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

Lauren F. Chun, BA; Farzad Moazed, MD;
Michael A. Matthay, MD; Carolyn S. Calfee, MD MAS; Jeffrey E. Gotts MD PhD
Department of Medicine, Pulmonary Division
University of California San Francisco
UCSF Tobacco Center of Regulatory Science

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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

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

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

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

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

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

Potential for immunosuppressive effects

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

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

IQOS emissions pose risk for pulmonary toxicity

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

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

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

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

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

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

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

Additional concerns

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

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

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

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

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

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

Conclusion: FDA should deny the IQOS MRTP application

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

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

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

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

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

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