organic" cigarettes are no less harmful than other cigarettes do not deter inaccurate beliefs that natural cigarettes are less harmful.[62] In fact, government-mandated disclaimers in advertising have been shown to increase consumer confusion and often have effects on consumer perceptions and beliefs opposite of those intended.[63]

Furthermore, not only should PMI provide evidence that current adult smokers will understand what is meant by the phrase "switching completely," but the MRTP application should also contain evidence that switching completely from combustible cigarette smoking to the IQOS system will be the predominant use pattern in the US population.

Epidemiologic evidence demonstrates that for other non-cigarette tobacco products, switching completely has not been the most common outcome. Among US adults who use electronic cigarettes, 75% to 82% use e-cigarettes in combination with at least one other form of combustible tobacco,[64] and only 20% of e-cigarette users are recent quitters of combustible

[62] Byron MJ, Baig SA, Moracco KE, Brewer NT. Adolescents' and adults' perceptions of 'natural', 'organic' and 'additive-free' cigarettes, and the required disclaimers. *Tob Control* 2016;25(5):517-20 (PMC PMC4887411)

[63] Green KC, Armstrong JS. Evidence on the effects of mandatory disclaimers in advertising. *Journal of Public Policy & Marketing* 2012;31(2):293-304

[64] Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, Kaufman AR, Bansal-Travers M, Travers MJ, Kwan J, Tworek C, Cheng YC, Yang L, Pharris-Ciurej N, van Bemmel DM, Backinger CL, Compton WM, Hyland AJ. Tobacco-Product Use by Adults and Youths in the United States in 2013 and

cigarettes.[65] Among adult US males who currently use smokeless tobacco on some days, 45% also smoke cigarettes.[66] In the data PMI submitted as part of this MRTP application (Executive Summary Figure 35), only 15% of study participants provided with THS (PMI's "Tobacco Heating System") had adopted what PMI labels as a "THS use pattern." More often, participants used both THS and combustible cigarettes.

PMI has not provided a clear definition of what "switching completely" to Tobacco Heat Sticks means. The MRTP application (Executive Summary pages 128 and 147) defines THS use as "≥ 70% of tobacco products used were HeatSticks" but does not provide the units or measures used to calculate this percentage. It is not known whether this percentage relates to the number of cigarettes and HeatSticks used, total nicotine intake, frequency of use, types of tobacco products used, or some other measure. Lack of knowledge of the actual behavior patterns among PMI study participants impedes adequate interpretation of the research findings. ***Regardless of the specific denominator used, 70% conversion still leaves 30% of consumption as conventional cigarettes, which represents dual use not "switching completely, which would be 100%."***

As is the case for the consumer perception studies, FDA did not post the actual scientific studies upon which PMI's application relies, including the perception and behavior assessment studies, until 5 months after the public comment period began in June 2017. This delay has not allowed sufficient time for researchers and the public to independently verify or analyze the results in detail. FDA should not approve the MRTP application without allowing outside parties sufficient time to review these critical studies.

PMI's packaging, labeling, and brochures do not give specific instructions on how to use the product to get the proposed reduction in risk or exposure, or specific instructions on how to avoid using the product in a way that could reduce or eliminate the potential benefit or increase the risk of using IQOS

PMI's MRTP application for IQOS does not meet the requirements of Section 911(d) because it does not contain the essential "conditions for using the product," i.e., to get the desired reduction in exposure or risk, users must stop using any other tobacco product and use IQOS exclusively. The application mentions that PMI addresses the FDA's guidance on MRTP application to include "specific instructions on how to use and store the product to get the proposed reduction in risk or exposure" (p. 12) in their User Guide (A3.4.1), but the language is limited to using only HeatSticks (e.g. "Never use IQOS holder with a conventional cigarette, or other products/objects", p.7). ***In particular, the IQOS packaging, labeling, instructions for use, users guide, and other advertising materials submitted by PMI do not specifically instruct***

2014. *N Engl J Med* 2017;376(4):342-53 (PMC PMC5317035) ; Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *Int J Public Health* 2016;61(2):177-88 (PMC PMC4819498)

[65] Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *Int J Public Health* 2016;61(2):177-88 (PMC PMC4819498)

[66] Tomar SL, Alpert HR, Connolly GN. Patterns of dual use of cigarettes and smokeless tobacco among US males: findings from national surveys. *Tob Control* 2010;19(2):104-9 (PMC PMC2989167)

consumers that they must not use IQOS concurrently with other tobacco products (including conventional cigarettes, e-cigarettes, hookah, or other tobacco products), and do not clearly explain that consumers will not get the stated reduction in risk or exposure if they engage in dual- or poly-use of IQOS products with other tobacco products.

This omission is especially critical for young adult and potential adolescent users, who typically use more than one kind of tobacco product concurrently.[67,68,69] Importantly, PMI did not submit any studies demonstrating that youth, adolescents, or even adults understand this essential condition for use.

PMI's IQOS labeling and advertising are likely to mislead consumers, especially adolescents and youth

In their MRTP application, PMI includes three proposed label and marketing statements, two focused on claims of reduced risk and one focused on the claim of reduced exposure.

The first proposed label and marketing statement concerning reduced risk states:

Claim #1 (Section 2.7.6 Part B, Table 18):

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.

[67] McKelvey, K, Ramo, D, Delucchi, K, Rubinstein, M. (Under review) Polydrug use among urban adolescent cigarette smokers. *Addict Behav;* Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med*. 2015;49(2):199-206; Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res*. 2016;18(5):654-659.; Haardörfer R, Berg CJ, Lewis M, et al. Polytobacco, marijuana, and alcohol use patterns in college students: A latent class analysis. *Addict Behav*. 2016;59:58-64; Huh J, Leventhal AM. Progression of poly-tobacco product use patterns in adolescents. *Am J Prev Med*. 2016.

[68] Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use:. *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

[69] Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use:. *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11; Kowitt, SD, Patel, T., Ranney, LM, Huang, LL, Sutfin, EL, Goldstein, AO. Poly-tobacco use among high school students. Int J Environ Res Public Health. 2015 Nov; 12(11): 14477–14489.
Published online 2015 Nov 13. doi: 10.3390/ijerph121114477. PMCID: PMC4661661; Soneji, S., Sargent, J, Tanski, S Multiple tobacco product use maong US adolescents and young adults. Tobacco control, 25(2), 2016.

- Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.

The second proposed label and marketing statement concerning reduced risk states:

Claim #2 (Section 2.7.6 Part B, Table 19):

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

The third proposed label and marketing statement, concerning reduced exposure states:

Claim #3 (Section 2.7.6 Part B, Table 20):

- 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 cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

The law[70] requires PMI to demonstrate that consumers and potential consumers, including youth and adolescents, will not be misled by labels and advertising. However, there is no evidence that consumers and non-consumers, especially youth, will understand PMI's proposed reduced risk and reduced exposure statements.

The warnings proposed by PMI to be used in their IQOS marketing are particularly problematic when considering youth. The second sentence in the first warning statement ("The best way to reduce your risk of tobacco-related disease is to completely quit tobacco use") should be expanded to add the following phrase at the end: "**including use of nicotine-containing products such as IQOS."** Adolescents who perceive a tobacco product to be "less harmful" compared to cigarettes are more susceptible to use that product.[71] Additionally, when adolescents were polled on their beliefs about risks of smoking "light" cigarettes (a hypothetical "reduced harm" product), it was shown thought that they felt they would be significantly less likely to get lung cancer, have a heart attack, die from a smoking-related disease, get a bad cough, have trouble breathing, and get wrinkles when smoking light cigarettes, compared with regular cigarettes.[72]

The second and third warning statements ("HeatSticks contain nicotine, which is addictive," and "Using the IQOS system can harm your health") are virtually meaningless to adolescents. It is well-established that adolescents do not grasp the concepts of harm, including

[70] Section 911(g)(2)(B)(iii) of the Family Smoking Prevention and Tobacco Control Act.
[71] Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. JAMA. 2015;314(17):1871-1873
[72] Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

addiction, or of a substance being addictive. While adolescents have received the message that cigarettes are addictive, they are uncertain regarding the definition of addiction and have not recognized that addiction means experiencing difficulty quitting and continuing to smoke longer than expected.[73] Moreover, the same study showing adolescent beliefs about smoking "light" cigarettes[74] found when participants were asked how long it would take to become addicted to smoking regular or light cigarettes, they thought it would take significantly longer to become addicted to light versus regular cigarettes; that their chances of being able to quit smoking were higher with light versus regular cigarettes; and that they thought it would be significantly easier for them to quit smoking light cigarettes than regular cigarettes.[75] Furthermore, there is a significant association between regular, experimental, and non-smokers' perceptions about their personal susceptibility to addiction, with regular smokers showing the greatest optimistic bias about their ability to quit smoking, a measure of addiction.[76] Finally, evidence shows that smoking initiation is directly related to smoking-related perceptions of risks ("harm") and benefits. Thus, efforts to reduce adolescent uptake of tobacco products should continue to communicate the particular health risks of smoking and counteract perceptions of benefits associated with smoking.[77]

Because the scientific evidence provided by PMI in support of using these labels does not include youth or adolescents, PMI did not meet its burden of demonstrating that the labels will be understood by and will not mislead the population as a whole. Past research on labels on other tobacco products and advertising suggests that adolescents are likely to misinterpret these messages, believing that the messages being conveyed are simply indicating that IQOS are not harmful.[78] ***When youth do not adequately understand messages, they make assumptions that the tobacco products are safe, and are more likely to initiate and continue using that product***.[79]

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[73]Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior*. 2016 April; 43(2):156-64;

[74] Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

[75] Kropp, RY, Michels, TM, & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking light cigarettes. Presented at the American Public Health Association Annual Meeting, San Francisco, CA, November 18, 2003

[76] (Twigg & Byrne, 2015)

[77] Song, AV, Morrell, HE, Cornell, JL, Ramos, M.E., Biehl, M., Kropp, R.Y., Halpern-Felsher,B.L. Perceptions of Smoking-Related Risks and Benefits as Predictors of Adolescent Smoking Initiation. American Journal of Public Health. 2009 Mar; 99(3):487-92. PMID: 19106420.

[78] Peebles K, Hall MG, Pepper JK, Byron MJ, Noar SM, Brewer NT.Adolescents' Responses to Pictorial Warnings on Their Parents' Cigarette Packs. J Adolesc Health. 2016 Dec;59(6):635-641.

[79] Roditis, M.L., Lee, J., & Halpern-Felsher, B. Adolescent (Mis)Perceptions about Nicotine Addiction: Results from a Mixed-Methods Study. *Health Education & Behavior*. 2016 April; 43(2):156-64.

Furthermore, the proposed "warnings" from PMI are text-only, which will likely limit their effectiveness. Compared with text-only warnings, pictorial warnings on cigarette packs better hold attention, elicit stronger cognitive and emotional reactions and more negative attitudes towards the pack and smoking, and increase intentions to quit smoking.[80] Additionally, a randomized controlled trial showed that participants who carried cigarette packs labeled with pictorial warnings, compared with those with text-only warnings, were more likely to quit or attempt to quit smoking during the trial, had greater intentions to quit, had more negative emotional reactions and conversations about quitting, and thought more about the harms of smoking.[81] There is strong evidence that compared with text-only warnings, pictorial warnings are more effective in conveying the harms of tobacco product use, are more noticeable, and result in more quit attempts. ***Any warnings should include graphic elements to maximize effective communication of the warnings.***

A modified exposure claim is likely to be misunderstood as a modified risk claim, so PMI should not be permitted to market IQOS with a modified exposure claim.

To issue a modified exposure order, section 911(g)(2)(B)(iii) requires the applicant to demonstrate that "testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product— (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than 1 or more other commercially marketed tobacco products." PMI has failed to meet this burden, so FDA should not grant it a modified exposure order.

The PMI qualitative studies (THS-PBA-02-US and THS-PBA-04-US) explicitly show that consumers perceive reduced exposure claims as reduced risk claims. For example, focus group participants' comments on the "Reduced exposure claim" show consumers' confusion about reduced exposure claims:

- "It does look nice and it seems like It's going to be less harmful ... (what makes you say It seems like It could be less harmful?) Just the kind of wording: get the flavor and taste satisfaction you expect from a cigarette so it seems like it wants to substitute. It's an innovation of product that maybe is trying to replace the harmful risks that a regular cigarette contains ... " (AS Hale 36-50 Menthol LTN/ SLTN Chicago P2)"

- "It reduces your body's exposure to the chemicals ... that would be my biggest take-away .. .it suggests that it is better for you than a traditional cigarette. (Better - In what way?) It's the lesser of two evils; it's a better bad choice ... It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco -related disease." (AS Female 21-34 LTN/ SLTN Phoenix P2)

[80] Brewer NT, Hall MG, Lee JG, Peebles K, Noar SM, Ribisl KM. Testing warning messages on smokers' cigarette packages: a standardised protocol. Tob Control. 2016 Mar;25(2):153-9.
[81] Peebles K, Hall MG, Pepper JK, Byron MJ, Noar SM, Brewer NT.Adolescents' Responses to Pictorial Warnings on Their Parents' Cigarette Packs. J Adolesc Health. 2016 Dec;59(6):635-641.

In evaluating all claims, the PMI (THS-PBA-02-US Study report) summarized that ***all messages (including reduced exposure claims) were perceived by smokers as statements about lower harm. The fact that even the research firm that prepared the report does not distinguish between consumers' perceptions of reduced risk versus their perceptions of reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.*** For example, this statement related to evaluation of reduced exposure claims appears several times:

"After reading Product Message L, all participants perceive THS 2.2 to be:

• a lower risk of exposure to harmful compounds than conventional cigarettes, but a higher risk than e-cigarettes, NRTs and cessation

• a lower risk of developing tobacco-related diseases than conventional cigarettes, but a higher risk than e-cigarettes, NRTs and cessation."

In short, the actual reports, transcripts, and data presented by PMI provides FDA with substantial evidence that consumers perceive reduced exposure claims as reduced risk claims, which contradicts what PMI states and directly contradicts the letter and intent of the law.

For a modified risk order, section 911(h)(1) requires any advertising or labeling to "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 of the diseases and health-related conditions associated with the use of tobacco products." ***Because PMI failed to demonstrate that the public comprehends these health issues, or that the public can distinguish between "reduced exposure" and "reduced risk" claims, FDA should deny PMI's MRTP application.***

PMI's proposed warnings are also problematic, because PMI's data do not provide conclusive evidence that IQOS provides significant reduction in risks of cardiovascular or other diseases.[82] Even if the reduced risk claim is dropped, the reduced exposure claim (to harmful and potentially harmful chemicals) can still imply that IQOS is risk-free or poses substantially less risks of tobacco-related diseases. Indirect persuasion using metaphors and implicit claims is widely used in advertisements to make consumers receptive to multiple positive inferences about the promoted product and lead the audience to a conclusion that would be considered misleading if stated directly.[83] Comparative claims have shown to mislead consumers to form (erroneous) favorable generalizations on promoted products.[84] ***Because PMI has not demonstrated that***

[82] Glantz S. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigs. Public Comment submitted to FDA (tracking number: 1k1-8zrx-juh9)

83 McQuarrie EF, Phillips BJ. Indirect Persuasion in Advertising: How Consumers Process Metaphors Presented in Pictures and Words. Journal of Advertising. 2005;34(2):7-20.

84 Andrews JC, Burton S, Netemeyer RG. Are Some Comparative Nutrition Claims Misleading? The Role of Nutrition Knowledge, Ad Claim Type and Disclosure Conditions. Journal of

IQOS is associated with lower risks, FDA should not permit PMI to market IQOS with modified exposure claims because such claims are likely to be misunderstood as modified risk claims.

Both the modified risk and modified exposure claims could result in less cigarette cessation.

Based on experience with e-cigarettes, the most common users of e-cigarettes are current cigarette smokers.[85] Dual use of e-cigarettes with cigarettes is common in the general population, including among low[86] and very low-income populations.[87] Nicotine dependence is high among low and very-low-income smokers, and much higher among dual and poly-users.[88] Higher nicotine dependence is associated with a lower likelihood of successful cessation of combustible cigarettes. Thus, the introduction of IQOS may increase nicotine dependence in a population of smokers that is already highly dependent on nicotine, which may reduce the likelihood of successful cessation of combustible cigarette smoking.

Dual and poly-use of tobacco is associated with decreased successful cessation,[89] even though dual users may be more likely to make quit attempts.[90] The claim that switching completely to MRTPs could reduce harm and tobacco-related diseases assumes that people who switch will be more successful at cigarette smoking cessation. However, evidence suggests that cigarette smokers who switch or use other tobacco products for smoking cessation are much less

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Advertising. 2000;29(3):29-42.

[85] McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. Nicotine Tob Res. 2015 Oct;17(10):1195-202

[86] Kalkoran S, Alavardo N, Vijayaraghavan M et al. Patterns of and reasons for electronic cigarette use in primary care patients. 2017. J Gen Intern Med. [epub ahead of print

[87] Kish DH, Reitzel LR, Kendzor DE et al., Characterizing Concurrent Tobacco Product use among Homeless Cigarette Smokers. Nicotine Tob Res. 2015; 17(9):1156-60; Baggett TP, Campbell EG, Chang Y, Rigotti NA. Other tobacco product and electronic cigarette use among homeless cigarette smokers. 2016. Addict Behav.60: 124-130; Vijayaraghavan M, Hurst S, Pierce J. A qualitative examination of smoke-free policies and e-cigarettes among sheltered homeless adults. 2017 May;31(3):243-250

[88] Kish DH, Reitzel LR, Kendzor DE et al., Characterizing Concurrent Tobacco Product use among Homeless Cigarette Smokers. Nicotine Tob Res. 2015; 17(9):1156-60; Baggett TP, Campbell EG, Chang Y, Rigotti NA. Other tobacco product and electronic cigarette use among homeless cigarette smokers. 2016. Addict Behav.60: 124-130

[89] Zawertailo L, Pavlov D, Ivanova A, Ng G, Baliunas D, Selby P. Concurrent E-cigarette use Concurrent E-Cigarette Use During Tobacco Dependence Treatment in Primary Care Settings: Association With Smoking Cessation at Three and Six Months. Nicotine Tob Res. 2017 Feb;19(2):183-189 ; Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9 ; Popoval L and Ling P. Alternative tobacco product use and smoking cessation: a national study. Am J Public Health. 2013;103(5):923-30 ; Grana R, Popova L, Ling P. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Intern Med. 2014;174(5):812-813.

[90] Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9

likely to succeed than people who don't use these products. People who tend to use other tobacco and nicotine products to quit cigarette smoking are more likely to be nicotine dependent and experience difficulty with smoking cessation, evidenced by the increased number of quit attempts, without successful quitting.[91]

Because PMI's proposed warnings do not specifically inform consumers that continuing to smoke while using IQOS could reduce the likelihood of quitting smoking, which would result in increased harm, FDA should deny PMI's MRTP application.

Conclusion

PMI did not demonstrate that the proposed marketing of IQOS as a MRTP: 1) will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes; 2) will not lead to substantial product appeal (and subsequent use) among youth, non-smoking adults, and former smokers; 3) that the proposed marketing claims are consistent with the scientific evidence of actual harm and exposure; 4) that the proposed reduced risk and reduced exposure claims are consistent with how those marketing claims will be interpreted and perceived by potential consumers; and 5) that the proposed labeling will not mislead consumers, especially youth and adolescents, about the health risks of IQOS and the relative risks compared with not using any tobacco product. FDA should deny PMI's MRTP application because it does not include sufficient evidence to address these points.

[91] Messer K, Vijayaraghavan M, White MM et al., Cigarette smoking cessation attempts among current US smokers who also use smokeless tobacco. 2015. Addict Behav; 51:113-9 ; Shi Y, Pierce P, White M et al., E-cigarette use and smoking reduction or cessation in the 201/2011 TUS-PS longitudinal cohort. BMC Pub Health. 2016;16(1):1105.

Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS

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Docket Number: FDA-2017-D-3001

December 9, 2017

This comment is a detailed analysis of the Executive Summary of Philip Morris International's application, including commentary on specific statements in the Executive Summary. For detailed discussion of these issues, including relevant references, see the public comments that the UCSF TCORS has submitted.[1]

While there are many issues raised in the Executive Summary Philip Morris International (PMI) submitted, there are four overarching problems that represent fatal flaws in the application:

- The application completely ignores anyone under the legal age to purchase tobacco products. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires MRTP applicants to submit, and FDA to consider, scientific evidence of how the product effects nonusers, which includes kids. Based on the experience of e-cigarettes, it is highly likely that IQOS products will appeal to kids and create or increase their nicotine addiction. And based on the experience with e-cigarettes, many of these kids will go on to use conventional cigarettes. Even if they do not, adopting the IQOS product will have adverse health effects on youth.

- The health risk assessment aspects of the application assume 100% switching from conventional cigarettes to IQOS, despite the fact that PMI's own data on use patterns, both in their experimental studies and population monitoring in other countries, show substantial levels of dual use. Section 911 requires MRTP applicants to demonstrate that their product "as it is actually used by consumers" will reduce harm and risk of diseases to individual users and benefit the the health of the population as a whole. An accurate assessment of health effects therefore needs to assess dual use of IQOS and other tobacco products, including not only conventional cigarettes but also e-cigarettes and smokeless tobacco products since dual and poly use is an increasingly common pattern. This is another area where the experience with e-cigarettes is likely informative, because, while optimists may assume that the primary effect of e-cigarettes would be conventional cigarette smokers switching to them, the dominant use pattern remains dual use.

- While the aerosol chemistry, in vitro studies, and animal toxicology consistently show lower levels of adverse biological effects, the human studies do not show statistically significant differences between IQOS and conventional cigarettes for most of the biomarkers of potential harm. Because the human studies are closest to the real world, they deserve the

[1] https://tobacco.ucsf.edu/list-public-comments-fda-and-other-agencies-ucsf-faculty-and-fellows-and-others-links-comments

heaviest weight and do not support the claims of reduced risk. It is not at all unusual for a particular intervention to show an effect in vitro or even in animal models, yet not be effective in humans. This appears to be the case with IQOS.

- The evidence presented on warning labels shows that they are likely to be misunderstood and lead people to underestimate the risks associated with using IQOS. This is a particular problem with the reduced exposure claims because they will be minuderstood as reduced risk claims.

Following is a more detailed analysis of the Executive Summary with page references:

Page 10, paragraph 3: "For a smoker who switches to THS from cigarettes, this reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP." This statement and variants of it permeate the application, creating a very strong assumption that is not supported by the data PMI presents on actual use patterns, which show high levels of dual use. While there is nothing wrong with PMI assessing the effect of completely switching to IQOS, an accurate assessment of the individual and population health impacts of the new product require also studying dual use.

This is a very important point because for FDA to issue an MRTP marketing order, PMI must have demonstrated substantial evidence to support its claim that users are not misled by any labeling or advertising that purportedly warns consumers that they will not get the claimed reduction in harm unless they completely switch from all other tobacco products (including but not limited to conventional cigarettes, cigars, hookah, and e-cigarettes) to IQOS.

Considering dual use is important because emerging evidence from e-cigarettes shows that dual use of e-cigarettes and conventional cigarettes is more dangerous than using either product alone. This is true despite the fact that e-cigarettes have an overall lower toxic burden than conventional cigarettes.

Considering the likelihood of dual use is also important in assessing the warning messages and consumer education. The research that PMI summarizes here does not address that question at all.

Page 11, paragraph 4: "The first step in the assessment program was the chemical characterization of the aerosol generated by THS, which confirmed that THS aerosol contains substantially reduced levels of HPHCs (~90% overall reduction) compared with CC smoke." Here and in many other places in the application, we see this statement that IQOS reduces HPHCs by 90%. While this is what the data Philip Morris presents shows, there is already at least one independent study (Auer R, et al. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med*. 2017;177(7):1050-1052. doi:10.1001/jamainternmed.2017.1419) that shows substantially higher levels of toxins than Philip Morris reports.

Page 12, last three paragraphs: This is another place where the application explicitly limits itself to the effects of *complete switching* from conventional cigarettes to IQOS. This is an incomplete analysis of the likely effects of the new product.

Page 13, paragraph 2: Here PMI accurately states the legal requirement that the IQOS be assessed "as it is actually used by consumers," yet their analysis assumes that all IQOS consumers will completely switch from conventional cigarettes. This assumption is inconsistent with the data actually shown in the application.

Page 14, paragraph 4: PMI explicitly notes, albeit obliquely, that dual use exists when they say: "Furthermore, an actual use study showed that after 6 weeks, approximately 15% of the study participants had switched from cigarettes to either exclusive *or predominant use* of THS." The "predominant users" are dual users, not people who switched completely.

Page 18, paragraph 1: Here PMI repeats the mantra that "'nicotine itself is not a highly hazardous drug' and that 'most of the harm caused by smoking arises not from nicotine, but from other components of tobacco smoke'" (this time from the UK Royal College of Physicians). This statement, while accepted uncritically in some circles, ignores the many, many harmful effects of nicotine beyond addiction, including promotion of cancer, lung disease and heart disease through its effect on the nicotinic acetylcholine receptors as well as adverse effects on pregnancy and the developing fetus. Saying that nicotine is not the most dangerous thing in cigarette smoke does not mean that it is without risk.

And of course, addiction risk itself is a problem, especially if it leads to non-users initiating with IQOS, as well as IQOS serving as gateway to cigarettes . PMI also ignores risk of nicotine poisoning with kids akin to nicotine poisoning risk to kids and infants by e-cigarettes.

Page 18, paragraph 2: "An important corollary of achieving population harm reduction with MRTPs is that consumers will actually use them, *ideally* replacing the use of more harmful products with products that significantly reduce the exposure to toxic compounds, thus reducing harm and the risk of tobacco-related disease [emphasis added]." This is another of the many places in which PMI builds the application on the assumption, unsupported by PMI's own data, that the dominant behavior will be complete substitution.

Moreover, looking at the marketing (and just thinking about profit maximization) strongly suggests that PMI wants *new* users as well as switchers. That's why they have the slick Apple-like design of products and stores – to attract new young adults certainly, and probably teens and kids too (who always want to imitate older siblings)

Page 18, paragraph 2: "… These products should not attract persons who do not currently use tobacco products, i.e., never smokers or former smokers." This statement Is based on the strong implicit assumption in the whole analysis that IQOS *won't* attract never smokers or former smokers. The experience with e-cigarettes certainly violates this assumption. Indeed, some of PMI's own data indicates that some never and former smoker adults will be attracted to the product. While one could theoretically argue that these people would have relapsed to smoking cigarettes anyway, no evidence is presented to support such an argument.

Page 19, paragraph 1: This is another place where the assumption is made that IQOS will not attract never smokers or negatively impact the intention of smokers to quit. Again, the experience of e-cigarettes seriously calls into question this assumption which is never tested in the application.

Page 19, second bullet: The same assumption is applied again in a different context.

Page 20, bulleted list: Ultrafine particles are missing from this list. They are a major actor in creating many of the adverse cardiovascular and pulmonary effects of smoking and e-cigarettes (and likely the IQOS product) because the key way that IQOS works is by delivering an aerosol of ultrafine particles and nicotine, similar to cigarettes and e-cigarettes.

Page 20, paragraph 4: The analysis is completely limited to HPHCs that have been identified in cigarette smoke. Given that the IQOS HeatSticks are manufactured using a different process than cigarettes, there is a very good chance that it will have a different toxic profile than cigarettes and deliver different compounds. There is no assessment of any potential unique exposures generated by the IQOS.

Page 24, paragraph 1: "Second, it is acknowledged that product-specific epidemiological evidence is not available…" Philip Morris makes the point that there is no specific epidemiological evidence related to IQOS, but information from e-cigarettes would be relevant and should be discussed in the application.

Page 24, paragraph 1: "The assessment of the candidate MRTP therefore needs to address this complexity by demonstrating through a broad array of indicators that — *compared with smoking* — the use of a candidate MRTP leads to a significant reduction in exposure to HPHCs, which in turn leads to a significantly reduced impact on mechanisms leading to tobacco-related diseases [emphasis added]." Why is the comparison limited to smoking? PMI (and FDA) should be comparing IQOS to similar alleged "reduced harm" products like e-cigarettes and smokeless tobacco. In determining whether to issue a MRTP order, section 911(g)(2)(B) requires FDA to find that "the product as actually used by consumers will not expose them to higher levels of other harmful substances *compared to the similar types of tobacco products then on the market…* [emphasis added]." (FDA, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012, p. 4) E-cigarettes are a "similar type of tobacco product" currently on the market, and are certainly more similar than conventional cigarettes to IQOS HeatSticks. Like e-cigarettes, the subject IQOS HeatSticks are electronically heated using batteries that are charged using a USB power adaptor. Smokeless tobacco may also be considered a "similar type of tobacco product" since many manufacturers and advocates consider and market smokeless products as "reduced harm."

Additionally, FDA is required to evaluate the benefit of the MRTP candidate product to the health of individuals and to the population as a whole. In evaluating this, FDA is required by section 911(g)(4) to take into account many factors, including "the increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product." Although at the time the Family Smoking Prevention and Tobacco Control Act (FSPTCA) was enacted, e-cigarettes were not a significant

consideration and were not under the jurisdiction of the FDA, today any serious consideration of the impact on "existing tobacco product users" must necessarily consider e-cigarette users.

If it is determined that e-cigarettes are less harmful than IQOS, an existing e-cigarette user who switches to IQOS would actually *increase* their harm and the risk of tobacco-related disease, rather than "significantly reduce harm and the risk of tobacco-related disease." Indeed, this seems likely considering e-cigarettes do not contain actual tobacco leaf (although they contain nicotine derived from tobacco) and the e-liquid is typically heated to 400 degrees F as compared with 650 degrees F for IQOS.

Page 26, figure 4: Although just a schematic, the assumption here is that the effects of changing exposures is linear. Many of the effects, particularly for cardiovascular disease, are highly nonlinear, with big effects occurring in low levels of exposure. There may be similar evidence for some pulmonary outcomes.

Page 27, paragraph 1: It is important to consider the independence and integrity of the people who wrote the papers upon which PMI's application relies. Peter N. Lee, while represented as an "independent statistical consultant," has a longtime association with Philip Morris, British American Tobacco, the Tobacco Institute, and the tobacco industry in general. It is possible that some or all of the other authors, whose credentials appear to be independent statisticians and epidemiologists, may also be either employed by the industry or industry apologists.

Page 29, item A, III: Here PMI is just comparing the toxins in IQOS aerosol with cigarette smoke. Given the differences in the construction of the IQOS heat sticks compared to a conventional cigarette, there is a strong possibility that will it will have a different toxicological profile that includes elements that may not be present in cigarette smoke. Complete assessment of the toxicity of the product would require looking beyond cigarettes.

Page 30, Table 1, B, Step (7): PMI's post-market surveillance includes "cross-sectional surveys to monitor prevalence and cohort studies to monitor the ongoing health effects of switching to THS." This presumes that the only behavior will be switching. It is also very important to monitor dual use, youth initiation and relapse among former smokers.

When determining whether the candidate product benefits the health of individuals and the population as a whole, FDA is required under section 911(g)(4) to take into account "the increased or decreased likelihood that persons who do not use tobacco products [including youth who have not yet begun smoking and former smokers who had quit smoking] will start using the tobacco product that is the subject of the application." These groups also would need to be monitored post-market, as well as carefully scrutinized before FDA may issue a MRTP order.

Page 31, paragraph 1: All the comparisons are against 3R4F research cigarettes. The comparisons should be made against Marlboros, since those are the cigarettes which are currently being used in the market. Moreover, this is particularly important for this application because the new IQOS will be co-branded with Marlboro.

Page 32, paragraph 3: The International Conference on Harmonization (ICH) works closely with industry to influence regulators to accelerate review times and minimize the regulatory

process for new products (https://fda.gov/downloads/Drugs/NewsEvents/UCM446914.pdf). It is therefore questionable for FDA to rely on recommendations made by the ICH when considering the health consequences of IQOS and PMI's MRTP application.

Page 33, paragraph 2: "The PMI list of analytes and constituents does not cover the components of flavor systems." Flavors should not have been excluded. Flavors are an important part of all tobacco products, and especially of the new IQOS. Two of the three product variants for which PMI seeks MRTP marketing orders are flavored products: Marlboro Smooth Menthol HeatSticks, and Marlboro Fresh Menthol HeatSticks. The fact that PMI created two different variants of just one flavor – menthol – further highlights the importance of flavors to PMI's product profiles.

Page 34, second bullet: Philip Morris sets the goal of assessing the aerosol particle size to confirm that the aerosol is respirable. It is also important to investigate if the particles are smaller, and hence more dangerous, than particles generated in cigarette smoke. This is the case for many e-cigarettes.

Page 35, top two lines: "PMI chose to include those 18 HPHCs in its testing protocols along with additional analytes [that fulfilled certain criteria]." Why did PMI leave the others out and what is the impact of leaving these out? PMI should also be screening for biologically important toxins outside this list because IQOS are not conventional cigarettes and likely have a different toxicological profile.

Page 36, table 2: This table shows that neither nicotine free dry particulate matter nor total particulate matter are associated with any health risks. This is clearly incorrect.

Page 45, second paragraph: The nicotine exposure level that PMI used as a benchmark comes from the Occupational Safety and Health Administration. This is a level of occupational exposures which are substantially higher than would be considered acceptable as an environmental exposure in the general population.

Page 45, last paragraph: How accurate are the neutral red uptake assay, the Ames bacterial mutagenicity assay, and the mouse lymphoma mammalian mutant indigenous city assay for determining dose response, as opposed to simply identifying toxins as positive or negative?

Page 53, clinical pathology parameters: How does the fact that the IQOS line simply falls along the same line as for conventional cigarettes for blood neutrophil counts and alkylene phosphatase activity indicate reduced risk?

Page 53, histopathology of the respiratory tract: The changes observed in the respiratory tract (reserve cell hyperplasia and respiratory epithelium) and the nasal cavity (nose level I) in female rats exposed to IQOS aerosol are about half that of conventional cigarettes.

Page 54, hyperplasia, arythenoid projections: The changes observed in the larynx (hyperplasia, arythenoid projections) in female rats exposed to IQOS aerosol are about half that of conventional cigarettes.

Page 75, third paragraph: While dual use of IQOS and conventional cigarettes was not allowed during the confinement studies, it was only "discouraged" during the ambulatory period of the study. The results of the study, presented later, show substantial levels of dual use.

Page 91, table 10: These two studies measuring oxidative stress reveal that **there is no statistically significant difference between IQOS and conventional cigarettes** for the clinical risk endpoint 8-epi-PGF2α.

Page 92, table 11: These two studies measuring platelet activation reveal **there is no statistically significant difference between IQOS and conventional cigarettes** for the clinical risk endpoint 11-DCTX-B2. Even Philip Morris acknowledged at the bottom of page 91 that "the magnitude of the change is smaller than expected." However, they failed to point out that it was not a statistically significant change.

Page 94, table 12: The difference in FEV_1 between IQOS and conventional cigarettes is not significantly different from zero.

Page 95, table 13: The difference between IQOS and conventional cigarettes for HDL-cholesterol was not statistically significant.

Page 96, table 14: The difference in white blood cell counts between IQOS and conventional cigarettes was not statistically significant.

Page 97, table 15: There was a statistically significant drop in sICAM-1 in IQOS users compared to conventional cigarettes. This is a measure of endothelial function. Of all the clinical endpoints that PMI measured in people, this was the only statistically significant improvement associated with IQOS. Given that PMI did 24 tests, one would expect 1 false positive, so this is likely to be a chance finding.

Page 97, summary of clinical endpoints: "In summary, 90 days after switching from menthol cigarette smoking to menthol THS use, there was a shift in the same direction for all (except WBC in the US study) of the clinical risk endpoints." While this is a true statement, it ignores the fact that ***all but one of these shifts was not statistically significant.***

The failure to document statistically significant improvements in these biomarkers raises serious questions about any claims of reduced risk associated with IQOS. While Philip Morris's data does show that there are reductions in several measures in isolated cell systems and even animals, ***failure to reach significance in humans is a serious problem*** and trumps all of the lower level data. There are many examples of clinical interventions which look promising in *in vitro* studies or even animals that ended up not working in people. ***The data Philip Morris presents in this application is consistent with that larger pattern and calls into question any reduced risk claims that might be made.***

Moreover, the fact that there is not actual reduced risk in people suggests that approving any reduced exposure claims could be fundamentally misleading because consumers would

inevitably read the claim of reduced exposure as equating to reduced risk. Section 911(g)(2)(B) is crystal clear on this point: To issue a reduced risk order, FDA must "find that the applicant has demonstrated that… (iii) ***testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product (I) is or has been demonstrated to be less harmful*** [emphasis added]." FDA's Guidance on MRTP applications admonishes applicants to submit specific kinds of scientific studies concerning consumer perception and understanding that should inform FDA's evaluation. PMI has failed to meet this burden.

Page 98, paragraph 1: "The shifts in the clinical risk endpoints of smokers who switched to mTHS were of similar magnitude to those seen following 90 days of smoking abstinence. Therefore, PMI has met its objectives for Evidence Level IV (Reduced Exposure and Risk)." PMI may have met its own objectives, but no reasonable independent reader would agree that they have made a convincing case that switching to IQOS actually reduced risks.

As noted above, except for one outcome (which is likely a chance finding), there was not a statistically significant improvement in the biomarkers that PMI examined. In addition, the statement as worded suggests that the effects were the same or comparable to the effects of smoking cessation. Looking at the table shows that the point estimates of the effects of smoking cessation were always larger than the point estimates associated with using IQOS.

Page 113-114, perception and behavior assessment (PBA) framework: Nothing in this framework discusses effects on kids, a very serious omission.

Page 114, first full paragraph: "…PMI built its premarket PBA program leveraging on available best practice guidelines related to other categories than tobacco, such as Over-the-Counter drugs." There is no justification for doing this since there are no therapeutic benefits associated with IQOS. A more appropriate standard to use would be best practices in tobacco control as embodied in the Framework Convention on Tobacco Control and CDC best practices for tobacco control.

Page 117, bullet points: Again, nothing in this analysis discusses effects on kids.

Page 119, item 2: The whole model begins with young adult non-smokers of legal age through 25; however, it completely fails to consider kids, who are likely to be substantially affected by the existence of this new product.

Page 120, paragraph 3: It would be useful to have more details about these inserts and onserts since research that UCSF researchers have been doing in the industry documents clearly indicates that Philip Morris knows how to prepare such materials so that they will or purposefully will not effectively communicate.

Page 120, paragraph 4: Again, this analysis contains no mention of kids.

Page 126: An important question which PMI completely ignores in this analysis is how the existence of IQOS will affect kids starting IQOS and how that will relate to their smoking

initiation and cessation behavior later. What about the possibility that kids, thinking IQOS is safe, will initiate with cigarettes figuring that they can later switched IQOS just as they often think that they can later simply quit smoking? These are important population level of facts which are completely ignored in the analysis.

Sections 911 (g)(1)(B), 911(g)(2)(B)(iv), and 911(g)(4)(C) and FDA's Guidance are unambiguious on the point that ***all MRTP applications must consider the effect on tobacco use initiation among non-users, which necessarily includes kids.*** The Guidance states at page 20, "***A critical population health consideration*** under section 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users (both never users and former users). ***An MRTPA must contain scientific evidence regarding the effect the product and its marketing will have on increasing the likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application.*** [emphasis added]." Because PMI failed to provide this critical evidence, the law requires FDA to deny its MRTP application.

Page 128, first bullet in the second set of bullets: PMI defines "exclusive THS use" as IQOS consisting of at least 70% of total tobacco usage. This means that someone who is consuming 30% of their total tobacco product use as conventional cigarettes would be counted as having "completely switched" IQOS. These people would much more reasonably considered dual users. Philip Morris gives no breakdown of the distribution of use between IQOS and conventional cigarettes in this group. Given that Philip Morris makes such a big deal out of the benefits of *switching completely* from cigarettes to IQOS, it is very misleading to count people who are still consuming 30% of their tobacco use with conventional cigarettes as having "completely switched." This definition masks a lot of dual use in all of the subsequent analysis and needs to be corrected so that switchers are indeed 100% switchers.

Additionally, section 911(h)(3)(B) provides that FDA may require that the labeling of a proposed MRTP product include the conditions of use "if the conditions of use of the tobacco product may affect the risk of the product to human health." PMI has not provided the required showing that the labeling of IQOS clearly or effectively communicates that a condition of use for the product is to switch completely from conventional cigarettes, nor does PMI demonstrate that consumers understand that they need to switch completely to IQOS to get the purported benefits.

Page 129, first bullet: The 70% cut off for "exclusive use" is used again here.

Page 135, table 25: This table invites the question, how many of the people presented in this table would be attracted to IQOS instead of simply quitting smoking entirely? This is an important question which PMI's application ignores. Importantly, section 911(g)(4)(B) *requires* FDA to take into account "the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to [IQOS]."

Page 136, table 26: The same comment applies to this table. PMI should have compared with people who would have just quit smoking.

Page 137, figure 28: Is either number of former smokers who have a positive attitude toward intending to use IQOS high enough to matter? PMI fails to compare this number with normal relapse rates in long-term former smokers.

Page 138, first full paragraph: While Philip Morris talks about "intentions to quit," what does "quit" mean? Does it mean stopping using nicotine products entirely, or stopping conventional cigarettes and switching to IQOS? This is an important consideration that FDA is required to consider under section 911(g)(4)(B).

Page 140, top bullet: "Adult Smokers with the Intention to Quit smoking did not substantially change their intention to quit smoking and the use of tobacco products even though they expressed interest in the trial and use of THS [IQOS]." An alternative explanation of the data would be that the changes were consistently associated in the direction of lower intent to quit being associated with the availability of IQOS.

Page 140, third to last paragraph: PMI failed to explain the consequences of so many consumers using the product incorrectly.

Page 141, last paragraph: This is another place where "complete substitution" is considered people who use IQOS for 70-100% of their total product usage. This includes a lot of dual users; as many as 30% of so-called "complete switchers" are using other tobacco products, including convention cigarettes, using PMI's own figures. Given that PMI makes such a big deal out of the benefits of complete substitution of IQOS for conventional cigarettes in their health effects modeling, the behavioral data should explicitly present what fraction of users have comletely switched. PMI also needs to explore the health effects of dual use, which is high.

Page 142, figure 31: It is important to note that Philip Morris did collect data where "exclusive use" is defined as 95% or more IQOS use, so they obviously have thought about this issue. But, except for the Japanese study, they used the 70% cut off in the right-hand part of this figure. For the reasons stated above, this is at the very least misleading.

Page 144, figure 33: This figure does not make clear whether the THS consumers smoke any conventional cigarettes during the 90 days.

Page 144, second paragraph: Philip Morris makes the point that subjects were highly compliant to their assigned product in the Japanese study. But, "during the ambulatory period, 91% of the subjects used mTHS. Eighty-two percent of these subjects used mTHS 100% of the time throughout the 85 days in the ambulatory period." ***This means that 18% were dual users or went back to conventional cigarettes. That's a big effect.***

Page 146, bottom: The fact that "THS delivers nicotine to the users at comparable levels compared with cigarettes" means that THS has the same addictive potential and abuse liability, which is a direct consequence of the statements at the beginning of page 147.

Page 147, figure 35: This figure shows that even using Philip Morris's loose definition of "complete conversion" to IQOS (≥70% of total tobacco consumption), 22.4% of users are dual users at the end of six weeks. And that does not account for what fraction of the 14.6% who are counted as converters are actually dual users. ***This is a substantial level of dual use, which points to the importance of assessing the health effects of dual use.***

Page 148, first paragraph: It is not obvious from the graph that this statement is correct. Some of the people can switch back to conventional cigarettes.

Page 148, last paragraph: "In summary, this study showed that approximately 15% of the participants were able to switch from cigarettes to THS and to adopt it as a substitute for cigarettes." As noted above, PMI's loose definition of "substitution" draws this statement into question. This could easily be read as saying that these people converted completely from conventional cigarettes to IQOS, when in fact many of them were still dual users with conventional cigarettes.

Page 149, figure 36: This chart, looking across several countries, shows that dual use is a substantial behavior. Using PMI's definition of dual use (the tan areas on the graph) approximately 30 to 50% of users are dual users. In addition, as noted above, many of the people identified as converters to IQOS (the blue bars) only represent 70% conversion, so many of these people are probably also dual users.

Page 149, first sentence: "The results of the WOTs show that between 10% and 37% of adult daily smokers, depending on the country, were able to adopt THS as *a substitute* to their cigarettes [emphasis added]." For the reasons discussed above, this is an inaccurate statement, since the data do not present the numbers for complete substitution.

Page 150, second paragraph: It is not clear what the 4.1% figure is a percentage of. Is it IQOS users and smokers? The fact that by mid-September the IQOS market share in Japan reached 4.1% in a situation where the ratio of the number of IQOS devices and the estimated number of Japanese adult smokers was 9.5% suggests that about half the IQOS users were still dual using the cigarettes.

Page 150, last paragraph: The Market Research Panel panel that PMI established in Japan "include only adult IQOS purchasers who registered their device in a PMI database, and who agree to participate." As PMI notes in the next sentence, "due to this potential selection bias, the panel presents some limitations in the generalizability of the findings." This limitation is very important in interpreting the subsequent results because the biases that Philip Morris identifies are almost certainly substantial, which can lead to an overestimate of IQOS use and probably an underestimate of dual use. This limitation, which PMI recognizes, needs to be kept in mind in interpreting all of the results from this database.

Page 151, figure 38: It is important to note that in this figure the exclusive IQOS users are defined as those people who use IQOS for 95% or more of their tobacco consumption. This is a more reasonable definition of exclusive users than the 70% used in all the other studies. Even with this more stringent definition, however, about 30% of the users in the Philip Morris Japan

Registry are dual users. (See previous note on the biases that are built into the way the registry was created.)

Page 152, middle of first paragraph: "The repeated exposure to various forms of communication facilitates adoption among adult smokers, not only by those who are usually the first to try innovative products ("innovators") but also by those who tend to adopt products when they have become more generally acceptable." As PMI says, the panel is likely biased toward IQOS enthusiasts. Even so, about 50% are dual users.

Page 153, first paragraph: "This suggests that, once converted and IQOS use becomes familiar, the adoption of the new ritual and satisfactory experience seems to prevent IQOS users from switching back to other tobacco products. IQOS users who are in a "situational" status have a similar probability to either convert or remain in the same category and continue to use IQOS in conjunction with other tobacco products (51.9% and 41.6% respectively for May 2016 cohort)." In interpreting these numbers, it is important to remember that the biases built into the Japanese sample could be seriously affecting these estimates compared to the general population.

Page 154, figure 41: These transition probabilities are biased toward IQOS only use because of the difficulties with the Japanese registry sample discussed above.

Page 154, second paragraph: 1.2% initiation among adult never smokers is a lot of initiation among adults.

Page 155, second line: Based on the discussion earlier, it is not clear that the data support the conclusion that "the rate of initiation and relapse associated with IQOS commercial availability are very low." This statement is based on the biased (by PMI's own admission) Japanese registry.

Page 159, figure 45: This figure seems to show that if people quit smoking after about 30 days, their cravings are lower than if they use the IQOS product or continue smoking. Does this raise the possibility that the existence of IQOS would further discourage smoking cessation? FDA is required by law to consider this possibility, and if it determines that IQOS would discourage cessation, it should deny PMI's MRTP application.

Page 159, first paragraph: "Second, THS does not deliver additional addictive substances compared with cigarettes." This raises the interesting question of what other additional addictive substances cigarettes deliver beyond nicotine.

Page 159, second paragraph: "Based on the totality of the available evidence, THS has a similar abuse liability than cigarettes and there is no significant evidence that THS is attractive to non-users of tobacco." Nothing in the report so far shows that this is true because Philip Morris did not look at kids. Most smokers start smoking before age 18, and this group of people were systematically excluded from this work.

Page 160, first paragraph: The logical conclusion of this paragraph is that THS has the same abuse liability as a cigarette.

Page 160, second paragraph: "Results on product consumption and use patterns, both in controlled as well as in near real-world conditions, suggest that THS is likely to be adopted by current cigarette smokers." This is overstated.

Page 160, second paragraph: "Furthermore, smokers who switch to THS do not increase their overall tobacco consumption, and most studies demonstrated that total tobacco consumption actually decreased in those smokers who completely switched to THS." It is not clear where PMI showed this in the Executive Summary.

Page 160, third paragraph: "…the level of THS consumption tended to stabilize to reach levels comparable to what was reported at baseline for cigarettes." It is not clear where PMI showed this in the Executive Summary. Moreover, this statement contradicts the statement made in the paragraph above just commented on.

Page 160, paragraph 4: "The PBA study data on the THS messages consistently demonstrated that the product messages generated substantial Intent to Use THS among adult smokers including smokers with the intention to quit smoking. However, the data also shows that nine out of ten smokers who expressed an intention to quit stated that THS did not change their overall intentions." That leaves the other 10%, who may have been discouraged from quitting.

Page 161, paragraph 3: Again, this does not include kids.

Page 161, last paragraph: The study in question only involved 30 adult former smokers and six adult never smokers, which puts Philip Morris in the position of drawing very small conclusions based on extremely small sample sizes.

Page 163, second paragraph: "Among Adult Former Smokers, across all THS messages, positive Intention to Try ranged from 0% to 4.2% and positive Intention to Use from 4.1% to 15.7%." It is important to recognize that 4.2% is a big number if you are talking about encouraging people who previously quit smoking to take up THS. Likewise, having a 6% intention to use THS among young adult former smokers is also quite high.

Page 163 third paragraph: The statement that "all three studies [references omitted] confirmed a consistent low or very low Intention to Use THS among adult non-smokers" is an overstatement affecting 4 to 6% of these adult former smokers, which is significant.

Page 163, third paragraph: Saying that 9.6% of Adult Former Smokers expressed a positive Intention to Try is a lot of people, even though Philip Morris characterizes this as being "in the low single digits." That 5.3% of these smokers also expressed an Intention to Use of 5.3% is also a lot.

Page 164, table 29: All these percentages are based on very small numbers.

Page 164, last paragraph: "Furthermore, the propensity to initiate with THS is not significantly different from that of initiating with a comparator product (cigarettes or e-cigarettes). In addition,

young adult LA-25 never smokers (LA-25) appeared to have the same or even lower interest in product trial and use than Adult Never Smokers in general. Taken together, all these results indicate that THS is not likely to increase tobacco use at the population level." ***There is no way that PMI can make the statements without information about kids,[2] which is the main group that initiates tobacco use. Kids are also the group in which e-cigarette use has penetrated the market most, not adult smokers.***

Page 165, first paragraph: "Whereas a commercial MRTP could be of benefit to the smokers who switch completely from cigarettes, it could also have a negative impact on the population as a whole by encouraging nonsmokers to start using a tobacco product or alter the decision of current smokers who intend to quit either smoking or the use of all tobacco products." This statement ignores the possibilities of dual use, which would also have negative health effects. Moreover, this is another example of a sweeping statement made in the face of ignoring the effects of IQOS on youth.

Page 165, last paragraph: The studies about comprehension of the warning labels did not address the issue of reading level at all. What evidence has Philip Morris's presented that the reading level of these warnings is comparable to the typical smoker who is less educated than the population on the average? Also, Philip Morris did not do any studies of how these warning labels are perceived by kids. What about non-English speakers? PMI and other tobacco companies advertise in languages other than English; they should also warn in these other languages.

Page 166, figure 46: PMI did not address the question of how many of these people understood the warning labels as indicating that IQOS was "safe." This is something that is important to test and report as part of the MRTP application. Indeed, section 911(g)(2)(B)(iii) requires that to issue an MRTP order, FDA must find that PMI demonstrated that "testing of actual consumer perception shows that, as [PMI] proposed to label and market [IQOS], consumers will not be misled into believing that [IQOS] is or has been demonstrated to be less harmful…" As stated above, PMI has also failed to demonstrate that consumers understand that to attain the purported benefits of IQOS, they would have to switch completely from cigarettes to IQOS.

Page 167, second paragraph: These statements all ignore the effects that could encourage kids to use the product.

Page 168 second paragraph: The information here ignores the question of how many people would interpret these warnings as indicating that IQOS is "safe."

Page 169, first paragraph: This is another place where PMI talks about brochures on the Heat Stick pack and in direct mail communications, but does not really provide much information about the nature of these communications. FDA needs to pay particular attention to whether PMI's proposed materials are presented in a way that would both attract attention and be read and comprehended by consumers.

[2] Neither PMI nor any other tobacco company should be permitted to conduct, directly or indirectly, studies on kids because of the high risk that the resulting information will be used to sell their products to kids. PMI should rely on research conducted completely independent of the tobacco industry.

Page 170, both paragraphs: PMI failed to analyze issues of nonlinear dose-response, where the reduction in risk is not proportional to the reduction in exposure. In addition, given that Philip Morris's data in general shows no significant reduction in biomarkers of harm in actual people, it seems that presenting information on reduced exposure would be inappropriate or even misleading. Simply presenting information on exposure level is what you would do if you did not have any information about biological activity at all, or at least not in humans.

Page 173, bullets at the bottom: Again, there is no information at all here relating to kids.

Page 174, paragraph 1: "There are some challenges presented by reduced risk versus reduced exposure claim, primarily based on the finding that consumers believe that a reduction in exposure leads to a reduction in risk of harm and tobacco-related disease. PMI has demonstrated this to be true." ***This a very important statement because it has Philip Morris recognizing that reduced exposure claims are interpreted as reduced harm claims.*** As noted above, however, even though Philip Morris presents data on reduced exposure, the human data generally does not show reduced harm. ***For the reasons that Philip Morris points out, they should not be allowed to make reduced exposure claims because they would be fundamentally misleading to the readers.***

This is in many ways a legal issue, but it is informed by the labeling issue. Really depends on consumer perceptions and understanding of the labels, labeling, and marketing (PMI calls this "LLM"), and needs to be addressed. Even if PMI could prove reduced health harms and/or reduced exposure claims, this is not enough if the labels are misleading or downright deceptive. Bonnie's input is key here. See Chapter 6.4 and FDA guidance for more details.

Page 174, paragraph 5: The statements about overall population levels of harm completely ignore the effects on kids. The summary statement also ignores the implications of the high levels of dual use documented in the work and does not adequately address the risk of relapse to smoking among people who would otherwise quit.

Page 176, bottom: The epidemiological risk compounding in the model is all based on reductions of exposure, not risk. As noted above, Philip Morris's own data show that despite substantial reductions in exposure, there is generally not a statistically significant reduction in biomarkers of risk in human beings.

Page 179, paragraph 2: This scenario is ridiculous because it is based on highly questionable assumptions.

Page 180, all the text: There is nothing in the model to account for new youth smokers being attracted to use IQOS.

Page 181, first paragraph: The statement that there would only be 2% dual users is inconsistent with the data presented in this report. Dual use is much higher than that.

Page 182, figure 55: There is no mention of effects on youth in the initiation/cessation use patterns part of their post-marketing surveillance.

Page 183, cross-sectional surveys: There is no mention of collecting data in kids, which as noted above, are a very important part of the population in terms of overall population impact. (As noted above, such data would need to be collected completely independent of PMI or any other tobacco company or affiliated unit.)

Page 190, items 6 and 7: Philip Morris states that their studies have shown "significantly reduced exposure to HPHCs," which is accurate. In item 7, however, they only say that "clinical studies have shown that switching from cigarette smoking to THS results in *positive changes* in clinical risk markers that are similar to those seen following smoking cessation [emphasis added]." This statement is misleading on two counts. First, unlike the changes in exposure, the changes in clinical risk markers were *not statistically significant*. Second, while the point estimates were in the direction toward smoking cessation, they were not as large a change as were observed with smoking cessation. Someone reading this statement quickly or who is not familiar with the nuances of statistical significance versus just a change in the point estimate could easily misread this statement to indicate that there were statistically significant benefits both in terms of reduced exposure and also reduced clinical risk markers. That is not what the data show.

Because PMI has not demonstrated that IQOS is associated with lower risks, FDA should not permit modified exposure claims, because such claims are likely to be misunderstood as modified risk claims

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Docket Number: FDA-2017-D-3001
December 11, 2017

Philip Morris International (PMI) proposes to market IQOS with reduced exposure and reduced risk claims. The tobacco industry has a long history of using reduced exposure claims to mislead consumers, including adolescents,[1] into believing that the products in question have reduced risk, most notably through the use of "light" and "mild" cigarette claims. ***Therefore, it is particularly important that the FDA take care not to give legal sanction for PMI to market their IQOS product to mislead the public in the same way that it has done with earlier products. In particular, the FDA should not allow marketing of IQOS that claims or implies modified exposure.***

The inherently deceptive nature of reduced exposure and reduced risk marketing claims were at the core of the U.S. Department of Justice's Racketeer Influenced and Corrupt Organization (RICO) Act lawsuit against the major cigarette companies for defrauding the public about the dangers of smoking. In August 2006 Judge Gladys Kessler held[2] that the tobacco companies, including Philip Morris, were liable for violating RICO by fraudulently covering up the health risks associated with smoking and for marketing their products to children. Judge Kessler found that the companies "have engaged in and executed – and *continue to engage in and execute* -- a massive 50-year scheme to defraud the public, including consumers of cigarettes, in violation of RICO [emphasis added]." In her 1,683 page opinion with extensive Findings of Fact, Judge Kessler found, among other fraudulent acts, that Philip Morris and other tobacco companies deceptively marketed cigarettes characterized as "light" or "low tar," while knowing that those cigarettes were at least as hazardous as "full flavored" cigarettes; misled smokers, former smokers, and non-smokers to believe that these cigarettes were safer; and deliberately targeted the youth market. Importantly, the court found that there was a reasonable likelihood that defendants would continue to violate RICO in the future.

[1] Kropp, RY & Halpern-Felsher, BL. Adolescents' beliefs about the risks involved in smoking 'light' cigarettes. Pediatrics. 2004 Oct. 114(4): e445-e451. PMID: 15466070.
[2] *United States v. Philip Morris USA Inc*., 449 F.Supp.2d 1 (D.D.C. 2006), available at http://www.publichealthlawcenter.org/sites/default/files/resources/doj-final-opinion.pdf.

Among many relevant Findings, paragraph 2402 on page 888 of the opinion states: "According to [Brand Manager of Marlboro from 1969 to 1972, James] Morgan, Philip Morris made a calculated decision to use the phrase "lower tar and nicotine" even though its own marketing research indicated that consumers interpreted that phrase as meaning that the cigarettes not only contained comparatively less tar and nicotine, but also that they were a healthier option."[3]

Paragraph 2403 on page 888 states: "Morgan, who later became CEO of Philip Morris, further explained in 2002 that rather than relying on the tar and nicotine numbers from the FTC Method, 'the major influence in people's perceptions in the tar of a cigarette would have come from the marketing positioning of a brand as opposed to people literally reading the FTC [tar and nicotine figures].'"[4]

Based on these and other Findings, the court concluded at paragraph 2627 on page 971 that Philip Morris and the other tobacco companies knew that "many smokers who were concerned and anxious about the health risks from smoking would rely on the health claims made for low tar cigarettes as a reason, or excuse, for not quitting smoking."[5]

PMI's modified risk tobacco product (MRTP) application for IQOS makes reduced risk claims about IQOS that, like its earlier "light" and "mild" claims that were deemed fraudulent in the RICO case, are not substantiated by PMI's own internal research reported in its application (Section 1 below). And PMI's reduced exposure claims in its labeling and marketing are likely to be misunderstood as reduced risk claims (Sections 2 and 3 below). Therefore, FDA should not permit PMI to market IQOS with either reduced risk or reduced exposure claims.

Following the 2006 RICO decision, in 2009 Congress recognized and described the tobacco companies' use of reduced exposure claims to mislead the public and Judge Kessler's findings in 14 of the 49 Findings for the Family Smoking Prevention and Tobacco Control Act.[6] Of particular relevance, Finding 46 states:

> If manufacturers state or imply in communications directed to consumers through the media or through a label, labeling, or advertising, that a tobacco product is approved or inspected by the Food and Drug Administration or complies with Food and Drug Administration standards, *consumers are likely to be confused and misled.* Depending upon the particular language used and its context, *such a statement could result in consumers being misled into believing that the product is endorsed by the Food and Drug Administration for use or in consumers being misled about the harmfulness of the product because of such regulation, inspection, approval, or compliance.*

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[3] *United States v. Philip Morris USA Inc*., 449 F.Supp.2d 1 (D.D.C. 2006), available at http://www.publichealthlawcenter.org/sites/default/files/resources/doj-final-opinion.pdf.
[4] *United States v. Philip Morris USA Inc*., 449 F.Supp.2d 1 (D.D.C. 2006), available at http://www.publichealthlawcenter.org/sites/default/files/resources/doj-final-opinion.pdf.
[5] *United States v. Philip Morris USA Inc*., 449 F.Supp.2d 1 (D.D.C. 2006), available at http://www.publichealthlawcenter.org/sites/default/files/resources/doj-final-opinion.pdf.
[6] Family Smoking Prevention and Tobacco Control Act, Public Law 111-31 (June 22, 2009).

If FDA authorizes PMI to make confusing (if not deliberately deceptive) claims in its labeling and/or advertising, it could result in consumers being misled into believing IQOS is endorsed by FDA or into misunderstanding IQOS's harmfulness. Indeed, FDA would be complicit in perpetuating PMI's engagement and execution in a decades-long scheme to mislead, if not defraud, the public, and in discouraging smokers from not quitting smoking.

1. PMI's own data presented in its application do not support any claim of modified risk in human users

As detailed in another public comment,[7] in its application PMI presents data on 24 biomarkers of potential harm in American human users, including measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. These human data are the most important information in the application because they represent direct evidence on how IQOS affects people. Based on details in section 6.1.4.4 of the PMI MRTP application, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of these 24 biomarkers in Americans in PMI's studies. This is indicated by the fact that 23 of the 95% confidence intervals include zero (i.e., no statistically significant difference).

Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five percent of 24 tests is 1.2 tests, which means that one would expect 1 or 2 false positive results. PMI had one positive result, which is what one would expect by chance.

In addition, as detailed in other public comments, PMI has not provided compelling evidence that IQOS HeatSticks are less dangerous than conventional cigarettes in terms of cardiovascular,[8] pulmonary,[9] hepatic,[10] and other risks.[11]

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[7]Glantz S. PMI's Own Data on Biomarkers of Potential Harm in Americans Show that IQOS is Not Detectably Different from Conventional Cigarettes, so FDA Must Deny PMI's Modified Risk Claims. Docket Number: FDA-2017-D-3001. November 13, 2017. Tracking number:1k1-8zrx-juh9.

[8] Springer ML, Nabavizadeh P, Mohammadi L. The evidence PMI presents in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS will not harm endothelial function; independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes. Docket Number: FDA-2017-D-3001. November 20, 2017. Tracking number: 1k1-8zxa-mq9v.

[9] Chun LF, Moazed F, Matthay MA, Calfee CS, Gotts JE. IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not issue an order permitting IQOS to be labeled or marketed with reduced risk claims. Docket Number: FDA-2017-D-3001. November 30, 2017. Tracking number: 1k1-903a-mnpl

[10] Chun LF, Moazed F, Matthay MA, Calfee CS, Gotts JE. PMI's MRTP application for IQOS does not adequately evaluate potential for hepatotoxicity risk. Docket Number: FDA-2017-D-3001. November 30, 2017. Tracking number: 1k1-9039-d91g.

[11] St.Helen G, Jacob P III, Nardone N, Benowitz NL. Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure

Overall, PMI's own data support the conclusion that IQOS is no different from conventional cigarettes in terms of effects on these biomarkers of potential harm in American people; any marketing claims of modified risk are fundamentally misleading and should not be permitted.

2. A modified exposure claim is likely to be misunderstood as a modified risk claim, so PMI should not be permitted to market IQOS with a modified exposure claim.

To issue a modified exposure order, section 911(g)(2)(B)(iii) requires the applicant to demonstrate that "testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product— (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than 1 or more other commercially marketed tobacco products." ***PMI's own data submitted in the application show that consumers will be misled, so FDA should not grant it a modified exposure order.***

PMI's qualitative studies (THS-PBA-02-US and THS-PBA-04-US) demonstrate that consumers perceive reduced exposure claims as reduced risk claims. In particular, participants' comments on the "Reduced exposure claim" in PMI's qualitative studies demonstrate that they equated reduced exposure with reduced risk. Participants stated:

- "It does look nice and it seems like It's going to be less harmful ... (what makes you say It seems like It could be less harmful?) Just the kind of wording: get the flavor and taste satisfaction you expect from a cigarette so it seems like it wants to substitute. It's an innovation of product that maybe is trying to replace the harmful risks that a regular cigarette contains ... " (AS Hale 36-50 Menthol LTN/ SLTN Chicago P2)"
- "It reduces your body's exposure to the chemicals ... that would be my biggest take-away .. .it suggests that it is better for you than a traditional cigarette. (Better - In what way?) It's the lesser of two evils; it's a better bad choice ... It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco-related disease." (AS Female 21-34 LTN/ SLTN Phoenix P2)

In evaluating all claims, PMI summarizes (in THS-PBA-02-US Study report) that all messages (including reduced exposure claims) were perceived by smokers as statements about lower harm. The fact that PMI's report does not distinguish perception of reduced risk and reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims. For example, this statement appears several times related to evaluation of reduced exposure claims:

"After reading Product Message L, all participants perceive THS 2.2 to be:
• a lower risk of exposure to harmful compounds than conventional cigarettes, but a

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to toxicants during dual use with other tobacco products, FDA must deny PMI's application. Docket Number: FDA-2017-D-3001. November 29, 2017. Tracking number:1k1-902j-m8kv.

higher risk than e-cigarettes, NRTs and cessation
• a lower risk of developing tobacco-related diseases than conventional cigarettes, but a higher risk than e-cigarettes, NRTs and cessation."

In short, despite PMI's contradictory statements, the actual reports, transcripts, and data submitted by PMI provide substantial evidence that consumers perceive reduced exposure claims as reduced risk claims. FDA must make its determination based on objective scientific evidence, not on subjective and unsubstantiated assertions.

3. PMI's proposed advertising and labeling do not accurately describe the conditions of use and PMI failed to demonstrate that consumers comprehend these messages

For a modified risk order, section 911(h)(1) requires any advertising or labeling to "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 of the diseases and health-related conditions associated with the use of tobacco products." However, PMI has not demonstrated that the public comprehends IQOS's labeling or advertising messages. Instead, as detailed in another public comment,[12] the evidence cited in PMI's MRTP application indicates that *the proposed labeling and warnings for IQOS will mislead consumers*, particularly youth, about the product. Moreover, as detailed in another public comment,[13] despite the explicit requirements of section 911 and the recommendations of FDA's Guidance on MRTP applications, PMI's IQOS application does not adequately consider IQOS's appeal to or impact on youth or adolescents, and does not provide the necessary scientific evidence to support its MRTP claims of reduced risk or reduced exposure, especially as these claims affect youth and adolescents. In particular, PMI did not address the likelihood that adolescents who otherwise would not have used any tobacco product might find IQOS appealing and will initiate using IQOS as their first tobacco product. This outcome can be expected because adolescents, in addition to the public at large, are likely to be confused by and misinterpret reduced harm and reduced exposure claims.

As described in detail above, the evidence in PMI's application does not demonstrate that IQOS – even used alone – is less dangerous that conventional cigarette smoking. PMI also fails to address the combined risks of using IQOS while continuing to smoke conventional cigarettes (dual use), even though PMI's own data in the application show substantial levels of dual use

[12] Halpern-Felsher B, McKelvey K, Popova L, Kim M, Chaffee B, Vijayaraghavan M, Ling P, Lempert LK, Glantz SA. The evidence cited in PMI's MRTP Application indicates that the proposed labeling and warnings for IQOS will mislead consumers, particularly youth, about the product. Docket Number: FDA-2017-D-3001. December 8, 2017. Tracking number: 1k1-908n-holz

[13] Halpern-Felsher B, McKelvey K, Kim M, Chaffee B, Vijayaraghavan M, Popova L, Ling P, Lempert LK, Glantz SA. PMI's MRTP Application for IQOS Does Not Consider IQOS's Appeal to Youth or Adolescents, or the Likelihood that Youth and Adolescents will Initiate Tobacco Use with IQOS or Use IQOS with Other Tobacco Products. Docket Number: FDA-2017-D-3001. December 7, 2017. Tracking number: 1k1-9087-458e.

(e,g. PMI's study THS-PBA-08-US shows that over 6 weeks, only 5-8% of participants used HeatSticks exclusively, and most people used HeatSticks and conventional cigarettes together; Table 15.2.6.2.2).

Indeed, to be granted an MRTP order under section 911(g), PMI must demonstrate that the marketing of its IQOS product will or 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." For its modified exposure claim, PMI must further demonstrate that issuance of an exposure modification order would be "appropriate to promote the public health." Therefore, in its Guidance, FDA recommends that an MRTP application should contain *"an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality in the population as a whole."* In an effort to meet this requirement, PMI created its "Population Health Impact Model" (PHIM) that purports to estimate the potential impact on public health of marketing its IQOS as an MRTP. However, as described in detail in another public comment,[14] PMI failed to meets its burden to demonstrate that a MRTP order would "benefit the health of the population as a whole" or "promote the public health" because its PHIM makes several questionable assumptions and leaves out some important measures of health impact. Importantly, the PHIM completely ignores the possible health impacts of IQOS use on young adults and nonusers, and the PHIM assumes cigarette users will switch to IQOS use exclusively.

Even if one grants PMI's unsubstantiated assertion that switching completely to IQOS reduces risk, PMI failed to demonstrate that the public comprehends these health issues. Importantly, PMI failed to demonstrate that consumers understand that the risks of using its IQOS product are reduced *only if they do not use other products concurrently with IQOS*, and failed to demonstrate that consumers understand the meaning of the words "switch completely" used in IQOS labeling. Section 911(h)(3)(B) provides that FDA may require the labeling of "conditions of use" if the "conditions of use of the product may affect the risk of the product to human health." ***PMI's proposed advertising and labeling do not adequately describe the conditions of use – namely, that to (allegedly) reduce their risk of tobacco-related diseases, consumers must use IQOS exclusively, and may not use it with any other tobacco product – and PMI has not demonstrated that consumers understand these conditions of use.***

Indirect persuasion using metaphors and implicit claims is widely used in advertisements to make consumers receptive to multiple positive inferences about the promoted product and lead the audience to a conclusion that would be considered misleading if stated directly.[15] Comparative claims have been shown to mislead consumers to form (erroneous) favorable

[14] Max W, Lempert L, Sung H-Y, Lightwood J, Wang Y, PhD, and Yao T. Philip Morris's Population Health Impact Model Based on Questionable Assumptions and Insufficient Health Impact Measures Does Not Adequately Support its MRTP Application. Docket Number: FDA-2017-D-3001. November 22, 2017. Tracking number: 1k1-8zy0-6rfg.

[15] McQuarrie EF, Phillips BJ. Indirect Persuasion in Advertising: How Consumers Process Metaphors Presented in Pictures and Words. Journal of Advertising. 2005;34(2):7-20.

generalizations on promoted products.[16] ***That is exactly what the tobacco companies did with "light" and "mild" cigarettes and what it seeks FDA permission to do with IQOS.***

Conclusion

Because PMI has not demonstrated that IQOS is associated with lower risks to humans, FDA should not permit modified exposure claims, because such claims are likely to be misunderstood as modified risk claims. FDA should not put its imprimatur on PMI's claims and thereby implicitly, if not explicitly, participate in and continue PMI's deceptive practices.

[16] Andrews JC, Burton S, Netemeyer RG. Are Some Comparative Nutrition Claims Misleading? The Role of Nutrition Knowledge, Ad Claim Type and Disclosure Conditions. Journal of Advertising. 2000;29(3):29-42.

Americas Tobacco: Expect regulation news to heat up in the coming months

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We expect increased newsflow around tobacco regulation in the US in the coming months including (1) the Tobacco Products Scientific Advisory Committee (TPSAC) meeting to discuss PM's IQOS Modified Risk Tobacco Products Application (MRTPA) next week; and (2) a potential decision on the IQOS Premarket Tobacco Application (PMTA) in February. While it is difficult to assess the probability and timing of any FDA decision on tobacco given limited history, we expect to gain some clarity around key issues the FDA/TPSAC is focused on regarding the MRTPA and believe IQOS has potential to see PMTA approval given extensive scientific research conducted on IQOS by PM and the product's success in Japan/Korea. We remain Buy rated (on CL) on PM and Neutral rated on MO.

TPSAC meeting to discuss IQOS MRTPA is scheduled for next week

On January 24-25, 2018, the TPSAC will meet to discuss PM's MRTPAs for the IQOS system. PM submitted MRTPAs for three variants of IQOS in December 2016 and the applications were accepted by the FDA for scientific review in May, 2017. The initial deadline for public comment period of December 12 has been extended with a new deadline not yet established. Last week, the FDA also made available to the public several amendments that PM filed clarifying various issues and responding to FDA's request letters. Ahead of next week's meetings, we provide our views on the following key questions.

- **What do we expect from the meetings next week?**

All MRTPAs need to be referred to TPSAC for discussion and this is only the second time that TPSAC is meeting on an MRTP application (first meeting was on Swedish Match's application on its snus products back in April 2015). The full agenda is not up yet but we expect presentations from PM, FDA, public health officials and other industry participants to review existing scientific literature, assessment of PM's research on toxicology, clinical trials conducted on IQOS by PM, premarket consumer tests, and impact to public health of the population as a whole. There presentations are likely to follow the TPSAC asking questions on various topics and discussions among the Committee members.

For the FDA to determine that IQOS can make a modified risk claim, it would need to be convinced that IQOS, based on sound science, significantly reduce harm and

the risk of tobacco-related disease to individual tobacco users, and benefit the health of the population as a whole, taking into account both users of tobacco products and people who do not currently use tobacco products. Since the TPSAC will submit reports or recommendations to the FDA, we could get some clarity on issues that the TPSAC is focused on from the line of questions and comments.

- **Who are the members of the TPSAC?**

The TPSAC comprises 12 members (including the Chair), who are selected by the FDA Commissioner or designee from a pool of individuals knowledgeable in the fields of medicine, medical ethics, science, or technology involving the manufacture, evaluation, or use of tobacco products. There are nine technically qualified voting members (physicians, dentists, scientists, or health care professionals practicing in the area of oncology, pulmonology, cardiology, toxicology, pharmacology, addiction, or any other relevant specialty) and three non-voting members representing the industry interests. Current Committee members and their background are as follows (from FDA website and published research).

1. Philip Huang (Chair), MD, researcher on smoking cessation
2. William Bailey, PhD, representative of tobacco growers, non-voting member
3. Laura Bierut, MD, researcher on genetic and environmental factors of addiction, her published research suggests a favorable view of NGPs
4. Pebbles Fagan, PhD, does behavioral research on smoking cessations & switching to e-vapor
5. Gary Giovino, PhD, researches youth/young adult addiction, published a study on e-vapor as a gateway to cigarettes/substance abuse, does not seem well-disposed toward NGPs
6. Willie McKinney, PhD, MO representative, non-voting member
7. Robin Mermelstein, PhD, studies the effects of marketing & labelling on tobacco products, research seems to favor NGP
8. Richard O'Connor, PhD, behavioral scientist, studies efficacy of cigarette replacements, he is explicitly in favor of e-cigs and very low nicotine cigarettes (VLNCs)
9. Deborah Ossip, PhD, clinical psychologist, has published studies warning of potential health risk of e-vapor, doesn't seem to support NGPs
10. James Thrasher, PhD, studies marketing & labelling of cigarettes, has mentioned the potential benefit of switching to e-vapor from cigarettes in published work
11. Michael Weitzman, MD, pediatrician, very much in favor of alternative tobacco products

- **What are likely stock reactions around the meetings?**

There has been increased investor focus on next week's meetings so we could see heighened trading volatility in both PM and MO shares, particularly if the tone and the questions at the meeting are decisively more positive or negative. That said, we are not

expecting significant volatility (seen during menthol meetings in 2010-2011) given investor expectations around PM obtaining MRTPA in the near term appear muted, based on our conversations with investors. Moreover, the make-up of the TPSAC appears more balanced based on several member's published research views that tend to favor non-combustible tobacco products compared to prior TPSAC members during the menthol review and these meetings are deciding on potential upside optionality rather than any negative changes to current regulation.

- **When do we expect a decision on MRTPA?**

FDA has begun its scientific review of IQOS MRTPAs in May 2017. FDA's goal is to review and act upon the application within 360 days of receipt, assuming the application contains the inforamtion required. This could potentially put the timing of FDA's decision to be May 2018, but we do not expect to get a decision until late-2018, at the earliest. For one, the public comment period has already been extended with no new deadline established. Even if deadline is set for the next few months, FDA will need time to review all the new public comments that have been submitted. Second, there may be additional information the FDA may request from PM, as it has already done during the course of 2017.

PMTA approval on IQOS could be issued in February

Another key event we are awaiting is FDA's decision on PM's application for pre-market approval on IQOS in the US. The PMTAs were filed in March 2017 and FDA began its substantative review in August 2017. As part of its review, FDA may refer the applications to the TPSAC but a formal review by TPSAC is **not** required for PMTA decision.

According to FDA, PMTAs "must provide scientific data to demonstrate that the new tobacco product is beneficial to the population as a whole including users and non-users." After completing its review, FDA intends to issue an order within 180 days whether a new product may or may not be introduced to consumers, which means PMTA decision on IQOS could come out by February 2018.

We note that an MRTPA decision is not necessary for a product to gain premarket approval. The FDA issued premarket orders for Swedish Match's snus products in November 2015 but rejetcted the MRTPA on the same products in December 2016.

Buy PM, as US IQOS is an upside optionality while global IQOS opportunity should be sizable

A premarket approval for IQOS should be a positive catalyst for both PM and MO as it allows the commercialization of IQOS in the US. We remain Buy rated on PM (on CL), as we believe the company is on the cusp of accelerating revenue growth to a sustainble high-single-digit-plus rate, even without US being a meaningful contributor any time soon. We also note that any sales of IQOS in the US would be incremental to PM's profit (even if it is only receiving a royalty/manufacturing fee from MO) since PM does not have any combustible business in the US that could potentially come under pressure from IQOS launch. For MO, we see the company's ability to commercialize

IOQS (with a potential reduced risk claim) as a competitive advantage but near-term financial impact is less clear given the potential investment, limited tax advantage and the royaty fee structure.

Valuation

MO - Our $81, 12-month price target is based on 18X 2019E EPS. Key risks include regulatory changes, increased competitive intensity (market share losses), better industry volume, excise taxes.

PM - Our $140, 12-month price target is based on a sum-of-the-parts valuation, applying a 19X PE to 2019E combustible EPS and 6X EV/Sales to iQos. Key risks include worse volume/price, less favorable FX, share loss, slower NGP growth.

Disclosure Appendix

Reg AC

We, Judy E. Hong, Freda Zhuo, CFA and John McNeil, hereby certify that all of the views expressed in this report accurately reflect our personal views about the subject company or companies and its or their securities. We also certify that no part of our compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

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Growth is based on a stock's forward-looking sales growth, EBITDA growth and EPS growth (for financial stocks, only EPS and sales growth), with a higher percentile indicating a higher growth company. **Financial Returns** is based on a stock's forward-looking ROE, ROCE and CROCI (for financial stocks, only ROE), with a higher percentile indicating a company with higher financial returns. **Multiple** is based on a stock's forward-looking P/E, P/B, price/dividend (P/D), EV/EBITDA, EV/FCF and EV/Debt Adjusted Cash Flow (DACF) (for financial stocks, only P/E, P/B and P/D), with a higher percentile indicating a stock trading at a higher multiple. The **Integrated** percentile is calculated as the average of the Growth percentile, Financial Returns percentile and (100% - Multiple percentile).

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Disclosures

Coverage group(s) of stocks by primary analyst(s)

Judy E. Hong: America-Beverages US, America-Tobacco US.

America-Beverages US: Boston Beer Co., Brown-Forman Corp., Coca-Cola Co., Coca-Cola European Partners, Coca-Cola European Partners, Constellation Brands, Cott Corp., Dean Foods Co., Dr Pepper Snapple Group, Molson Coors Brewing Co., Monster Beverage Corp., PepsiCo Inc..

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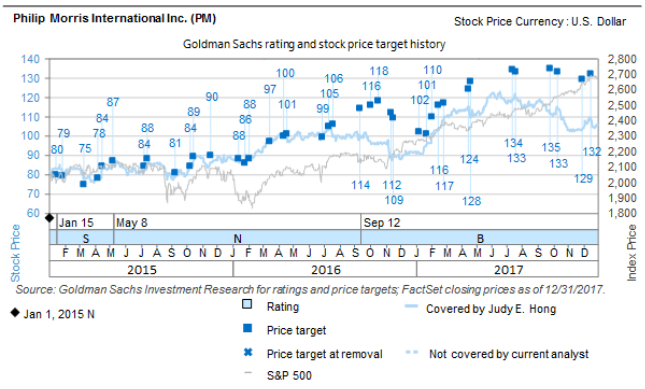

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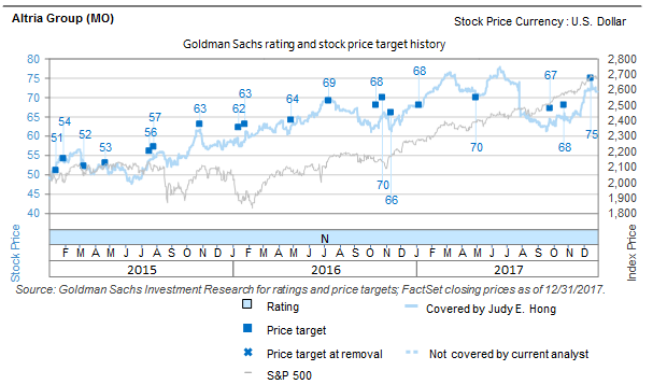

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