

**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**

Gideon St.Helen, PhD<sup>1,2</sup>; Peyton Jacob III, PhD<sup>1,2</sup>; Natalie Nardone, PhD<sup>1,2</sup>;  
Neal L. Benowitz, MD<sup>1,2,3</sup>

<sup>1</sup>Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco; <sup>2</sup>UCSF Tobacco Center of Regulatory Science; <sup>3</sup>Department of Bioengineering and Therapeutic Sciences, University of California San Francisco

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 According to FDA’s draft guidance, an MRTP is “any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially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.”<sup>1</sup> 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.

---

<sup>1</sup> 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 Draft Guidance.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.”<sup>2</sup> The FDA has an established list of 93 HPHCs.<sup>3</sup> 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

---

<sup>2</sup> <https://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponents/ucm20035927.htm>

<sup>3</sup> <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.<sup>4</sup> 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***

---

<sup>4</sup> 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.*<sup>5</sup> 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

---

<sup>5</sup> Sleiman, M., J. M. Logue, V. N. Montesinos, M. L. Russell, M. I. Litter, L. A. Gundel, and H. Destailats. 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.<sup>6,7</sup> In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.<sup>8</sup>

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.<sup>9</sup> 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

---

<sup>6</sup> 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.

<sup>7</sup> Bansal V., K-H. Kim (2016). “Review on quantitation methods for hazardous pollutants released by e-cigarette (EC) smoking.” *Trends in Analytical Chemistry*, 78: 120-133. DOI:10.1016/j.trac.2016.02.015

<sup>8</sup> Khlystov, A. and V. Samburova. 2016. “Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping.” *Environmental Science & Technology* 50(23): 13080-85.

<sup>9</sup> Klupinski TP, Strozier ED, Friedenber 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. PMID: 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.<sup>10</sup> FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

---

<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.):**

---

<sup>11</sup> 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.

<sup>12</sup> 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,<sup>13,14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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

---

<sup>13</sup> 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.

<sup>14</sup> 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.

<sup>15</sup> 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.

<sup>16</sup> 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.<sup>17</sup> The most likely scenario if IQOS is allowed

---

<sup>17</sup> 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.**