PMPSA's supplemental modified risk tobacco product application for IQOS 3 does not support the conclusion that IQOS will not harm vascular endothelial function and does not address new published research, so FDA should not issue an exposure modification MRTP order for IQOS 3

Lauren Kass Lempert, JD, MPH; Matthew L. Springer, PhD; Leila Mohammadi, M.D.; Daniel D.W. Han, BA; Poonam Rao, MBBS; Stanton A. Glantz, PhD; Bonnie Halpern-Felsher, PhD; Pamela Ling, MD, MPH
University of California San Francisco TCORS

Docket No. FDA-2021-N-0408
Modified Risk Tobacco Product Application: Application for the IQOS 3 System Holder and Charger Submitted by Philip Morris Products S.A.

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The supplemental modified risk tobacco product application for IQOS 3 (sMRTPA) does not address new published research and information on the risks to vascular endothelial function from exposure to IQOS aerosol and does not demonstrate benefits to individual or population health. FDA requires all applicants to demonstrate that their proposed MRTP products 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,"[1] and FDA is required to base its determination on whether to issue a MRTP order on "(A) the scientific evidence submitted by the applicant; and (B) scientific evidence and other information that is made available to the Secretary."[2] However, ***Philip Morris's sMRTPA does not address new published research providing scientific evidence regarding the vascular harms of IQOS and does not demonstrate benefits to individual or population health. Therefore, FDA should not issue an MRTP order for IQOS 3.***

1. Background

Philip Morris Products S.A. (PMPSA) submitted to FDA a supplemental modified risk tobacco product application (sMRTPA) for its IQOS 3 system holder and charger on March 18, 2021. In its sMRTPA, PMPSA stated that the IQOS 3 is essentially the same as the IQOS 2.4 and therefore PMPSA did not conduct additional studies with the IQOS 3 or provide any new health risk information or data about the IQOS 3. Instead, PMPSA cross-referenced to its previous MRTP and PMTA applications to demonstrate that the IQOS 3 system generates an aerosol that is comparable to that generated by the IQOS 2.4 system, exposes users to similar levels of the HPHCs it analyzed in its IQOS 2.4 applications, and that therefore there is sufficient evidence to support the modified risk claim that this process "significantly reduces the

[1] Family Smoking Prevention and Tobacco Control Act section 911(g)(1)(B), Pub. L 111-31, June 22, 2009.
[2] Family Smoking Prevention and Tobacco Control Act section 911(g)(3), Pub. L 111-31, June 22, 2009.

production of harmful and potentially harmful chemicals."[3] However, as we discuss below, ***since these premarket applications were submitted, important new evidence has been published that PMPSA did not report to FDA.*** These new studies strengthen the case that IQOS is not appropriate for the protection of the public health.

Because PMPSA did not address these new studies in its sMRTPA, the application does not satisfy the statutory requirements for MRTPAs[4] nor FDA's MRTPA Guidance that calls for applications to contain scientific studies and analyses and all research findings, "both favorable and unfavorable."[5]

Indeed, FDA should have refused to file the sPMTA for IQOS 3 at the outset because it did not include these studies as required by FSPTCA section 910(b)(1)(A),[6] which provides:

> (1) Contents.– An application under this section *shall* contain–
>
> (A) Full reports of all information, published or known to, or which should reasonably be known to, the applicant, concerning investigations which have been made to show the health risks of such tobacco product and whether such tobacco product presents less risk than other tobacco products.

In light of the new evidence, FDA should revisit and revoke its premarket tobacco product marketing orders for IQOS 2.4[7] and IQOS 3 and its reduced exposure modified risk order for IQOS 2.4,[8] and these orders should not be relied on to support the sMRTPA for IQOS 3.

On August 31, 2018, PMPSA submitted as Amendment 2 to its MRTPA for IQOS 2.4 the last update to its list of references, which included 7733 references. Since PMPSA submitted its MRTPA for the IQOS 2.4, more than 100 papers have been published on IQOS (see attached table of IQOS publications). PMPSA's Supplemental Premarket Tobacco Product Application (sPMTA)[9] for IQOS 3, which is cross-referenced in and used to support the IQOS 3 sMRTPA,

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[3] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, IQOS 3 System Holder and Charger Supplemental MRTP Application Executive Summary, Module 2.4 and Summary of Health Risk Investigations, Module 6.1. Available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

[4] Family Smoking Prevention and Tobacco Control Act section 911(g), Pub. L 111-31, June 22, 2009.

[5] US Food and Drug Administration, Guidance for Industry: Modified Risk Tobacco Product Applications, Draft Guidance (March 2012).

[6] Family Smoking Prevention and Tobacco Control Act section 910(b)(1)(A), Pub. L 111-31, June 22, 2009.

[7] Lempert LK, Glantz S. Analysis of FDA's IQOS marketing authorisation and its policy impacts. Tob Control. 2020 Jun 29:tobaccocontrol-2019-055585. doi: 10.1136/tobaccocontrol-2019-055585. Epub ahead of print. PMID: 32601147; PMCID: PMC7952009.

[8] Lempert LK, Bialous S, Glantz S. FDA's reduced exposure marketing order for IQOS: why it is not a reliable global model. Tob Control. 2021 Apr 2:tobaccocontrol-2020-056316. doi: 10.1136/tobaccocontrol-2020-056316. Epub ahead of print. PMID: 33811155.

[9] Philip Morris Products S.A. IQOS 3 System Holder and Charger Supplemental Premarket Tobacco Product Application (PMTA), Module 9 (m9): References, posted July 1, 2021. Available at:

includes references for only 14 additional papers, only six of which were published since August 2018 (one of which is written in French). However, at least three papers published since 2018 that address the impacts of IQOS on cardiovascular health are not discussed in PMPSA's sMRTPA for IQOS 3. We discuss this new literature below.

Even though ***PMPSA apparently failed to report this recent literature in any of its PMTA and MRTP applications for IQOS 2.4 and IQOS 3***, FDA must base its decisions on the best available current science. The new research, summarized and attached to this comment, reinforces our earlier comment concluding that PMPSA's MRTP application failed to show that IQOS aerosol exposure leads to less vascular endothelial dysfunction than cigarette smoke exposure and that ***Philip Morris failed to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals and failed to prove that IQOS would benefit the health of the population as a whole as required by FSPTCA section 911(g). Importantly, section 911(g)(4) unambiguously states that this showing is required for reduced exposure as well as reduced risk MRTPAs.***

To obtain an exposure modification MRTP marketing order, applicants are required to demonstrate that the product, as it is actually used by consumers, will "benefit the health of the populations as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products" (FSPTCA section 911(g)(2)(B)(iv)) and that issuance of an exposure modification order would be "appropriate to promote the public health." (FSPTCA section 911(g)(2)(A)(i)) To assess the potential effect that marketing the product with the proposed exposure modification claims may have on tobacco-related morbidity and mortality in the population as a whole, FDA recommends that MRTP applicants submit quantitative estimates that "integrate *all of the information* regarding the marketing of the product and its potential effects on health, tobacco use behavior and tobacco use initiation."[10]

Moreover, to help FDA determine whether continued marketing of IQOS is appropriate for the protection of public health or if there are grounds for FDA to withdraw marketing authorization, the marketing orders for IQOS 2.4[11] and for IQOS 3[12] each require under FSPTCA section 910(f) PMPSA to submit to FDA on an annual basis:

> **A summary of significant findings in publications not previously reported and full copies of the article. This must include any new scientific data (published or otherwise)** on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of

https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/pmi/Cross-referenced%20PMTA%20Submission%20%28PM0000364%29.zip

[10] FDA, Guidance for Industry: Modified Risk Tobacco Product Applications, Draft Guidance, March 2012. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modified-risk-tobacco-product-applications

[11] FDA, Marketing Order IQOS System Holder and Charger, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks, April 30, 2019, FDA Submission Tracking Numbers (STNs): PM0000424-PM0000426, PM0000479,Available: https://www.fda.gov/media/124248/download

[12] FDA, Marketing Granted Order IQOS System Holder and Charger, December 07, 2020, FDA Submission Tracking Number (STN): PM0000634. Available: https://www.fda.gov/media/144700/download

tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.

There is no publicly available evidence that PMPSA met this requirement.

2. Exposure to IQOS aerosol may impair vascular endothelial function

In November 2017 we submitted a public comment regarding the IQOS 2.4 MRTPA (Docket Number: FDA-2017-D-3001). In that comment, attached and incorporated by reference, we investigated PMPSA's assertion that IQOS aerosol exposure involves less cardiovascular risk than smoke exposure. We found that PMPSA used inappropriate criteria, and that endothelial function assessed by arterial flow-mediated dilation (FMD) is a better and validated measure of cardiovascular health effects. Independent research done in a more relevant physiological model shows that IQOS harms endothelial function as much as conventional cigarettes. Considering these concerns, we concluded that the evidence PMPSA presented in its MRTP application for IQOS is misleading and does not support the conclusion that IQOS aerosol exposure leads to less vascular endothelial dysfunction than cigarette smoke exposure. Thus, we demonstrated that ***Philip Morris had failed to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals and failed to prove that IQOS would benefit the health of the population as a whole as required by section 911(g). Importantly, section 911(g)(4) unambiguously states that this showing is required for reduced exposure as well as reduced risk MRTPAs.***

3. Independent research shows that IQOS impairs endothelial function comparably to conventional cigarettes

In November 2018 we published a peer-reviewed paper[13] based on our earlier comment that found flow-mediated dilation (FMD), a measure of vascular endothelial function and an important predictor of cardiovascular disease, was impaired by exposure to IQOS aerosol comparably to cigarette smoke, and that IQOS use does not necessarily avoid the adverse cardiovascular effects associated with smoking cigarettes. Using a validated rat model of FMD that strongly reflects human FMD in pharmacological, physical, and physiological aspects,[14] we measured FMD after exposure to undiluted Marlboro Red smoke or IQOS aerosol, or air control, and demonstrated that FMD was comparably reduced by a single smoking session (pulsatile exposure to mimic cycles of a single puff followed by clean air until the next puff). The IQOS exposure session resulted in high nicotine uptake than the Marlboro Red smoking session on a puff-per-puff basic, but even when we lowered the number of IQOS puffs to achieve the same serum nicotine levels as that from the cigarette smoking session, FMD was still impaired. We incorporate by reference and attach this study.

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[13] Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob III P, Springer ML. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 2018 Nov;27(Suppl 1):s13-s19. doi: 10.1136/tobaccocontrol-2018-054325. Epub 2018 Sep 11. PMID: 30206183; PMCID: PMC6202192.

[14] Heiss C, Sievers RE, Amabile N, Momma TY, Chen Q, Natarajan S, Yeghiazarians Y, Springer ML. In vivo measurement of flow-mediated vasodilation in living rats using high-resolution ultrasound. Am J Physiol Heart Circ Physiol. 2008 Feb;294(2):H1086-93. doi: 10.1152/ajpheart.00811.2007. Epub 2007 Nov 30. PMID: 18055528.

Several other new papers [15, 16, 17, 18] published since August 2018 address the potential vascular harms of IQOS. ***Although PMPSA apparently failed to report this recent literature in any of its PMTA and MRTP applications for IQOS 2.4 and IQOS 3, FDA must base its decisions on the best available science.*** Ioakeimidis et al.[16] found that in humans who smoked one tobacco cigarette or one IQOS HeatStick, arterial stiffness (higher is bad) measured as carotid/femoral artery pulse wave velocity and augmentation index acutely increased to comparable extents, although augmentation index subsequently decreased back to baseline in the IQOS users sooner than in the tobacco cigarette smokers. (Given that the initial magnitude of arterial stiffness was comparable, the significance of the faster resolution time after the acute IQOS exposure is unclear.) In agreement with the earlier rat results discussed above,[13] Biondi-Zoccai et al.[17] reported that FMD was impaired in humans by smoking a cigarette, smoking an IQOS HeatStick, or vaping an e-cigarette.

Popova et al.[18] showed that biomarkers of bioavailable nitric oxide, which is an important positive mediator of vascular endothelial function, were reduced in the saliva of people who had used IQOS for 2 or 3 years relative to non-users, and endothelin-1, which is a negative mediator of endothelial function, was conversely increased; with these changes being of greater magnitude in the 3-year users than in the 2-year users. This new research, incorporated by reference and attached to this comment, reinforces our earlier study and comment concluding that exposure to IQOS emissions represents potential health risks for consumers because of potential harms to vascular endothelial function.

Philip Morris did not address any of these studies in addition to failing to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals and failed to prove that IQOS would benefit the health of the population as a whole as required by section 911(g). Importantly, section 911(g)(4) unambiguously states that this showing is required for reduced exposure as well as reduced risk MRTPAs.

4. Conclusion

PMPSA did not report all available published scientific evidence related to IQOS emissions and vascular endothelial harms or that IQOS may harm endothelial function as much

[15] Fried ND, Gardner JD. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. Am J Physiol Heart Circ Physiol. 2020 Dec 1;319(6):H1234-H1239. doi: 10.1152/ajpheart.00708.2020. Epub 2020 Oct 2. PMID: 33006919; PMCID: PMC7792702.

[16] Ioakeimidis N, Emmanouil E, Terentes-Printzios D, Dima I, Aznaouridis K, Tousoulis D, Vlachopoulos C. Acute effect of heat-not-burn versus standard cigarette smoking on arterial stiffness and wave reflections in young smokers. Eur J Prev Cardiol. 2020 Apr 28:2047487320918365. doi: 10.1177/2047487320918365. Epub ahead of print. PMID: 33611437.

[17] Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. J Am Heart Assoc. 2019 Mar 19;8(6):e010455. doi: 10.1161/JAHA.118.010455. PMID: 30879375; PMCID: PMC6475061.

[18] Popova, T., Nakonechna, O., Tishchenko, O., & Kryvenko, L. (2021). The Vascular Endothelium Function Indicators in Oral Liquid of IQOS Smoking Adolescents. Ukrainian Dental Almanac, (2), 118-123. https://doi.org/10.31718/2409-0255.2.2021.21

as conventional cigarettes. ***Because PMPSA and FDA have not presented or made publicly available evidence refuting these points and failed to otherwise demonstrate that IQOS 3 would benefit the health of individuals and of the population as a whole, we strongly recommend that FDA deny PMI's Supplemental MRTP application for IQOS 3.***