IQOS emissions create risks of immunosuppression and pulmonary toxicity and the supplemental modified risk tobacco product application for IQOS 3 does not address new published research on these risks, so FDA should not issue an exposure modification MRTP order for IQOS 3

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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 evidence Philip Morris Products S.A. (PMPSA) is using to support its supplemental modified risk tobacco product application (sMRTPA) for IQOS 3 is the same evidence it used to support its MRTPA for IQOS 2.4. However, PMPSA has failed to demonstrate reductions in pulmonary toxicity among IQOS users as compared to conventional cigarette smokers and IQOS emissions may create novel risks of immunosuppression not observed with conventional cigarettes. Additionally, the sMRTPA for IQOS 3 does not adequately address new published research and information on the risks of immunosuppression and pulmonary toxicity and does not demonstrate benefits to individual or population health. Among other findings, all applicants are required 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 adequately address new published research providing scientific evidence regarding the potential 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

[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.

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 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 and FDA should not have authorized the marketing of IQOS in the first place. FDA should therefore revisit its premarket tobacco product marketing orders for IQOS 2.4[4] and IQOS 3 and its reduced exposure modified risk order for IQOS 2.4,[5] 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 spreadsheet). However, ***at least nine of these papers that address immunosuppression and/or pulmonary toxicity, discussed below, are not discussed in PMPSA's sMRTPA for IQOS 3.*** PMPSA's Supplemental Premarket Tobacco Product Application (sPMTA)[6] for IQOS 3, which is cross-referenced in and used to support the IQOS 3 sMRTPA, includes references for only 14 additional papers, only six of which were published since August 2018 (one of which is written in French), and none of which discuss pulmonary harms or immunosuppression.

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. The new research, summarized and attached to this comment, reinforces our earlier comment concluding that ***PMPSA's MRTP applications fail to show reductions in pulmonary toxicity from IQOS emissions as compared with conventional cigarettes, fail to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals, and fail 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.***

Because PMPSA did not address these new studies in its sMRTPA, the application does not satisfy the statutory requirements for MRTPAs[7] nor FDA's MRTPA Guidance that calls

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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] 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.

[5] 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.

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

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

for applications to contain scientific studies and analyses and all research findings, "both favorable and unfavorable."[8]

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),[9] 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[10] and IQOS 3 and its reduced exposure modified risk order for IQOS 2.4,[11] and these orders should not be relied on to support the sMRTPA for IQOS 3.

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."[12]

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

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

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

[10] 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.

[11] 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.

[12] 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

authorization, the marketing orders for IQOS 2.4[13] and for IQOS 3[14] 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 tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.

There is no indication in the public record that PMPSA met this requirement.

2. Exposure to IQOS emissions create risks of immunosuppression and pulmonary toxicity

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 discussed *in vivo* studies submitted by PMPSA in its MRTP application which showed that female rats exposed to IQOS had elevated levels of blood neutrophils, signaling possible acute inflammation and signs of thymic atrophy in male and female animals exposed to IQOS emissions. Based on these results, we concluded that ***IQOS emissions may have novel effects on host immune defenses not observed with conventional cigarettes that could be important for human users.*** Additionally, we found that PMPSA failed to show reductions in pulmonary inflammation and function in its human clinical studies and failed to show no statistically significant difference between IQOS users and conventional cigarette smokers in plasma WBC, plasma CRP (C-reactive protein) or plasma fibrinogen. Therefore, ***PMPSA failed to show any reduction in pulmonary toxicity in people who used IQOS compared to conventional cigarettes.***

Thus, we demonstrated that ***Philip Morris had failed to prove that IQOS will significantly reduce exposure to harmful substances or 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 exposure to IQOS emissions may create pulmonary and immunomodulatory risks

[13] 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

[14] 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

In November 2018 we published a peer-reviewed paper[15] based on our earlier comment. In that paper, attached and incorporated by reference, we found that among rats exposed to IQOS that found there was evidence of pulmonary inflammation and immunomodulation and in human users, there was no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who were switched to IQOS. We concluded that IQOS is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to IQOS in Philip Morris's studies. Philip Morris also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products.

In January 2020, FDA posted an amendment to the IQOS 2.4 MRTPA. The amendment was a December 20, 2019 summary report prepared by PMI in response to FDA's November 20, 2019 Request for Information about PMI's *in vivo* study on lung cancer tumorigenesis in A/J mice exposed to IQOS aerosol. The study showed an increase in morbidity (PMI uses the term "moribundity") and mortality in the A/J male mice exposed to the IQOS aerosol. PMI's summary report tried to rationalize this result by claiming that the result "was not plausibly related to the [IQOS] aerosol but rather is a strain-specific finding."

PMPSA argued that "the increased early moribundity/morbidity observed in the male mice exposed to high levels of [IQOS] aerosol was due to a strain-specific susceptibility in the male urogenital tract," i.e., male A/J mice are different from their female counterparts in terms of susceptibility to impairment of the urogenital tract. PMI argued that this is most likely due to the *sister x brother* mating scheme in the inbred colonies their study used, and that the mortality due to congenital abnormalities in the urogenital tract of this inbred mouse strain "has limited relevance" to humans. Further, PMI argued that they could not identify putative factors in IQOS aerosol that might be responsible for this result. However, PMI also concluded that the mechanism for this finding remains "elusive," and that this problem did not occur in their rat studies. Despite PMPSA's attempts to obscure the results of its own study, ***the data show that A/J male mice exposed to IQOS aerosol have a serious adverse event.***

PMPSA's statement that a causal link to IQOS aerosol cannot be established contradicts their own findings in their studies. The hypothesized link to a problem with sister x brother inbreeding is just a hypothesis. PMPSA provided no studies that prove or disprove this idea. And even if this inbreeding contributed to the result, it would still be relevant that it occurred in the male mice exposed to IQOS aerosol.

FDA properly flagged this problem and asked the right question; however, PMPSA's response was not satisfactory. This exchange further demonstrates why FDA should deny PMPSAs MRTP application for IQOS 3 and should not allow IQOS to be marketed with MRTP claims.

[15] Moazed F, Chun L, Matthay MA, Calfee CS, Gotts J. Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. Tob Control. 2018 Nov;27(Suppl 1):s20-s25. doi: 10.1136/tobaccocontrol-2018-054296. Epub 2018 Aug 29. PMID: 30158203; PMCID: PMC6252496.

We attach and incorporate by reference the public comment we submitted in February 2020 to the IQOS 2.4 docket that makes these points.

4. Newly published research demonstrates potential adverse pulmonary, cytotoxic, and other impacts from IQOS

In addition to our November 2018 peer-reviewed published study, since August 2018, the date of the most recent list of references submitted by Philip Morris to FDA in support of its MRTP application for IQOS 2.4 (and the only list publicly available), at least eight other papers have been published that also demonstrate potential adverse pulmonary, cytotoxic, and other impacts from IQOS.

A 2021 study[16] identified irritating and carcinogenic compounds including aldehydes and polycyclic aromatic hydrocarbons (PAHs) in IQOS mainstream aerosol, ***suggesting that IQOS products are in fact generating smoke rather than pure aerosol.*** The study found ultrastructural changes in the rat trachea and lung parenchyma consistent with changes due to aldehyde exposure and upregulation of pro-inflammatory markers. It demonstrated that IQOS mainstream induces lung enzymes that activate carcinogens, increases tissue reactive radical concentration; promotes oxidative DNA breaks and gene level DNA damage; and stimulates mitogen activated protein kinase (MAPK) pathway which is involved in the conventional tobacco smoke-induced cancer progression. Taking these effects together, ***this study confirmed that IQOS mainstream contains pyrolysis and thermogenic degradation by-products, the same harmful constituents found in traditional cigarette smoke, and showed that it causes lung damage and promotes factors that increase cancer risk in the animal model.***

A similar 2021 study[17] looking at the effects of short-term inhalation of IQOS aerosols on lung damage and immune-cell recruitment to the lungs in mice found significantly increased levels of albumin in the bronchoalveolar (BAL) fluid of mice exposed to IQOS aerosol as well as cigarette smoke. It also found total numbers of leukocytes infiltrating the lungs were equivalent following both IQOS and cigarette smoke exposure and increased T-cell immune response in both groups and similar elevated levels of pro-inflammatory cytokines and chemokines in mice exposed to IQOS and cigarette smoke. While some findings corroborate a few of PMPSA's claims (e.g., that IQOS aerosols are associated with a lower absolute number of neutrophils and macrophages), other findings (specifically, albumin as a marker of lung epithelial cell damage in IQOS) undermine PMPSA's studies. Overall, ***this study presents extensive evidence that short-term inhalation of aerosols from IQOS generates damage and proinflammatory changes in the lung that are substantially similar to that generated by cigarette smoke exposure, suggesting that IQOS exposure is associated with impaired lung function.***

[16] Vivarelli F, Canistro D, Cirillo S, Elias RJ, Granata S, Mussoni M, Burattini S, Falcieri E, Turrini E, Fimognari C, Buschini A, Lazzaretti M, Beghi S, Girotti S, Sangiorgi S, Bolelli L, Ghini S, Ferri EN, Fagiolino I, Franchi P, Lucarini M, Mercatante D, Rodriguez-Estrada MT, Lorenzini A, Marchionni S, Gabriele M, Longo V, Paolini M. Unburned tobacco cigarette smoke alters rat ultrastructural lung airways and DNA. Nicotine Tob Res. 2021 May 24:ntab108.

[17] Bhat TA, Kalathil SG, Leigh N, Muthumalage T, Rahman I, Goniewicz ML, Thanavala YM. Acute Effects of Heated Tobacco Product (IQOS) Aerosol Inhalation on Lung Tissue Damage and Inflammatory Changes in the Lungs. Nicotine Tob Res. 2021 Jun 8;23(7):1160-1167.

A published letter[18] responding to a commentary that had suggested possible opportunities associated with new products such as IQOS highlighted the authors' recent study[19] comparing the ill effects of cigarette smoke to e-cigarette and IQOS emissions on human bronchial epithelial cells and primary human airway smooth muscle cells. The study found that all tested pathological biomarkers (including CXCL8, matrix proteins [fibronectic and collagen-1], and markers of mitochondrial dysfunction) were elevated in cells exposed to IQOS smoke suggesting pathological cellular injury and abnormalities and that IQOS emissions have the potential to activate epithelial-to-mesenchymal transition (EMT)-related changes in the airways of IQOS users and that IQOS can exaggerate respiratory infections by increasing microbial adherence to the airways. ***Their study showed IQOS to be just as toxic as cigarette smoke to the cells, evidenced by decreased cellular viability and integrity, and that IQOS use interfered with cellular energetics.*** In particular, the results of their study corroborate current research showing that IQOS is detrimental: biomarkers including CXCL8, matrix proteins (fibronectic and collagen-1), and markers of mitochondrial dysfunction suggest damage in response to IQOS and vaping and further suggest that IQOS may activate EMT-related changes in the airways and exaggerate respiratory infections by increasing microbial adherence. ***The letter concluded that the terms "aerosol," "vapor," and "harm reduction" are incorrect and misleading with regard to IQOS emissions.***

Some of these authors and colleagues published another paper[20] in 2020 that explored the possibility that smoking, including smoking IQOS, can upregulate angiotensin-converting enzyme-2 (ACE2) receptors, may increase vulnerability to respiratory diseases, and may be associated with Covid-19 transmission. The paper called for collecting data on smoking status in Covid-19 cases and conducting further research to understand the association between IQOS and Covid-19.

In addition to respiratory impacts, several studies explored the cytotoxic effects of IQOS. A 2018 study[21] comparing the cytotoxic effects of IQOS on human bronchial epithelial cells found that the metabolic activity of cells decreased significantly after exposure to IQOS. Overall, the study found that IQOS emissions damaged bronchial epithelial cells and that their cytotoxic effect was higher compared with e-cigarettes, but lower compared with conventional cigarettes.

A 2019 study[22] comparing the cytotoxicity of IQOS aerosols to conventional cigarette smoke showed, among other findings, that although IQOS exposure did not lead to cell death in

[18] McAlinden KD, Eapen MS, Lu W, Sharma P, Sohal SS. The Ill Effects of IQOS on Airway Cells: Let's Not Get Burned All Over Again. Am J Respir Cell Mol Biol. 2020 Aug;63(2):269-270.
[19] Sohal SS, Eapen MS, Naidu VGM, Sharma P. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. *ERJ Open Res* 2019;5:00159-2018.
[20] Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). J Clin Med. 2020 Mar 20;9(3):841.
[21] Leigh NJ, Tran PL, O'Connor RJ, Goniewicz ML. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. Tob Control. 2018 Nov;27(Suppl 1):s26-s29.
[22] Davis B, To V, Talbot P. Comparison of cytotoxicity of IQOS aerosols to smoke from Marlboro Red and 3R4F reference cigarettes. Toxicol In Vitro. 2019 Dec;61:104652.

most trials, it did adversely affect critical cellular functions and that for some cell types, IQOS aerosol and 3R4F reference cigarette smoke were equally cytotoxic for comparisons made at the high concentrations. These findings led the authors to express their concern about the equivalent cytotoxicity observed with IQOS aerosol and 3R4F research cigarette smoke and the sensitivity of human bronchial epithelial cells and lung fibroblasts to IQOS aerosols. Further, while the authors cautioned that their data cannot be directly extrapolated to human health, they clearly show a need for additional studies on IQOS products.

After reviewing the increase in IQOS use, its effects on health and safety, and its effectiveness as a smoking cessation method, the Spanish Society of Pulmonology and Thoracic Surgery published an official statement[23] in 2019 concluding that although some studies showed the emission of toxic substances was lower in IQOS than in conventional cigarettes, there is not enough evidence to guarantee the safety of IQOS emissions in the short, medium, and long term. Moreover, these products present a demonstrated risk to people, especially children, who passively inhale the fumes and aerosols of these devices. The Society notes that toxicity should not be compared between these devices and conventional cigarettes, but between the use of these devices and abstinence from any type of tobacco use. Further, these devices cannot be commended as effective cessation devices. Importantly, the statement also points out that most published papers that minimize the health risks of IQOS are studies sponsored by tobacco companies, and their safety conclusions have been questioned.

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. 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 pulmonary, cytotoxic, and immunosuppressive harms and other health risks 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 section 911(g). Importantly, section 911(g)(4) unambiguously states that this showing is required for reduced exposure as well as reduced risk MRTPAs.***

5. Conclusion

Published scientific evidence that has not been reported by PMPSA demonstrates that IQOS emissions are associated with pulmonary, cytotoxic, and immunosuppressive harms. ***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.***

[23] Signes-Costa J, de Granda-Orive JI, Ramos Pinedo Á, Camarasa Escrig A, de Higes Martínez E, Rábade Castedo C, Cabrera César E, Jiménez-Ruiz CA. Official Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on Electronic Cigarettes and IQOS®. Arch Bronconeumol (Engl Ed). 2019 Nov;55(11):581-586. English, Spanish.