IQOS emissions create risks of immunosuppression and pulmonary toxicity, so FDA should not accept PMI reduced risk claim

My colleagues at the UCSF TCORS just submitted this public comment to the FDA and PMI's application to market IQOS as a modified (less) risk tobacco product. There is a PDF of the comment here and the tracking number is 1k1-903a-mnpl.

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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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 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***.

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 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.***

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]).

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 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.***

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

[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.

[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.

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

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[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.

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tobacco use in Japan after the commercialization of a heat-not-burn alternative (IQOS) to cigarettes. P. Science. www.pmiscience.com, Philip Morris International.

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[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.

[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.

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

My colleagues at the UCSF TCORS just submitted this public comment to the FDA and PMI's application to market IQOS as a modified (less) risk tobacco product. There is a PDF of the comment here and the tracking number is 1k1-9039-d91g.

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

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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 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 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***.

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.***

[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-har...

[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

[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.

PMI left a lot of important things out of its toxicology studies of IQOS submitted to the FDA

My colleagues at the UCSF TCOS just put this public comment in on Phlilip Morris' MRTP application for IQOS. The tracking number is 1k1-902j-m8kv. A PDF of the comment is available here.

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.

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.):**

1. ***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 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.

2. ***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.
3. ***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 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 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 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.

4. ***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.
5. ***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.

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

1. ***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.):**

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:

1. ***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.

2. ***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.
3. ***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 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.***
4. ***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 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.**

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

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