1400 EYE STREET, N.W. • SUITE 1200 • WASHINGTON, DC 20005
PHONE (202) 296-5469 • FAX (202) 296-5427

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Caryn Cohen
Office of Science
Center for Tobacco Products
U.S. Food and Drug Administration
Document Control Center
Bldg. 71, Rm. G335
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Docket No. FDA-2017-N-5994, Tobacco Products Scientific Advisory Committee, 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.

The Campaign for Tobacco-Free Kids (Tobacco-Free Kids) submits these comments in connection with the meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) to consider the above-referenced modified risk tobacco product applications, 82 Fed. Reg. 27487 (June 15, 2017). These are preliminary comments meant to inform the discussion before TPSAC, but because the formal comment period is open and will not close until after the TPSAC meeting and because the record that has been made available to the public is not complete and some of what has been made available has only been available for a short time, Tobacco-Free Kids reserves the right to submit more extensive comments on these applications prior to the close of the comment period.

We have broken our preliminary comments into five sections.

- Section I summarizes the major concerns with the iQOS application that we want to bring to TPSAC's attention. These concerns are discussed in detail in Section V of our Preliminary Comments.

- Sections II and III set forth the statutory standards by which every MRTP application must be evaluated and the historical reasons for these standards. These provide critical context to guide the review of this and future MRTP applications.

- Section IV identifies several key statutory standards, such as the fact the Applicant, in this case Philip Morris International (PMI), bears the burden of proof on each key issue and if it fails to satisfy that burden, the proper response is to deny the application unless and/or until it does so.

- Section V identifies significant areas in which the application fails to provide essential information.

I. SUMMARY OF PRELIMINARY COMMENTS SPECIFIC TO THE IQOS APPLICATION FOR CONSIDERATION BY TPSAC

Our review of the materials provided to date identifies at least four significant issues that must be adequately addressed before FDA could consider granting the application: (1) the likely impact of iQOS on youth risk perception and youth initiation of tobacco usage, overall and in relation to menthol, a subject on which the application appears to provide no data; (2) the predominance of dual usage of iQOS and cigarettes, documented in studies PMI has submitted, rather than complete replacement of cigarettes by iQOS, as the likely outcome for most iQOS users; (3) the absence of any analysis of the impact of marketing mentholated iQOS products on the African-American population despite the disproportionate use of mentholated products among African-American smokers; and (4) the existence of several significant questions regarding the individual health impacts of using iQOS.

Other important issues may also need to be addressed, but the massive volume of this application, coupled with FDA's failure to make important parts of the application available until very recently, has not afforded the public adequate time to conduct the kind of review that would ensure that such issues are identified. Many of the most critical scientific studies were not made public until November 28, 2017 and many others were made public only shortly before that date. As a result, the public has not had the opportunity to review the materials adequately. Moreover, we understand that FDA expects the applicant to submit amendments to the application subsequent to the TPSAC meeting. Thus, TPSAC is being presented midstream with an application that is incomplete and may well be subject to change before FDA considers it.

Although TPSAC can provide guidance that may inform FDA's ongoing review, unless TPSAC is later given the opportunity to address the complete application, including amendments submitted subsequent to this meeting, it cannot provide FDA with the guidance contemplated by the statute.

II. SUMMARY OF STATUTORY MODIFIED RISK STANDARDS

The Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act or TCA) assigns TPSAC a unique and central role in FDA's assessment of modified risk applications. Unlike applications for drug approval, where the convening of an advisory committee is discretionary with FDA, the involvement of TPSAC in evaluating modified risk

products is mandatory under the TCA.[1] Therefore, it is essential that TPSAC have a full understanding of the statutory standards for modified risk applications, as well as the tobacco industry conduct that led to their enactment and should inform their application to any particular application.[2]

The iQOS application must meet the standards set out in Section 911 of the Food, Drug and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act of 2009 (Section 911). Section 911 was enacted as a response to the false and misleading tobacco industry claims that certain tobacco products were less dangerous than other products that persuaded health-conscious consumers to switch to the "reduced risk" products instead of quitting altogether.

In enacting the Tobacco Control Act, Congress made specific findings about the potential harm to public health from modified risk claims that should guide FDA in its consideration of any modified risk product application. Congress found that "unless tobacco products that purport to reduce the risks to the public of tobacco use actually reduce such risks, those products can cause substantial harm to the public health. . . ." Sec. 2(37). Congress also found that "the dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk products are complete, accurate, and relate to the overall disease risk of the product." Sec. 2(40). Congress determined that it is "essential that manufacturers, prior to marketing such products, be required to demonstrate that such products will meet a series of rigorous criteria, and will 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." Sec. 2(36).

Under the Tobacco Control Act, a "modified risk tobacco product" is defined as a 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. A product is "sold or distributed" for such a use if, in relevant part,

(1) [its] label, labeling, or advertising, either implicitly or explicitly [represents] that

[1] *See* Section 911(f)(1) of the Food, Drug and Cosmetic Act, as amended by the Tobacco Control Act, provides that FDA "shall refer" to TPSAC "any application" for a modified risk order.

[2] Tobacco-Free Kids has addressed TPSAC's role in evaluating modified risk tobacco applications in multiple comments filed with FDA in recent years and incorporates those comments by reference. *See* Comments of Tobacco-Free Kids in Docket No. FDA-2017-N-0001, April 6, 2017 TPSAC meeting re review of modified risk applications (March 22, 2017); Comments of Tobacco-Free Kids, et al., in Docket No. FDA-2014-N-0001, April 18, 2014 TPSAC meeting re modified risk tobacco products (April 2, 2014; Comments of Tobacco-Free Kids, et al., Docket No. FDA-2013-N-0001-0056 re evaluation of risk and benefits of proposed modified risk tobacco products to population as whole (August 1, 2013); Comments of Tobacco-Free Kids in Docket No. FDA-2013-N-0001, April 30, 2013 TPSAC meeting re process for TPSAC consideration of modified risk tobacco product applications (April 23, 2013).

(i) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;

(ii) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or

(iii) the tobacco product or its smoke does not contain or is free of a substance, or

(3) . . . the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the label, labeling, or advertising…that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or its free of, a substance or substances.

Thus, a modified risk product is defined in terms of the manufacturer's claims of reduced risk or reduced exposure in marketing the product, as well as its actions that may suggest to consumers that a product reduces risk or exposure to hazardous substances.

In evaluating an application under section 911, FDA must consider both the product itself and the modified risk claims sought to be made by the manufacturers. Even though a product may meet the standard for the grant of a marketing application, the manufacturer may not make reduced risk or reduced exposure claims unless FDA has granted an separate application under Section 911 authorizing the making of such claims pursuant to the standards set forth in that section. With respect to Swedish snus products marketed by Swedish Match North America, for example, FDA granted an application to market a number of new tobacco products,[3] but denied the manufacturer's application under section 911 to make the modified risk claims the company proposed in connection with the products.[4]

Under Sec. 911(g)(1), the burden is on the applicant seeking an order allowing the marketing of the product with a modified risk claim to demonstrate that the 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 population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." (emphasis added).

Sec. 911(g)(4) further requires FDA to take into account the following specific empirical factors in determining whether the (g)(1) standard has been met:

[3] U.S. Food and Drug Administration, Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review, Swedish Match North America, Inc. (Nov. 11, 2015).
[4] U.S. Food and Drug Administration, response letter from Benjamin J. Apelberg, CTP Office of Science to Swedish Match North America (Dec. 14, 2016).

(A) The relative health risks to individuals of the tobacco product that is the subject of the application;

(B) The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application;

(C) 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;

(D) The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence.

Thus, FDA must consider not only the effects of the asserted modified risk product on those who use it, but also its population-wide impact on tobacco use initiation, cessation and relapse, including an assessment of the likelihood that smokers would actually switch to the modified risk product. It is not enough for an applicant to show that the product is less hazardous to users than other tobacco products; in order for a modified risk application to be granted, the applicant is required to show that the benefits of risk reduction to the individual (considering the likelihood of smokers switching to the modified risk product) outweigh the risks of increased initiation or diminished cessation. In short, the statute requires FDA to make scientific judgments not only about the physical effect of the product's use, but also about the likely responses of potential consumers (both smokers and non-smokers) to the product's marketing as a modified risk product.

III. RELEVANT HISTORICAL BASIS FOR SECTION 911

TPSAC's application of the statutory standards set out in Section 911 must be mindful of the historical context that led Congress to enact those standards.

The provisions of Section 911 were enacted in response to a massive evidentiary record of fraudulent health and "reduced risk" claims made by tobacco product manufacturers over the course of more than fifty years. Those claims caused millions of Americans to initiate cigarette smoking who otherwise would not have done so and caused millions of American smokers to continue smoking when they otherwise would have quit. In the absence of this massive industry fraud, literally millions of deaths, and untold suffering, would have been avoided.

The voluminous evidence of the industry's use of these false health-related claims was presented to the United States District Court for the District of Columbia in *United States v. Philip Morris, U.S.A., Inc.*[5] and furnished critical support for the court's conclusion that the defendant tobacco companies had engaged in a conspiracy to defraud the American public so

[5] 449 F. Supp.2d 1 (D.D.C. 2006), *aff'd in relevant part,* 566 F.3d 1095 (D.C. Cir. 2009), *cert. denied,* 130 S.Ct. 3501 (2010).

massive as to constitute racketeering under federal law. A central component of the fraud was the representation of "light" and "low-tar" cigarettes as safer than other cigarettes, when the companies knew, as actually used by smokers, such cigarettes were no less hazardous. The court found:

> Even as they engaged in a campaign to market and promote filtered and low tar cigarettes as less harmful than conventional ones, Defendants either lacked evidence to substantiate their claims or knew them to be false. Indeed, internal industry documents reveal Defendants' awareness by the late 1960s/early 1970s that, because low tar cigarettes do not actually deliver the low levels of tar and nicotine which are advertised, they are unlikely to provide any clear health benefit to human smokers, as opposed to the FTC smoking machine, when compared to regular, full flavor cigarettes.[6]

Applicant PMI was, at the time of the court's ruling, a wholly-owned subsidiary of Philip Morris Companies, Inc. (now Altria), a defendant in the *Philip Morris* case and, as such, a subject of the court's conclusion that the defendants had violated civil racketeering laws in perpetrating decades-long fraudulent conduct that included the "light" and "low-tar" fraud. Indeed, defendant Altria will be the exclusive distributor of the iQOS product in the U.S.

In addition to enacting safeguards against future claims of reduced risk or exposure, Section 911 also specifically prohibits the use of the descriptors "light," "mild," "low" or similar terms in the absence of an order from FDA finding that the requirements of Section 911 have been met. However, tobacco companies, including Philip Morris, began using color-coding schemes to evade the statute's restrictions and terms like "gold" and "silver" have replaced "light" and "ultra-light." For example, consumers who previously smoked Marlboro Lights were told that they could now purchase "Marlboro Gold" and "Marlboro Silver."[7] Philip Morris placed notes on packs of Marlboro Lights reading "Your Marlboro Lights package is changing, but your cigarette stays the same" and directing customers to "in the future, ask for Marlboro in the gold pack."[8] Indeed, in rejecting industry arguments that the restrictions on these descriptors in Section 911 render unnecessary the corrective statements ordered by the District Court as a remedy for the RICO violations of the major cigarette companies, the U.S. Court of Appeals for the D.C. Circuit specifically noted Altria's use of packaging colors to continue to mislead consumers.[9]

The District Court found the corrective statements remedy necessary because the defendants, including Altria, were likely to continue their fraudulent conduct into the future. It therefore ordered them to sponsor the corrective statements as a remedy to deter such fraud, in

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[6] *Id.* at 430-31.
[7] Duff Wilson, "Coded to Obey Law. Lights Become Marlboro Gold," *New York Times*, Feb. 18, 2010.
[8] Duff Wilson, "FDA seeks explanation of Marlboro Marketing," *New York Times*, June 17, 2010.
[9] *U.S. v. Philip Morris USA Inc.*, 786 F.3d 1014, 1024 (D.C. Cir. 2015).

newspapers, on television, on company websites and on package onserts, including this statement to remedy the "light" and "low-tar" fraud:

> A federal court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about low tar and light cigarettes being as harmful as regular cigarettes.
>
> - Many smokers switch to low tar and light cigarettes rather than quitting because they think low tar and light cigarettes are less harmful. They are **not**.
> - "Low tar" and "light cigarette smokers inhale essentially the same amount of tar and nicotine as they would from regular cigarettes.
> - **All** cigarettes cause cancer, lung disease, heart attacks, and premature death – lights, low tar, ultra lights, and naturals. There is no safe cigarette.

After years of litigation and other delaying tactics by the defendants, including Altria, these corrective statements recently have begun to run in newspapers and on television. They serve as reminders of the history of false claims of "reduced risk" products by the tobacco companies, including PMI's former affiliates and its intended iQOS U.S. distributor. In light of that history, particularly the finding by a federal court that Altria and the other RICO defendants are likely to continue their fraudulent conduct, making corrective statements necessary as an antidote to that fraud, TPSAC should insist that the statutory standards, enacted by Congress to prevent a similar public health disaster from ever repeating itself, are rigorously applied to PMI's iQOS application.

IV. KEY TENETS IN APPLYING STATUTORY CRITERIA

Section 911 of the Tobacco Control Act, as informed by the relevant Congressional findings and the history of industry fraud that led to its enactment, provides key principles to guide TPSAC and FDA in their evaluation of modified risk applications, including the iQOS application.

A. Applicant's burden of proof

Section 911(g)(1) permits the issuance of a MRTP order "only if the Secretary determines *that the applicant has demonstrated that such product, as it is actually used by consumers, will*" substantially reduce individual harm and benefit the health of the population as a whole (emphasis added). Although FDA is permitted to consider evidence from sources other than the manufacturer, the absence of sufficient evidence to establish any element of the Section 911 standard justifies a denial of the application.

B. Harm to individual users

As noted, Section 911 requires FDA to evaluate whether the product "as it is actually used by consumers will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users." Adherence to this statutory requirement requires an evaluation of "the relative health risks to individuals of the tobacco product that is the subject of the application." In evaluating individual risk, FDA should address several key considerations.

First, because the TCA defines "modified risk tobacco product" by reference to explicit or implicit representations about the product, the evaluation of individual harm must be made in reference to such representations and their likely meaning to consumers. This requirement was a critical element in FDA's denial of the Swedish Match modified risk application for its Swedish snus products. The application sought deletion, for the subject products, of existing warnings of the risk of gum disease, tooth loss and mouth cancer. FDA determined that omission of these warning from a subset of smokeless tobacco products on the U.S. market would indicate that the products without the warning cannot cause gum disease, tooth loss and mouth cancer. FDA denied the application because the "totality of the scientific evidence" supports the proposition that smokeless tobacco, and the Swedish snus products in particular, can cause these conditions.[10]

Second, FDA must have sufficient information concerning how the product is actually used, a requirement that is mandated specifically in Section 911. The way the product is consumed is important in evaluating the level of delivery of toxicants and other harmful constituents. For example, how consumers actually smoked cigarettes labeled "light," and the consequent delivery of nicotine and toxicants to those consumers, differed greatly from the results yielded by smoking machines.

Moreover, a product that would benefit the individual user if used to displace the use of more hazardous products totally might not benefit such users if its use results in the concurrent or dual use of the MRTP and other tobacco products and/or discourages cessation. Thus, for example, in its evaluation of the Swedish Match modified risk application, FDA found that the company had not demonstrated that "U.S. consumers would use Swedish snus in the same manner as consumers in Sweden and Norway (e.g. frequency or intensity of usage; exclusive snus use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S. consumers, the products would substantially reduce the risk to smokers."[11]

Third, FDA must assess whether the product increases the risk of some diseases even if it reduces the risk of others. Thus, scientific evidence related to multiple disease risks is required. For instance, in evaluating the Swedish Match modified risk application for Swedish snus, although FDA found evidence that the snus products, as actually used by consumers in Sweden

[10] FDA MRTP Application – TPL Review for Swedish Match North America, Inc. (Nov. 2, 2016), at 9-10.
[11] *Id.* at 10.

and Norway, may substantially reduce the risks of some, but not all, tobacco-related diseases to individual users as compared to smoking cigarettes, it concluded that the "scientific evidence is insufficient to support that substantial reductions would be observed across the full range of risks posed by tobacco products, as implied by a generalized statement about health risks as compared to smoking (i.e., "substantially lower risks to health than cigarettes").[12]

Fourth, FDA should consider available evidence bearing on the abuse liability of the product. FDA's evaluation should also determine whether there is a risk that the product could be modified, or used in some other way, so as to increase the risk of addiction and harm.

C. Population-wide effects

As noted above, FDA's assessment of an MRTP application must consider the population-wide impact of the product on both users and non-users of tobacco products, including its impact on tobacco use initiation, cessation and relapse. This population-wide assessment has several key elements.

First, the applicant must demonstrate the likely impact of the product's modified risk claims on consumers of tobacco products, including its labeling, packaging and marketing. This process should include an assessment of whether current tobacco product users, when exposed to the proposed claim and the associated labeling and marketing, will switch to it completely from more dangerous tobacco products, or use it in conjunction with other products. (Thus, the impact of the product on current tobacco users may be regarded as relevant both to the determination of individual risk and population-wide effect.) This determination should also address the extent to which current users who might have quit tobacco use entirely may use the MRTP instead of quitting. FDA should also address the extent to which the availability and marketing of the MRTP would displace the use of cessation products that have been shown to be safe and effective.

Second, the applicant must furnish sufficient information to allow FDA to assess the impact of the proposed MRTP, and its labeling and marketing, on those who have never used tobacco. Because nearly 90% of adult smokers report that they started smoking by age 19,[13] this assessment is particularly important with respect to young people. FDA should consider whether modified risk claims associated with a MRTP, with its packaging and marketing, may influence the perception of risk by young people and lead them to initiate use of the MRTP rather than remaining tobacco-free.

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[12] *Id.*

[13] Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality. National Survey on Drug Use and Health (NSDUH), 2014. ICPSR36361-v1. Ann Arbor, MI: Inter-university Consortium for Political and Social Research distributor], 2016-03-22, http://doi.org/10.3886/ICPSR36361.v1.; See also, HHS, *Preventing Tobacco Use Among Youth and Young Adults, A Report of the Surgeon General*, 2012. HHS, *Preventing Tobacco Use among Young People: A Report of the Surgeon General*, 1994, http://profiles.nlm.nih.gov/NN/B/C/F/T/_/nnbcft.pdf, at 49.

The importance of determining the likely impact of a MRTP on young people is underscored by the sharp increase, in just a few years, of e-cigarette use among teenagers. According to the National Youth Tobacco Survey (NYTS), e-cigarette use among high school students increased ten-fold from 2011-2015[14] and, even though such use declined substantially in 2016,[15] e-cigarettes use among the young still exceeds use of cigarettes and other tobacco products. Moreover, data from the 2015 NYTS showed that 13.1% of high school students who have never used another tobacco product have tried e-cigarettes.[16] Even though no e-cigarettes were the subject of an MRTP order, there is no doubt that many users, including young users, perceive these products as safer than cigarettes.[17] Thus, there is a serious risk that new products, marketed as modified risk products, may attract significant usage among young people, many of whom may never have used a tobacco product.

Third, FDA must evaluate the risk that the availability and marketing of a proposed MRTP may convince those who have successfully quit smoking or other tobacco use to relapse into renewed use. Even if the MRTP were shown to be minimally harmful, MRTP claims and marketing could draw former smokers back into nicotine addiction and lead them eventually to the more harmful tobacco products they were using before they quit.

Assessing the likely impact of the MRTP on smokers, non-smokers and former smokers requires the applicant to present a rigorous analysis of consumer perceptions of the product, the associated modified risk claims and associated marketing, by each of these groups and the likely actions each will take in response. Deficiencies in the Swedish Match consumer perception survey were specifically cited by FDA in denying the company's modified risk application for Swedish snus.[18] Finally, any grant of a modified risk application must be accompanied by a requirement of post-market surveillance of the actual impact of the MRTP on consumers. However, although post-market surveillance is critical, it should not be regarded as a substitute for carefully designed pre-market consumer research to minimize the risk that the introduction of a MRTP will harm rather than benefit public health.

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[14] Centers for Disease Control, "Tobacco Use Among Middle and High School Students – United States, 2011-2015," *MMWR*, 65(14):361-367, April 14, 2016.
[15] Centers for Disease Control, "Tobacco Use Among Middle and High School Students – United States, 2011-2016," *MMWR*, 66(23):597-603, June 16, 2017.
[16] U.S. Dept. of Health and Human Services, *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.* Atlanta, GA: 2016.
[17] S.M. Amrock et al., "Perceptions of e-Cigarettes and Noncigarette Tobacco Products Among US Youth," *Pediatrics*, doi: 10.1542/ped.2015-4306 (Oct. 24, 2016).
[18] Letter from FDA to Swedish Match North America re MRTPAs (Dec. 14, 2016), at 3-4. *See generally*, Comments by Campaign for Tobacco-Free Kids and Tobacco Control Legal Consortium, Docket No. FDA-2014-N-1051, Modified Risk Tobacco Product Applications: Applications for 10 Products Submitted by Swedish Match North America, Inc. (November 14, 2014), at 33-45.

V. KEY QUESTIONS TPSAC SHOULD ADDRESS IN EVALUATING THE SCIENTIFIC EVIDENCE SUBMITTED IN SUPPORT OF THE PMI MODIFIED RISK APPLICATION

The record that has been made available to the public to date raises important questions TPSAC should consider in evaluating the iQOS application under the standards established by the TCA. Significant questions exist regarding the impact of iQOS on the individual user, implications of PMI's failure to include data on youth perceptions of iQOS, the evidence of potential significant levels of dual use with conventional cigarettes in the United States, and the absence of any analysis of the impact of marketing mentholated iQOS products on the African-American population.

A. Does the level and quality of the evidence indicate that use of iQOS will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users?

As noted above, Section 911 requires FDA to evaluate whether the product "as it is actually used by consumers will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users." This standard requires an evaluation of "the relative health risks to individuals of the tobacco product that is the subject of the application." A series of comments filed in this Docket and described below indicate that PMI's conclusions on this topic deserve serious scrutiny.

The comments indicate that the in vitro and animal toxicology studies provided by PMI do signal lower levels of adverse biological effects. However, these same comments raise concerns about whether the studies support the claims of reduced risk, noting that the "human studies do not show statistically significant differences between iQOS and conventional cigarettes for most of the biomarkers of potential harm."[19,20] Additional comments raise

[19] Comments by Glantz, S. and Lempert, L., Docket No. FDA-2017-D-3001, "Detailed analysis of the Executive Summary (Section 2.7) submitted by Philip Morris International in support of its MRTP application for IQOS," (December 9, 2017). Available at https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/Comments%20on%20Exec%20Summary%20-%20final.pdf

[20] Comments by Glantz, S., Docket No. FDA-2017-D-3001, tracking number 1k1-8zrx-juh9. "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," (November 13, 2017). Available at https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/Clinical%20studies%20do%20not%20show%20significant%20reduction%20in%20harm-1k1-8zrx-juh9.pdf

concerns about iQOS emissions posing a risk for pulmonary toxicity,[21] and the lack of adequate information regarding the potentially unique toxicities of iQOS.[22]

Separate comments relate to the levels of harmful and potentially harmful constituents (HPHCs) in the products. In addition to calling for reporting of the full range of HPHCs in iQOS aerosol, these comments raise the important question of whether the process used to generate the aerosol for iQOS produces "substances not found in the smoke of conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?"[23]

The authors also raise another critical issue for TPSAC to consider: whether noncompliance during some of the key studies "reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS."[24] These studies compared the level of reduction in biomarkers of HPHCs after use of iQOS with cessation (smoking abstinence) and with continued use of combustible cigarettes. However, the comparison is valid only if the study participants fully complied with their assigned criteria (particularly the smoking abstinence arm of the study). As the authors of the comment explain, if participants in the smoking abstinence group actually smoked cigarettes, then the study would be more likely to show comparable reductions in HPHC exposure with iQOS and "abstinence." Across the studies, compliance varied, and PMI noted that due to increased variability the results should be interpreted with caution.

A Reuters investigation published in December 2017[25] provides reason for further caution. The article details how former PMI employees and contractors described "a number of irregularities involving clinical trials" for iQOS and that one employee responsible for helping coordinate the clinical trials, "questioned the quality of some of the researchers and sites contracted to carry out those experiments." Among the concerns were the qualifications and

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[21] Comments by St. Helen, G. et al., Docket No. FDA-2017-D-3001, tracking number 1k1-902j-m8kv, "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," (November 29, 2017). Available at https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/Gideon-ClinPharm_Comments%20on%20aerosol%20and%20exposure_IQOS_11292017-FINAL.pdf

[22] Comments by Chun, L. et al., Docket No. FDA-2017-D-3001, tracking number 1k1-903a-mnpl. " IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should 1 not issue an order permitting IQOS to be labeled or marketed with reduced risk claims," (November 30, 2017). Available at https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/FINAL%20MRTP%20Comment%20Pulm%20and%20Immuno_Calfee%20Group.pdf.

[23] Comments by St. Helen, G. et al., Docket No. FDA-2017-D-3001, tracking number 1k1-902j-m8kv, "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," (November 29, 2017) at 9. Available at https://tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/Gideon-ClinPharm_Comments%20on%20aerosol%20and%20exposure_IQOS_11292017-FINAL.pdf.

[24] Comments by St. Helen, G. et al., Docket No. FDA-2017-D-3001, tracking number 1k1-902j-m8kv.

[25] Lasseter, T. et al., "Scientists Describe Problems in Philip Morris E-Cigarette Experiments," *Reuters*, Dec. 20, 2017. Available at https://www.reuters.com/investigates/special-report/tobacco-iqos-science/.

training of the Principal Investigators of certain studies, as well as the rigor of the screening process assuring that the study participants met the criteria for inclusion in a particular study.

Reuters outlined its findings about the iQOS trials to FDA, and the agency must carefully examine the information to determine whether audits of the facilities in question are necessary, and whether all of the studies adhered to standards for Good Clinical Practice.

Each of these issues is relevant to the statutory criterion FDA must apply: whether iQOS, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users. It is therefore important for TPSAC to evaluate them and provide its advice to FDA.

B. PMI's application provides no data on youth perceptions of iQOS, and no evidence on the potential for adolescent use. No accurate assessment of the impact on the health of the population as a whole can be made without consideration of data among those under age 18.

As noted above, FDA's assessment of an MRTP application must consider the population-wide impact of the product on both users and non-users of tobacco products, which includes its impact on tobacco use initiation.

PMI's MRTP application did not address the impact of the modified risk claims made for iQOS on adolescent risk perception or adolescent use of tobacco products. The only explanation for the absence of any such data is PMI's statement that "PMI internal policy prohibits the conducting of studies relating to tobacco products, which involves under legal age of smoking, a policy that is consistent with recommendations from the FDA."[26] This statement, which purported to explain why PMI had not submitted reports on the perceptions of the modified risk statements and marketing materials by youth and the potential impact on their behavior, is based on a misreading of FDA's standards. As the Guidance for the preparation of Modified Risk Tobacco Product Applications makes clear, FDA requires only that "all study subjects *receiving tobacco products* are current daily tobacco product users at least 21 years of age"[27] (emphasis added). Not only is this limitation not applicable to studies of promotional material such as modified risk claims to determine the effect of such materials on adolescent risk perception or interest in using the product, but the Guidance makes clear that inclusion of the effect on adolescent perception should be an essential feature of such studies. The Guidance states:

> To address the effect of the MRTP on tobacco use initiation, FDA recommends that applicants submit:
>
> - Human studies that evaluate consumer perception of the product, including its labeling, marketing and advertising.

[26] PMI, Sec. 2.7, p. 126.
[27] Draft Guidance, Modified Risk Tobacco Applications, March 2012, p. 29.

> These studies should be designed to provide evidence regarding the likelihood of population benefit or harm from the proposed product, including…:
>
> - The likelihood that consumers who have never used tobacco products, *particularly youth and young adults*, will initiate use of the tobacco product;[28] (emphasis added)

Moreover, the Guidance instructs companies to "estimate the attributable risk of all of the various health effects for various types of individuals in the U.S. population, as well as the total number of individuals of each type." The Guidance goes on to state, "The types of individuals may include, but are not limited to, the following … Non-users who initiate tobacco use with the proposed product, *such as youth*, never users, former users" (emphasis added).[29]

Thus, far from prohibiting the testing of such messages on adolescents, the FDA Guidance characterizes such testing as particularly important. In this light, PMI's failure to provide any evidence of the effect of these messages on adolescent risk perception is an inexplicable omission. PMI's failure to address the risk of health effects to youth ignores FDA's specific instruction to include such an analysis.

Contrary to PMI's assertion that FDA's policy precludes research regarding consumer perception of youth, FDA's guidance on MRTP applications describes how such research should be done. Recognizing that research among non-smokers, and non-smoking youth in particular, requires care, FDA offered applicants an opportunity to work with the agency to determine the best way to conduct studies involving youth:

> When designing consumer perception studies, applicants should take care that the studies themselves do not promote use of the product, particularly among vulnerable populations, such as youth, non-users of tobacco products, and pregnant women. FDA recommends that applicants meet with FDA to discuss research plans before embarking on research with vulnerable populations. Section IX.B of this guidance provides information on requesting a meeting with FDA.[30]

PMI's decision not to assess the impact of the marketing of iQOS on youth also contravenes recommendations made by the Institute of Medicine's (IOM) 2012 report, *Scientific Standards for Studies on Modified Risk Tobacco*, which recommended that "FDA should require studies to include populations of special relevance, including (but are not limited to) … adolescents"[31] and included an assessment of the effects on youth as "an essential element in

[28] *Id*. at p. 20.
[29] *Id*. at 22.
[30] FDA 2012 Draft Guidance, p. 26.
[31] Institute of Medicine, *Scientific Standards for Studies on Modified Risk Tobacco Products*, December 2011, at 14 ("IOM report").

establishing the public health benefit of an MRTP."[32] The report included research on adolescents in three of its "Evidence domains relevant to an MRTP application."[33] The need to consider the effects of promotional statements on youth is vitally important in light of the industry's documented history of marketing tobacco products in ways that attract adolescents and the role that youth initiation has played—and continues to play—in the recruitment of long-term adult smokers.[34]

According to IOM, perceptions of and intentions to use a given MRTP are also likely to differ by age group. Thus, IOM noted that it is "critical that studies include participants in the following age groups: children (≤ 12 years old), adolescents (13–17 years old), young or emerging adults (18–25 years old), adults (≥ 25 years old)."[35] As noted by IOM, "adolescents' perceptions of the risks and benefits of cigarette smoking play an important role in adolescents' decisions to smoke. Given that adolescence is a period of heightened vulnerability for the initiation of tobacco use, it is important to evaluate whether adolescents accurately understand the purported benefits of an MRTP. Of particular importance are adolescents' perceptions of the risks and benefits of using the product, and whether they intend to initiate tobacco use with the MRTP rather than a traditional tobacco product because they believe the former is a "safe" alternative."[36]

Similarly, the IOM report detailed ideas for how research on youth perceptions of risk of MRTPs can be conducted consistent with ethical standards of research.[37] For example, IOM suggests that such research could be appropriately done under the supervision of an independent third party.[38] Such a procedure would make it possible for an applicant to develop evidence regarding the effect of the marketing of a product on this population. IOM noted that, "Survey research or perception/messaging research among non-smokers is acceptable where the non-smokers are not being exposed to the product."[39] Even in the case of studies that include exposure to a particular tobacco product among non-users (which is not critical in this case), IOM concluded, "Experimental research that exposes non-users to products is ethically problematic; but such research cannot completely be ruled out because it could provide critically valuable information. The ethics, risks, and benefits need to be determined on a case by case basis."[40]

The importance of determining the likely impact of a MRTP on young people is underscored by the recent youth uptake of e-cigarettes. As noted above, although these products

[32] IOM report at 50.
[33] IOM report at 7 (Summary).
[34] Report of the Surgeon General (2012), 530-41, 603-27 and sources cited therein; *U.S. v. Philip Morris*, 449 F. Supp. 2d at 561-691.
[35] IOM report at 174.
[36] IOM report at 165.
[37] IOM report at 10.
[38] IOM report at 57.
[39] IOM report at 52.
[40] IOM report at 52-53.

are relatively new, e-cigarette use among the young now exceeds use of cigarettes and other tobacco products.[41] Moreover, data from the 2015 NYTS showed that 13.1% of high school students who have never used another tobacco product have tried e-cigarettes.[42] New products, marketed as modified risk products, may attract significant usage among young people, many of whom may never have used a tobacco product.

Even more importantly, available evidence indicates that iQOS itself has the potential to facilitate high rates of youth tobacco usage. Data from one Japanese study published in 2015 showed higher ever use rates of iQOS and Ploom (another heat-not-burn product) among adolescents and young adults than among older adults.[43] If an important objective in fashioning modified risk claims is to prevent them from facilitating the initiation of tobacco use by youth, it is essential for an applicant to present evidence regarding youth perception of such claims.

The importance of accurately assessing the effect of these claims on adolescents is enhanced by the fact that two of three iQOS products PMI proposes to market are mentholated products.[44] FDA's own exhaustive analysis in 2013 of the effect of marketing menthol cigarettes demonstrated that newer smokers, and particularly adolescents, disproportionately use mentholated cigarettes and that menthol in cigarettes is likely associated with increased initiation and progression to regular cigarette smoking.[45] Despite the high likelihood that marketing mentholated iQOS products would also have a disproportionately large impact on adolescents, PMI submitted no analysis of this impact.

Despite the express instructions in FDA's guidance on the preparation of modified risk applications, the extensive discussion in the IOM report on how research on youth risk perception could appropriately be conducted, and evidence of high rates of youth usage of iQOS in Japan, PMI has submitted an application that ignores the effects of the proposed modified risk claims on youth and provides a disingenuous rationale for doing so. TPSAC should evaluate whether an application that presents no evidence on the effect of modified risk claims on youth initiation or perception of risk can possibly meet the public health standard.

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[41] U.S. Centers for Disease Control and Prevention (CDC), "Tobacco Use Among Middle and High School Students — United States, 2011-2016," *Morbidity and Mortality Weekly Report (MMWR)* 66(23):597-603, June 16, 2017, https://www.cdc.gov/mmwr/volumes/66/wr/pdfs/mm6623a1.pdf.

[42] U.S. Dept. of Health and Human Services, *E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General.* Atlanta, GA: 2016.

[43] Tabuchi, T, et al., "Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan," *Addiction* 111:706-713, 2015.

[44] Executive Summary, p. 20.

[45] FDA, Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes at 5.

C. TPSAC should consider whether the introduction of iQOS with a modified risk claim would principally result in dual use of iQOS and conventional cigarettes, undermining any health benefit from the MRTP.

The Tobacco Control Act requires that FDA's evaluation both of the risk to the individual and the risk to the population as a whole must take account of the way the product is "actually used by consumers." PMI's application documents raise serious concerns regarding how the product will be used by consumers, particularly the high rates of dual use of iQOS and conventional cigarettes (even in individuals PMI considers to be "predominant" users of the tobacco heating system).

A substantial body of evidence supports the proposition that health benefits to an individual from quitting smoking occur only if the individual completely quits smoking. Merely reducing the level of smoking or smoking cigarettes and using other tobacco products concurrently does not eliminate the health risk.[46] Thus, even if iQOS might "significantly reduce harm and the risk of tobacco-related disease" if an individual quits smoking altogether and takes up iQOS instead, it might not do so for an individual who continues to smoke at the same time as he or she takes up iQOS.

The question of whether smokers who take up iQOS switch completely and abstain from smoking entirely or whether they use both products concurrently has extremely important health consequences. This question is critical in evaluating any potential benefit to health that might result from approval of this application. Indeed, the modified risk claims PMI seeks to make in this application are based on the assumption that iQOS users will switch completely away from cigarette smoking.

The evidence presented in PMI's application, in particular the studies conducted in the U.S., raises concern that smokers would not switch to exclusive iQOS use (i.e., the evidence does not demonstrate that smokers who take up iQOS would abstain from smoking cigarettes). In fact, the evidence suggests that a significant number of smokers in the U.S. who would use iQOS products would do so in conjunction with smoking, rather than switching entirely.

Information in the application indicates that, in the populations studied, dual users outnumber those who completely or near-completely switch to iQOS. Studies from the United States demonstrate this result. As shown in the table below, one PMI study of U.S. smokers (THS-PBA-07-US) found that the vast majority of smokers in the study (more than 92%) still used conventional cigarettes at the conclusion of the six-week study period, with a significant number combining cigarette use with some heat stick use. The study also found that, at the end

[46] U.S. Department of Health and Human Services (HHS), *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease*, U.S. Centers for Disease Control and Prevention (CDC), Office of Smoking and Health (OSH), 2010, at 9. HHS, *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*, CDC, OSH, 2012, at 22, http://www.surgeongeneral.gov/library/reports/preventing-youth-tobacco-use/index.html.

of six weeks, only 7.5% of U.S. smokers in the study transitioned to "exclusive" heat stick use (defined as use of heat sticks 95-100% of the time).[47] The study did not detail any patterns of use beyond the six week period.

Percent Use By Usage Category - Study Week 6
FAS Population (THS-PBA-07-US)

Usage Categories For Study Week 6	United States
Exclusive HeatStick (HS) Use 95-100% HS	7.5%
Predominant HeatStick (HS) Use 70-95% HS	7.0%
Combined mostly HeatStick (HS) Use 30-70% HS	22.4%
Predominant Conventional Cigarette (CC) Use 5-30% HS	28.2%
Exclusive Conventional Cigarette (CC) Use 0-5% HS	34.5%
Zero HeatStick and CC Use	0.3%
FAS (N=)	968

Studies provided by PMI also show large rates of dual use in other countries, even though smokers in other countries appear to more readily adopt at least some heat stick use than smokers in the U.S. As discussed below, at the conclusion of the 4-week study period in the multi-country Whole Offer Test ("WOT"), in every one of the countries studied a majority of heat stick users were dual users rather than exclusive users.

At the conclusion of the multi-country WOT, exclusive heat stick use (use of heat sticks 95-100% of the time) was highest in South Korea (15.7%) and Japan (13.6%) and below ten percent in the remaining countries, with exclusive use at 8.5% in Germany, 5.2% in Italy, and 4.3% in Switzerland.[48]

Given the significant variation in use patterns among countries in the WOT, the likelihood of dual use versus exclusive use in the United States cannot be reliably extrapolated from studies in other countries, particularly without understanding why the numbers vary so greatly from country to country. In its application, PMI noted differences across countries in multiple studies, "with differences between Japan and the U.S. populations consistently

[47] PMI, Section 6.2.2 at 99.
[48] PMI, Section 7.3.3, Data calculation from tables in the Analysis of Whole Offer Test Data, Summary Report.

observed, regardless of the type of studies."[49] PMI named a number of possible explanations, including cultural differences in taste preferences and interest in trying new products. They also noted that, "These cultural differences may also explain why complete switch was higher in some countries while combined/dual use of THS and cigarettes was the predominant pattern in other countries in observational studies."[50]

Note that for the multi-country WOT, PMI does not report the breakdown of usage categories for the Full Analysis Set (FAS) it its Full Summary Report or the accompanying Appendices. The table below presents usage categories for the entire FAS, which were determined by calculating the data presented for the "Usage Categories for Continued Use of *Heat Sticks*" and "Usage Categories for Early Stages of Using *Heat Sticks*" to yield data for the FAS.

Whole Offer Test (WOT) Percent Use By Usage Category of Participants - Study Week 4 - Calculated for Full Analysis Set (FAS) Population

Usage Categories For Study Week 4	Japan	Italy	Germany	Switzerland	South Korea
Exclusive HeatStick (HS) Use 95-100% HS	13.6%	5.2%	8.5%	4.3%	15.7%
Predominant HeatStick Use 70-95% HS	16.1%	6.9%	11.4%	5.5%	21.5%
Combined mostly HeatStick Use 60-70% HS	7.7%	4.3%	5.6%	5.3%	8.5%
Combined balanced Use 40-60% HS	16.3%	19.3%	15.4%	23.8%	18.3%
Combined mostly Conventional Cigarette ("CC") Use 30-40% HS	8.3%	14.4%	6.4%	10.3%	9.5%
Predominant CC Use 5-30% HS	27.7%	39.3%	24.7%	30.5%	17.3%
Exclusive CC Use 0-5% HS	10.0%	10.7%	26.5%	20.0%	8.5%
Zero HeatStick and CC Use	0.2%	0.0%	1.6%	0.2%	0.7%
FAS (N=)	638	535	377	416	843

Source: PMI, Section 7.3.3, Data calculation from tables in the Analysis of Whole Offer Test Data, Summary Report. See also 2.7 Executive Summary, Figure 36, p. 149

[49] PMI, Sec. 2.7, p. 160.
[50] PMI, Sec. 2.7, p. 160.

The results of PMI's multi-country WOT, while instructive, should not be extrapolated to the entire universe of smokers. In order to qualify for the study, participants had to express at least some interest in purchasing the product (those not interested in purchasing heat sticks were excluded) and the participants were provided heat sticks free of charge for the duration of the study (while they had to purchase conventional cigarettes at their own expense). Therefore, the level of adoption among smokers in the WOT may well be higher than it would be in the general population, and certainly may not apply to smokers in the U.S.

Because of the likely difference in health outcomes for those who completely quit smoking when they take up iQOS and those who use cigarettes and iQOS concurrently, it is essential that any modified risk claims for iQOS include clear and understandable statements to consumers advising them that any health benefits depend upon their switching entirely away from cigarettes. While the modified risk messages proposed by PMI do include language about "switching completely" as part of their overall message of reduced risk or reduced exposure, it is questionable whether consumers fully comprehend that "switching completely" means no use of cigarettes at all, or that consumers comprehend that the reduced risk and exposure outcomes only occur when one fully quits smoking conventional cigarettes.

With the high levels of dual use present in both the research studies and the real world experience, it is critical to understand whether consumers mistakenly believe that dual use of iQOS and other tobacco products would confer a health benefit when in fact it would not. It is also important to assess exposure to toxicants, including HPHCs, during periods of dual use of iQOS and conventional cigarettes, an issue not clearly addressed in the application.[51]

D. PMI did not analyze the impact of marketing mentholated iQOS products on the African-American population.

FDA's own study of the effect of the marketing of menthol cigarettes concluded that African-American smokers are much more likely to use menthol cigarettes than the general population of smokers. Moreover, as FDA noted, menthol in cigarettes is likely associated with reduced success in smoking cessation among African-American menthol smokers.[52] Given the disproportionate impact that marketing new mentholated iQOS products is expected to have on the African-American community, PMI should have conducted studies of the effect of these products—and these claims—on this specific population.

CONCLUSION

TPSAC should advise FDA that the application should not be granted unless and until PMI provides evidence on adolescent risk perception and potential adolescent tobacco use initiation and FDA has evaluated that evidence. TPSAC should advise FDA to take account of

[51] Comments by St. Helen, G. et al., Docket No. FDA-2017-D-3001, tracking number 1k1-902j-m8kv
[52] FDA, Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes at 130.

the evidence demonstrating that only a small minority of study subjects in every country in which studies have been conducted have switched to exclusive use of iQOS even where iQOS was supplied free of charge and that majority of study subjects who used iQOS throughout the period of the study also used conventional cigarettes. TPSAC should advise FDA to evaluate whether such results demonstrate that consumers exposed to the proposed modified risk claims understand that dual use produces little or no health benefit. Moreover, TPSAC should advise FDA to require the applicant to produce studies regarding the effect of the marketing of mentholated versions of iQOS on particularly vulnerable populations, such as youth and African-Americans. Additionally, TPSAC should provide FDA with advice regarding the individual health risks discussed in Section V of these comments. TPSAC should also ask FDA to resubmit the final application, including amendments that may be submitted subsequently, to TPSAC for further recommendations.

Respectfully Submitted,

Campaign for Tobacco-Free Kids