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December 20, 2024

Submitted via CTP Portal

Amber Koblitz
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Center for Tobacco Products
Food and Drug Administration
10903 New Hampshire Avenue
Building 71, Room G335
Silver Spring, MD 20993-0002

Subject: RESPONSE TO ADVICE/INFORMATION REQUEST for MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7

Dear Dr. Koblitz,

With submission of this letter and supporting attachments, PMIGSI[1], on behalf of PMP SA[2], is providing a complete response to the November 22, 2024, A/I Request[3] letter regarding the July 5, 2023, MRTPA[4] Renewals.

In response to Question 1, we include Table 1 to note which *IQOS* products were assessed in all studies listed. Additionally, we explain why the findings for studies conducted in countries outside of the United States are acceptable for bridging to the authorized MRTPs. With respect to Question 2, we provided evidence showing that the PLA[5] film supplier change did not result in any changes to the chemical composition or physical characteristics.

Regarding concerns of toxicity and increased risk raised in Questions 3 through 5, we explain how the current scientific evidence supports the toxicology conclusions reached from the original authorization, demonstrating that the levels of gamma-butyrolactone and 3-hydroxy tyrosine in *IQOS* aerosol are several orders of magnitude lower than the doses that cause psychoactive effects and determined that the $ELCR_c$[6] of *IQOS* aerosol, calculated using methodology from a recent FDA Memorandum, is approximately 80% lower than the cancer risk of 3R4F reference cigarette smoke. Additionally, we provide clarification to the chemical names and nomenclatures identified in Questions 6 and 7 and cross-referenced the 2024 Annual Report, PS0000333, for the latest safety update report requested in Question 8.

[1] Philip Morris International Global Services Inc.
[2] Phillip Morris Products S.A.
[3] Advice and Information Request
[4] Modified Risk Tobacco Product Application
[5] Polylactic acid
[6] Cumulative Excess Lifetime Cancer Risk

Although we provided a complete response addressing scientific issues of concern raised in your November 22, 2024, letter, we also note that the nature of some of these requests brings into question the original APPH[7] determination that was reached with issuance of the 2019 and 2020 PMTA MGOs[8]. For example, several of your questions focus on the toxicity of *IQOS* aerosol, which relates to the APPH determination. We believe the MRTPA renewal scope should focus on the PMSS[9] studies agreed upon by the Agency and whether the results of those studies support or refute the original MRTP authorization. More specifically, MRTPA renewal should focus on consumer use behavior related to the modified risk claim and not the validity of previous APPH determinations. Concerns with previous APPH determinations require several regulatory processes that are independent of and separate from MRTPA review, including the Agency offering the MGO holder an informal hearing[10] prior to taking any action. We object to the toxicology questions in your letter, as we believe they are not relevant to the decision that needs to be made on the renewal of a MRTP order.

We remain committed to providing the Agency with the information needed to support an MRTPA renewal and are confident that, with submission of this solicited amendment, we have demonstrated scientific evidence necessary for issuing MRGO renewals for *IQOS* 2.4, *IQOS* 3.0, and three *HEETS* variants. We look forward to further discussions with the Agency and are available if there are questions.

Respectfully,

(b) (6)

Laura Leigh Oyler
US Agent for PMP SA
Head, US Regulatory Affairs
PMI Global Services Inc.

cc: Elizabeth Do, Regulatory Health Project Manager, Office of Science

Please note that this submission contains confidential commercial information, and/or trade secret information, and the legal protections provided to such information are hereby claimed under the applicable provisions of United States law, including relevant provisions of the Federal Freedom of Information Act, 5 U.S.C. 552 et seq. (specifically, 5 U.S.C. 552(b)(4)), the Trade Secrets Act (18 U.S.C. 1905), the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq. (specifically FD&C Act §§ 301(j) and 906(c), 21 U.S.C. 331(j) and 387f(c)) and FDA's implementing regulations, 21 CFR Part 20 (specifically 21 CFR 20.47 and 20.61). PMP S.A. understands that FDA will hold this documentation confidential and will refrain from the public disclosure of the information contained in this submission in conformity with such provisions of the law. Accordingly, if FDA tentatively determines that any portion of this submission is disclosable to the public, FDA is required to provide PMP S.A. with notice and an opportunity to object in accordance with 21 CFR 20.47 and 20.61. PMP S.A. reserves all legal rights to protect against public disclosure of its trade secrets and confidential commercial information and to seek legal recourse against anyone who discloses such information without legal authorization.

[7] Appropriate for the Protection of Public Health

[8] As stated in the 2019 PMTA TPL review, "Although some of the chemicals [in IQOS] are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in combustible cigarettes."

[9] Post Market Surveillance Studies

[10] 21 CFR Sec. 1114.35- Withdrawal of a marketing granted order (www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=1114.35)

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FDA Questions Followed by Our Responses

FDA Question 1

1. Your renewal MRTPA identifies three *HeatSticks* – *Marlboro* Amber *HeatSticks* (previously *Marlboro HeatSticks*, also known as *HEETS* Amber), *Marlboro* Green Menthol *HeatSticks* (previously *Marlboro* Smooth Menthol *HeatSticks*, also known as *HEETS* Green), and *Marlboro* Blue Menthol *HeatSticks* (previously *Marlboro* Fresh Menthol *HeatSticks*, also known as *HEETS* Blue) – as the *HeatStick* products that are the subject of the application (MR0000254.PD5-PD7). After the modified risk granted order (MRGO) was issued for these products (MR0000059.PD1- MR0000061.PD1), you made manufacturing changes and modifications to the products reflected in change logs submitted with each postmarket surveillance and studies (PMSS) submission (PS0000119, PS0000175, PS0000284).

   Your renewal MRTPA (MR0000254.PD5-MR0000254.PD7) does not specify the characteristics (materials, ingredients, design, composition, heating source, or other features) of the *HeatStick* products that were used in each of the submitted studies and to which of the IQOS System and *HeatStick* products in the renewal MRTPA (MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-MR0000254.PD7) the submitted and cross-referenced evidence applies. Information about the characteristics (materials, ingredients, design, composition, heating source, or other features, including the harmful and potentially harmful constituent (HPHC) quantities and any variation in those quantities) of the *HeatStick* products used in each of the submitted studies and to which of the *HeatStick* products subject of the application the submitted and cross-referenced evidence applies is needed to fully characterize the products and determine whether the presented evidence applies to the products that are the subject of the application, and whether the products are expected to benefit the health of the population as a whole.

   We request that you:

   - Clarify which *HeatStick* product(s) were assessed in each of the studies listed below that were submitted or cross-referenced to support the renewal MRTPA (MR0000254.PD5-MR0000254.PD7). Clarification should outline if each *HeatStick* used in each study is identical to the authorized MRTP *HeatSticks* with an MRGO (MR0000059.PD1-MR0000061.PD1) (see Appendix C for Tables 1, 2, and 3 that reference certain characteristics of the authorized MRTP *HeatSticks*).
   - If the *HeatStick* products in each study do not have identical characteristics to the authorized MRTP *HeatSticks* (MR0000059.PD1-MR0000061.PD1), identify each modification. Additionally, if the modified product was authorized under a Supplemental Premarket Tobacco Product Application (sPMTA) or a Request for Exemption from Substantial Equivalence (EX Request), provide the submission tracking number (STN) for that product.
   - Provide bridging information for those studies that do not assess only the authorized MRTP *IQOS* System and *HeatSticks* to support why the study findings for each study submitted or cross-referenced to support the renewal MRTPA apply to the authorized MRTP *IQOS* System and *HeatSticks* (MR0000059.PD1-MR0000061.PD1). Utilize the list of studies below to aid in submitting this information.

Study Names

- P1-RMC-03-INT
- P1-ERS-EXT-SCR-PH-SHP
- P1-ERS-EXT-SCR-PH-RESP
- Phase II Tobacco Product Portfolio Study / Pilot Actual Use Study of *IQOS* 3.0
- THS-PBA-07-US/ US Premarket Actual Use Study
- ALCS-CMI-17-36-HT / *IQOS* Cross-sectional PACS
- Underage Tobacco Use Survey (UTUS)
- PM-PMX-01-JP (Year 5) – General Adult Population Sample
- PM-PMX-01-JP (Year 5) – *IQOS* User Sample
- P1-OHS-01-JP
- ZRHR-ERS-09-EXT-US
- P1-EXC-01-EU
- P1-PMX-02-IT
- P1-AAA-02-JP
- Annex 10: Stability Monitoring and Testing

PMIGSI RESPONSE

The studies cited in your request are listed in **Table 1** below with the products tested. Any study listed as using FDA-authorized products used the products as authorized by FDA (i.e., no modifications).[11]

Table 1. Studies Listed in Request #1 with Descriptions and Products tested

Study ID	Study Description	Product(s) Tested
P1-RMC-03-INT	Clinical study to demonstrate reduction in exposure to key toxicants, oxidative stress, and inflammation following at least 2 years of Tobacco Heating System (THS) use compared to cigarette smoking. Study conducted in in Asia (Japan) and Europe (Poland, Czech Republic, Bulgaria, Greece and Germany).	**No test products were provided to participants given the study design**. Study participants were using their usual *HEETS* products marketed in the countries where the study was conducted.
P1-ERS-EXT-SCR-PH-SHP	*Post hoc* analysis of data from ERS-09 and ZRHR-ERS-09-EXT-US studies.	MR0000059 (*HEETS* Amber) MR00000133 (*IQOS* 2.4 Device)
P1-ERS-EXT-SCR-PH-RESP	*Post hoc* analysis of data from ERS-09 and ZRHR-ERS-09-EXT-US studies.	MR0000059 (*HEETS* Amber) MR00000133 (*IQOS* 2.4 Device)
Phase II Tobacco Product Portfolio Study / Pilot Actual Use Study of *IQOS* 3.0	Actual use study where adult smokers in the United States were provided *IQOS* test products.	MR0000059 (*HEETS* Amber) MR0000060 (*HEETS* Green) MR0000061 (*HEETS* Blue) MR00000192 (*IQOS* 3.0 Device)
THS-PBA-07-US / US Premarket Actual Use Study	Actual use study where adult smokers in the United States were provided *IQOS* test products.	MR0000059 (*HEETS* Amber) MR0000060 (*HEETS* Green) MR0000061 (*HEETS* Blue) MR00000133 (*IQOS* 2.4 Device)

[11] The products were initially authorized under MR0000059.PD1 (*HEETS* Amber), MR0000060.PD1 (*HEETS* Green), MR0000061.PD1 (*HEETS Blue)*, MR0000133 (*IQOS* 2.4 Device), and MR0000192 (*IQOS* 3.0 Device).

Study ID	Study Description	Product(s) Tested
ALCS-CMI-17-36-HT / IQOS Cross-sectional PACS	Postmarket surveillance study for understanding awareness and prevalence of *IQOS* use among legal age adults in the United States, including *IQOS* products. **No test products were provided to study participants, given the study design.** However, participants were surveyed about *IQOS* products that were commercialized at the time in the United States.	MR0000059 (*HEETS* Amber) MR0000060 (*HEETS* Green) MR0000061 (*HEETS* Blue) MR00000192 (*IQOS* 3.0 Device)
Underage Tobacco Use Survey (UTUS)	Postmarket surveillance study for understanding awareness and prevalence of tobacco/nicotine use among underage persons in the United States, including *IQOS* products. **No test products were provided to study participants, given the study population and design.** However, participants were surveyed about *IQOS* products that were commercialized in the United States at the time.	MR0000059 (*HEETS* Amber) MR0000060 (*HEETS* Green) MR0000061 (*HEETS* Blue) MR00000192 (*IQOS* 3.0 Device)
PM-PMX-01-JP (Year 5) – General Adult Population Sample	Postmarket surveillance study	**No test products were provided to participants given the study design**. Study conducted in Japan with *IQOS* products marketed in this country.
PM-PMX-01-JP (Year 5) – IQOS User Sample	Postmarket surveillance study	**No test products were provided to participants given the study design**. Study conducted in Japan with *IQOS* products marketed in this country.
P1-OHS-01-JP	Clinical study to evaluate the effect of switching from cigarette smoking to the use of *IQOS* products in smokers with generalized chronic periodontitis on the response to mechanical periodontal treatment and oral health status.	**No test products were provided to participants given the study design.** Study conducted in Japan with *IQOS* products marketed in this country.
ZRHR-ERS-09-EXT-US	Study was an extension of the ERS-09 clinical study, in which adult smokers in the United States were randomized to use a reference cigarette or *IQOS* test products for 6 months. The extension study extended the actual use period by 6 months for a subset of participants.	MR0000059 (*HEETS* Amber) MR00000133 (*IQOS* 2.4 Device)
P1-EXC-01-EU	Postmarket surveillance study	**No test products were provided to participants given the study design**. Study conducted in Germany with *IQOS* products marketed in this country

Study ID	Study Description	Product(s) Tested
P1-PMX-02-IT	Postmarket surveillance study	**No test products were provided to participants given the study design**. Study conducted in Italy with *IQOS* products marketed in this country.
(b) (4)		
Annex 10: Stability Monitoring and Testing	Stability study to evaluate microbiological endpoints in *HEETS* products over time.	Not applicable.

The studies listed in Table 1 above are all studies that were ongoing or started after the products were authorized as MRTPs.[11] As shown in the table, while some studies tested or surveyed use of the authorized products,[11] some studies involved variants of the products available in other countries. Any variant of the *IQOS* products tested or commercialized globally is subject to our comparability assessment (see Q1a1_THS_2.2_Comparability_Strategy_v6.2). The comparability strategy is employed to scientifically determine that any changes made to *IQOS* products for any market will not impact the product performance over time. Thus, the HPHC deliveries will stay within the ranges dictated in Q1a1_THS_2.2_Comparability_Strategy_v6.2, regardless of the product design changes made. Given the FDA-authorized products[11] are the basis for the comparability strategy, any variant of the products available globally must be demonstrated as having comparable product performance to the FDA-authorized products before being commercialized or used for testing in any market. The comparison of every product change against the fixed product performance range ensures that the number and level of HPHCs of *IQOS* products in any market are always within these performance ranges. Therefore, all studies listed in your request performed in markets outside of the U.S., investigated *IQOS* products demonstrated as comparable to the FDA-authorized products.[11] Additionally, because the user behavior and user populations of product variants are similar across all markets globally, we assert the results of all clinical and observational studies performed on all variants are applicable to the U.S. authorized products and thus, this MRTPA renewal. That being said, we included the global studies for completeness, but if you believe these studies are not applicable to the authorized MRTPs, please disregard them from your evaluation of the MRTPA renewal.

FDA Question 2

2. In your original MRTPA submission (MR0000059.PD1-MR0000061.PD1), you stated that one of the intended functions of the polylactic acid (PLA) plug in the *HeatStick* products is to condense water in vapor phase, which reduces the perceived aerosol temperature. Therefore, the PLA plug is designed to manipulate the composition of the aerosol. In the manufacturing, facilities, and controls change logs submitted as part of your 2023 annual report (PS0000284) you listed the introduction of an alternate supplier of the PLA film used to manufacture these plugs in all *HeatStick* products. You stated that the chemical composition of the material is not impacted by this change. However, you do not provide any information regarding the physical characteristics of the original and replacement PLA film material. The performance of a filter will be affected both by the chemical composition and the physical properties of the material used to make the filter. Because one of the primary functions of the PLA plug is removing water from the aerosol, changes in filter performance

could change the aerosol yields of highly water-soluble harmful and potentially harmful constituents (HPHCs). Several of the *HeatStick* aerosol HPHCs that are the least reduced compared to HPHCs from conventional cigarette smoke are highly water soluble, including acetamide, acrylamide, ammonia, and pyridine. Without further information, FDA cannot determine if use of an alternate PLA film might cause emissions of some HPHCs in *HeatStick* aerosols to either exceed or become comparable to smoke yields in conventional cigarettes. Provide physical specifications, including thickness, weight per unit area, and permeability, for the original (MR0000059.PD1-MR0000061.PD1) and replacement (PS0000284) PLA film materials demonstrating that the two materials are physically equivalent. One way to provide this information would be through appropriate manufacturers' materials specification sheets for the original and replacement PLA films. Alternatively, provide data comparing aerosol yields of acetamide, acrylamide, ammonia, and pyridine from *HeatSticks* manufactured with the replacement PLA film material to smoke yields of the same HPHCs from conventional cigarettes.

PMIGSI RESPONSE

The only difference between the original and replacement PLA film is the supplier. The technical specification sheet for the original PLA film used ((b) (4)) is in the attached Q2a1_Tech_Sht_CMA014 and the technical specification sheet for the replacement PLA film used ((b) (4)) is in the attached Q2a2_Tech_Sht_CMA012 As shown in the technical specification sheets, the physical characteristics (e.g., thickness, grammage) are the same for both materials. (b) (4) (b) (4) (4) (b) (4) (b) (4) /(b) (4) (b) (4) . The PLA plug, which is manufactured from the PLA film, is designed to condense the water from the vapor phase. (b) (4) . However, all physical specifications listed on our technical specification sheets are identical for the original and new PLA films, and there is no change in composition. Since the composition and physical parameters that may impact permeability are the same for both materials, it is reasonable to expect the permeability of the new and original PLA films is the same.

FDA Question 3

3. You provided summaries of relevant published studies that raise concerns regarding toxicological effects of *IQOS* aerosols compared to cigarette smoke. Two of these studies found that mice exposed to cigarette smoke or *IQOS* aerosols developed comparable changes associated with emphysema (Gu et al., 2023; Nitta et al., 2022). A third study found that exposure to *IQOS* aerosols or cigarette smoke in rats led to similar cardiovascular toxic effects (Qiu et al., 2023). A fourth study found that mice prenatally exposed to *IQOS* aerosols had seminiferous tubule damage and reductions in daily sperm production at 5 weeks of age that were not observed in mice prenatally exposed to cigarette smoke (Yoshida et al., 2020). Your renewal MTRPA (MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7) did not adequately address the findings of Gu et al. (2023), Nitta et al. (2022), or Qui et al. (2023); you stated that the differences observed in Yoshida et al. (2020) may have been caused by differences in nicotine uptake.

   Previously submitted annual reviews note that methodological differences may account for differences between the studies submitted in MR0000059.PD1-MR0000061.PD1 and the subsequently published literature. However, these methodological differences are not specified in your renewal application or annual reviews, and you did not indicate whether or how these methodological differences impact study reliability. Although you previously submitted rodent studies evaluating effects of exposure to aerosols from MR0000059.PD1-MR0000061.PD1, the

previously submitted studies do not adequately address the toxicological concerns identified in Gu et al. (2023), Nitta et al. (2022), Qui et al. (2023), and Yoshida et al. (2020). It is unclear whether ApoE deficient mice and wildtype mice that express ApoE respond similarly to MR0000059.PD1-MR0000061.PD1 aerosols. Mice that express wildtype ApoE are the standard model for evaluating respiratory toxicity and it is unclear why your study used the ApoE deficient genotype because the homologous mutation is rare in humans and therefore this mouse strain may be less likely to predict human responses, including responses to aerosols generated from MR0000059.PD1-MR0000061.PD1. Further, the use of A/J mice may impair the detection of respiratory toxicity, because A/J mice spontaneously develop lung tumors, and these tumors may interfere with the detection of emphysema in these mice.

Moreover, your original MTRPA (MR0000059.PD1-MR0000061.PD1) included a Non-Targeted Differential Screening that identified 80 compounds in *IQOS* aerosols that were present at higher levels relative to the 3R4F reference cigarette. Notably, many of the compounds found at higher levels in MR0000059.PD1-MR0000061.PD1 aerosols compared to 3R4F smoke have potential respiratory, cardiovascular, or reproductive/developmental toxic effects. For example, compared to 3R4F smoke, MR0000059.PD1-MR0000061.PD1 aerosols contain higher levels of certain chemicals that can cause respiratory toxicity, including propylene glycol, furfural, glycidol, 3-chloro-1,2-propanediol, and butylated hydroxytoluene. Additionally, compared to cigarette smoke, MR0000059.PD1-MR0000061.PD1 aerosols contain higher levels of certain chemicals that can cause cardiovascular toxicity, including glycidol and 3-chloro-1,2- propanediol. Furthermore, compared to 3R4F smoke, MR0000059.PD1-MR0000061.PD1 aerosols contain higher levels of certain chemicals that can cause toxicity to male reproductive organs, including 2-tetrahydro-furanmethanol, glycidol, and 3-chloro-1,2-propanediol. Glycidol and 3-chloro-1,2-propanediol may have additive or synergistic effects (Liu et al., 2021).

However, except for furfural in MR0000060.PD1 and MR0000061.PD1, the Non-Targeted Differential Screening data that you previously submitted in MR0000059.PD1-MR0000061.PD1 did not provide reliable absolute quantities per HeatStick for the chemicals found to be higher in MR0000059.PD1-MR0000061.PD1 aerosols than 3R4F smoke.

Overall, the findings in Nitta et al. (2022), Gu et al. (2023), Yoshida et al. (2020), and Qiu et al. (2023) suggest that *IQOS* aerosols and cigarette smoke may have comparable effects related to respiratory, cardiovascular, and reproductive/developmental toxicity. These findings also raise the possibility that chemicals that were found at higher levels in MR0000059.PD1- MR0000061.PD1 aerosols than 3R4F smoke have toxicological effects in animal studies.

Provide a scientific justification for why the findings in Nitta et al. (2022), Gu et al. (2023), Yoshida et al. (2020), and Qiu et al. (2023) do not indicate that exposures to MR0000254.PD5 – MR0000254.PD7 aerosols have similar or higher toxicological risk than exposure to cigarette smoke for the development of emphysema, cardiovascular toxicity, and reproductive/developmental toxicity in male reproductive organs. In your response, take into consideration the potential toxicities of the chemicals that were found at higher levels in MR0000059.PD1-MR0000061.PD1 aerosols than 3R4F smoke, the limitations in your previously submitted rodent studies, and potential additive or synergistic effects of exposure to toxicants such as glycidol and 3-chloro-1,2-propanediol.

PMIGSI RESPONSE

In response to your concerns about using ApoE deficient and A/J mice in our studies, we remind you that the reports from these studies were provided in the original MRTPA and CTP has already reviewed and evaluated this information.[12,13,14] Therefore, it is unclear why FDA is now questioning their validity. Nevertheless, in order to be responsive, we are providing information to address your questions about the studies.

To add to the body of evidence already submitted in those documents and reviewed by you, we note there is no certainty that the wild-type C57BL/6J mice accurately mimic human responses and there is considerable published evidence that the ApoE -/- mouse model is appropriate for evaluating the toxicity of the authorized products. While the homologous ApoE mutation may be rare in humans, the ApoE -/- mouse model accurately mimics the atherosclerotic changes that likely begin early in the emphysema process also in humans, making the model translatable to humans (Lo Sasso et al., 2016). The ApoE -/- mouse model quite accurately replicates the connection between peripheral systemic alterations in lipid metabolism and lung dysfunction. First, emphysema was linked to increased lung inflammation in atherosclerosis-prone ApoE -/- mice exposed to cigarette smoke, highlighting the comorbidities of COPD (Arunachalam et al., 2010; Florence et al., 2018). Second, ApoE -/- mice on an atherogenic diet mirrored the systemic comorbidities of COPD, exhibiting increased systemic inflammation that led to lung damage and the onset of emphysema, even without exposure to cigarette smoke (Goldklang et al., 2012; Naura et al. 2009). Finally, using a single animal model to study these comorbidities adheres to two of the 3R principles: *Reduction*, which aims to minimize the number of animals used in each experiment or study, and *Refinement*, which seeks to reduce the pain, suffering, distress, or lasting harm experienced by the animals (Flecknell, 2002).[15]

Furthermore, as stated in our Commentary on the A/J mouse study[14], the primary objective of the A/J mouse lung cancer study 15020[13] was to characterize lung tumor incidence and multiplicity, the extent of lung inflammation and emphysematous changes in animals exposed to THS aerosol compared to cigarette smoke. Considering the body of evidence in the literature and our own historical laboratory-based experience showing other mouse strains are less susceptible than A/J mice to develop lung tumors as a result of life-time cigarette smoke exposure, we selected the A/J strain. In addition, the A/J mouse is known for developing emphysema, which mimics many aspects of human smoking-related emphysema, including inflammation, changes in pulmonary function, and the activity of matrix metalloproteinases in the lungs, supported by structural and functional alterations typical of COPD (March et al., 2006; Rangasamy et al., 2009). A/J mice are not recognized as being any less susceptible than the C57BL/6J strain (Guerassimov *et al*, 2004) and reportedly develop cigarette smoke-induced emphysema in approximately half the time when compared with C57BL/6J mice.[16]

Given the results have already been presented to and analyzed by CTP, we will not repeat them here. However, to summarize our conclusions based on the large body of evidence that we provided in the

[12] See Technical Project Lead (TPL) Review: MR0000059-MR0000061, MR0000133 from July 7, 2020. (www.fda.gov/media/139796/download?attachment)

[13] The A/J mouse lung cancer study report (P15020 THS SR) and all individual parts listed were submitted as part of an August 30, 2018 amendment to the original MRTPA. Additional commentary provided in document from footnote #4.

[14] Response to the FDA's November 20, 2019 Request for Information for MR0000059-MR0000061 and MR0000133 submitted on December 20, 2019.

[15] Russell WMS, Burch RL, Hume CW (1959) *The principles of humane experimental technique*. Methuen London

[16] 000646 - AJ Strain Details, accessed December 6, 2024 (www.jax.org/strain/000646)

original application (15020_Study_ Results_Overview[13]), the reduction in THS aerosol HPHC emission leads to all of the following:

1. A significant reduction in exposure to toxicants
2. A significant reduction in lung inflammation
3. A significant reduction in emphysematous change
4. A significant reduction in lung function loss
5. A significant reduction in lung tumor formation

None of the submitted studies would be suitable to discern the biological effects of individual constituents in the authorized MRTPs' aerosols or their specific additive or synergistic effects with one another. The aim of these studies was not to evaluate the toxicity of individual aerosol constituents but, rather, to evaluate the toxicity of the overall emissions generated from the authorized MRTPs. Therefore, the authorized MRTPs' aerosols were delivered in full to the animals; they contained the aerosol constituents identified to be present at higher levels in THS aerosol than cigarette smoke along with the significantly reduced amounts of HPHCs and other aerosol constituents. We consider this the appropriate testing approach, as the totality of the aerosol would be what a consumer is exposed to.

In our original MRTPAs, we provided the NTDS analysis of the aerosol composition for the authorized MRTPs[11]. The analysis identified 80 compounds in *IQOS* (THS 2.2) aerosols present at higher levels compared to the 3R4F reference cigarette smoke. Among these, eight aerosol constituents[17] exhibited structural alerts for genotoxicity and/or carcinogenicity. Four chemicals[18] were deemed toxicologically relevant based on their profiles. Based on the evidence submitted in the original MRTPA, CTP concluded:

> *"Although some chemicals of potential concern (not on FDA's HPHC list) may be higher in IQOS users, the increase in these constituents does not impact the conclusion that the substantial reduction in HPHCs and findings from the toxicological evidence are reasonably likely to translate to lower risk of tobacco-related morbidity and mortality. The toxicological studies that indicated the potential for lower toxicity were based on the complete mixture of chemicals produced by the IQOS system, which would capture the impact of any increases in chemical concentrations relative to combusted cigarette smoke."*[12]

In addition, CTP stated:

> *"Despite higher levels of some chemicals that are of toxicological concern (e.g., carcinogens, mutagens, respiratory toxicants), Heatstick aerosols contain lower levels of established and potential carcinogens (↓ 82.2%) ...when compared to 3R4F RCS. These changes are reasonably expected to reduce overall exposure to certain harmful and potentially harmful chemicals in cigarette smokers that switch to completely to Heatsticks."*[19]

A recently published NTDS study indicated the majority of analytical features detected with GC×GC-MS and LC-MS methods are more abundant in cigarette smoke than in aerosol from an unflavored THS 2.2 consumable produced from the same tobacco, with 92.6% being unique or higher in cigarette smoke

[17] 1,2,3-Propanetriol, diacetate, 1,2,3-Propanetriol, 1-acetate, Butylated hydroxytoluene, 1,2-Diacetin, Pyranone, 5,7-Dimethoxycoumarin, 1,2-dioxo-Cyclohexane and 2-Cyclopentene-1,4-dione
[18] 2-furanmethanol, furfural, glycidol and 3-chloro-1,2-Propanediol (3-MCPD)
[19] Toxicology Review of MR0000059, MR0000060, MR0000061, MR0000133

(Lang et al., 2024) (see Figure 1). A similar finding was obtained in a study aimed at thoroughly characterizing the chemical composition of a THS 2.2 aerosol using non-targeted analytical methods, where only 46 out of the 529 constituents (8.7%) with a yield above 100 ng/item in THS 2.2 aerosol were more abundant than in 3R4F reference cigarette smoke (Bentley et al., 2020).

Table 2 Number of analytical features by direction of increase and statistical significance ($P \leq 0.05$)

	LC–MS features	GC–MS features	Total features	Fraction of total features [%]
Unique in CC	0	584	584	15.8
CC > THS (sign.)	2020	825	2845	76.8
Difference non-sign	15	129	144	3.9
THS > CC (sign.)	69	55	124	3.3
Unique in THS	0	7	7	0.2

Fig. 2 Distribution of yield ratios of all analytical features detected in both THS and CC (bar height indicates the number of features within a given logarithmic yield ratio interval)

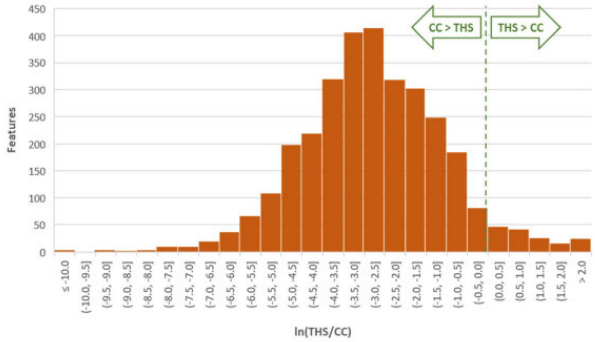

Figure 1. Illustration of Table 2 and Figure 2 extracted from Lang et al., 2024.

Considering all of this context, we analyzed the four studies cited in your request. To ensure independent research can be meaningfully compared with our observations, such studies must be conducted with a high degree of scientific rigor, equivalent to the standards expected from our company (and presumably from CTP). To meet these standards, study design and results must do the following:

- Study designs use fit-for-purpose and validated methods
- Scientifically appropriate conclusions drawn from study results

The studies by Gu et al. (2023), Nitta et al. (2022), Qiu et al. (2023), and Yoshida et al. (2020) all have significant limitations and do not meet the necessary standards for reliable conclusions. Hence, **they do not invalidate our findings of the reduced impact of THS aerosol on cardiovascular and respiratory parameters compared with cigarette smoke**. The major limitation of all four studies was uncontrolled animal exposure without monitoring the atmosphere in exposure chambers. More specifically, there was no verification of exposure uptake controlled by biomonitoring parameters (i.e., biomarkers of exposure were not measured or reported). This lack of control complicates the comparison of exposure effects between reference and test items. By contrast, in our studies, we characterized the test atmosphere in the breathing zone of the animals, and we analyzed exposure biomarkers. Therefore, we can be confident that changes seen are true changes in response to cigarette smoke or THS aerosol. See Q3a1_Study_comparisons for a tabular comparison of studies from this response.

While Gu et al. (2023) analyzed only inflammatory markers, malondialdehyde (MDA), and superoxide dismutase (SOD) activities in the lung lavage, we provided results from a more comprehensive

assessment in our rodent studies,[20,21] including the changes in total number of free lung cells, alveolar macrophages, dendritic cells, neutrophils, and lymphocytes. On the other hand, Nitta et al. (2022) analyzed inflammatory cells, but not inflammatory mediators in the lung lavage. In our studies, all analyzed parameters were significantly reduced in THS compared with CS exposed mice. The assessment of emphysema severity and progression also deviated between Gu et al., 2023 and our studies.[20,21] In addition to histopathological evaluation, we assessed emphysematous changes quantitatively by stereological analysis, which is the gold standard in lung morphometry (Hsia, et al., 2010; Ochs & Mühlfeld, 2013), whereas the studies by Gu et al. (2023) and Nitta et al. (2022) were less comprehensive and limited to mean linear intercept (MLI) and MLI and DI, respectively. Moreover, we have analyzed the inflammatory cell infiltration into the alveolar lumen of the exposed animals demonstrating reduced inflammation in the lungs of THS compared with CS exposed mice.

The major shortcoming of Qiu et al. (2023) is the lack of detail provided on how smoke and aerosol were generated from cigarettes and *IQOS* sticks, respectively. The study focused on proarrhythmic endpoints, and the analysis of the heart tissue was limited to staining of collagen fibers and microvessel density, whereas our study[21] was a 90-day inhalation toxicology study, compliant with OECD Test Guideline 413, in which potential local and systemic toxicity of THS aerosol were evaluated and compared to those of reference cigarette smoke. Heart histopathology did not highlight any adverse effects of exposure to either *IQOS* aerosol or cigarette smoke, despite the longer exposure duration. Another study demonstrated that while CS exposure resulted in significantly decreased ejection fraction and fractional shortening in the left ventricle of the mouse heart, exposure to THS aerosol at nicotine-matched concentrations didn't change these parameters compared with air exposed animals.[22]

In reference to the Yoshida et al. (2020) study, we have not conducted similar studies, as the product is not recommended for use during pregnancy. Additionally, there are no OECD-compliant studies that corroborate their findings.

Overall, our review of the cited studies suggests the study results are not directly comparable given the lack of specific information and methodological shortcomings of the cited studies, and differences in exposures and endpoints assessed between the cited studies and our studies. Despite this, our comprehensive assessment of the authorized MRTPs' aerosol toxicity, both i*n vitro* and *in vivo*, and the totality of evidence provided in our submissions supports the conclusion made previously by CTP (i.e., THS aerosol is less toxic than cigarette smoke and has a smaller impact on cardiovascular, respiratory and cancer endpoints in these rodent laboratory models).

FDA Question 4

4. In MR0000059.PD1-MR0000061.PD1, you indicated that gamma-butyrolactone (CAS 96-48-0) is found at higher levels in IQOS aerosols than 3R4F smoke, and 3-hydroxy tyrosine (CAS 587-45-1) is found at higher levels in MR0000061.PD1 aerosols than 3R4F smoke. Gamma-butyrolactone is a

[20] Phillips, et al., (2016). A six-month systems toxicology inhalation/cessation study in ApoE−/− mice to investigate cardiovascular and respiratory exposure effects of modified risk tobacco products, CHTP 1.2 and THS 2.2, compared with conventional cigarettes. *Food and Chemical Toxicology*, *126*, 113-141. https://doi.org/10.1016/j.fct.2019.02.008

[21] Wong, et al., (2020). Reduced Chronic Toxicity and Carcinogenicity in A/J Mice in Response to Life-Time Exposure to Aerosol from a Heated Tobacco Product Compared with Cigarette Smoke. *Toxicological sciences*, *178*(1), 44–70. https://doi.org/10.1093/toxsci/kfaa131

[22] Szostak, et al., (2020). Structural, functional, and molecular impact on the cardiovascular system in ApoE−/− mice exposed to aerosol from candidate modified risk tobacco products, Carbon Heated Tobacco Product 1.2 and Tobacco Heating System 2.2, compared with cigarette smoke. *Chemico-Biological Interactions*, *315*, 108887. https://doi.org/10.1016/j.cbi.2019.108887

psychoactive drug. The CAS number you provided for 3-hydroxy tyrosine is for a racemic mixture. One enantiomer of 3-hydroxy tyrosine is levodopa, a drug used for the treatment of Parkinson's disease. Provide a justification and scientific evidence to demonstrate that the higher levels of gamma-butyrolactone and 3-hydroxy tyrosine in the aerosols of your products (MR0000254.PD5 – MR0000254.PD7) compared to 3R4F smoke do not pose an increased risk to human health, including but not limited to, an increased risk of adverse psychoactive and dopaminergic effects, in consumers who use your products. The Non-Targeted Differential Screening data that you previously submitted (MR0000059.PD1-MR0000061.PD1) did not provide reliable absolute quantities per HeatStick for gamma-butyrolactone or 3-hydroxy tyrosine. Therefore, in your response, take into consideration the lack of reliable absolute quantitative data for the levels of gamma-butyrolactone or 3-hydroxy tyrosine in MR0000254.PD5 – MR0000254.PD7 aerosols.

PMIGSI RESPONSE

The following table provides a more detailed overview regarding the concentrations of gamma-butyrolactone and 3-hydroxy-tyrosine in our products:

Table 2. HeatStick Yields compared to 3R4F Cigarette Smoke (expressed as µg/stick)

	MR0000059/ MR0000254.PD5	MR0000060/ MR0000254.PD6	MR0000061/ MR0000254.PD7	3R4F
Gamma-butyrolactone (CAS 96-48-0)	4.08	2.94	3.55	0.728 0.861(1)
3-hydroxy tyrosine (CAS 587-45-1)	<3R4F	<3R4F	2.82	2.42

The values in the above table are a more detailed version of those already reported in the TOXICOLOGICAL ASSESSMENT REPORT - NON-TARGETED DIFFERENTIAL SCREENING ANALYSIS OF THS 2.2 (dated November 2017).

(1) Measured twice: once side-by-side with MR0000059 and MR0000060 analysis and second with MR0000061 analysis.

Gamma-butyrolactone (GBL, CAS 96-48-0) is a naturally occurring precursor of gamma-hydroxybutyrate (GHB), also known as sodium oxybate, an FDA-approved medication for treating narcolepsy (Goodwin, et al., 2006).[23] GBL is used recreationally (illicitly) in the United States as a central nervous system depressant (Holt, et al., 2021; Makoter and Krajnc, 2023). The levels of GBL in the emissions of MR0000059–MR0000061 (or MR0000254.PD5–PD7) are around 81.6, 58.8, and 71 µg per day, respectively, assuming consumption of 20 sticks per day (a heavy use assumption based on a recent FDA memo[24]). These concentrations are extremely low compared to the dose inducing euphoria (0.32 grams per dose (Oliveto, et al., 2010). Therefore, although GBL levels are higher in THS aerosols compared to cigarette smoke, they are still far too low to induce euphoria, sedation, or dissociative effects, as well as adverse psychoactive and dopaminergic effects.

As you noted, very little information is available for 3-hydroxy tyrosine (CAS 587-45-1), and levodopa (L-DOPA) is one enantiomer of 3-hydroxy tyrosine. Levodopa is the common name used in medical contexts, specifically in the treatment of Parkinson's disease (Chan, et al., 2012). The commonly used dose for the maintenance of Parkinson's disease starts from 300 milligrams per day[25]; the common dose to evaluate dopamine release following levodopa is around 250 milligrams per dose (De La Fuente-

[23] United States Drug Enforcement Administration (DEA). GHB - Gamma-Hydroxybutyric Acid [Online]. Available: https://www.dea.gov/factsheets/ghb-gamma-hydroxybutyric-acid [Accessed December 6, 2024].

[24] U.S. Food and Drug Administration (FDA) Memorandum: Calculating the Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications. (2024) https://www.fda.gov/media/180610/download?attachment [Accessed December 6, 2024]

[25] Gandhi KR, Saadabadi A. Levodopa (L-Dopa) [Updated 2023 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482140/

Fernández, et al., 2004). The level of 3-hydroxy tyrosine in the emissions of MR0000061 is around 56.4 µg per day, assuming a consumption of 20 sticks per day (a heavy use assumption[24]).[26] This level (56.4 µg per day) is far lower than the dose inducing dopamine release (250 mg per dose). Therefore, although 3-hydroxy tyrosine levels are higher in MR0000061 aerosol compared to cigarette smoke, it is still too low to induce psychosis (dopaminergic release).

Considering the NTDS method is not fully quantitative and can be more than 4-fold different from true value (plus or minus) when compared to quantitative data (Knorr, et al., 2019), the levels of GBL and 3-hydroxy tyrosine in the emissions of THS aerosols were at maximum 0.1% or less of the doses resulting in psychoactive effects. Therefore, the levels of GBL and 3-hydroxytyrosine in our HeatSticks do not raise public health concerns.

FDA Question 5

5. In MR0000254.PD5 – MR0000254.PD7, you submitted a computational toxicology study evaluating the potential genotoxicity and carcinogenicity of 80 compounds that were found at higher levels in MR0000059.PD1-MR0000061.PD1 aerosols than 3R4F cigarette smoke and some of the potential metabolites of these compounds. Compared to information that you previously submitted (MR0000059.PD1-MR0000061.PD1), this post-market computational toxicology study identified additional compounds as being potentially genotoxic or carcinogenic. Some of the parent compounds that were not predicted to be genotoxic or carcinogenic have metabolites with potential genotoxic or carcinogenic effects and may act as pro-carcinogens. Additionally, recently published studies have identified *in vivo* or *in vitro* genotoxic effects of *IQOS* aerosols (Vivarelli et al., 2021; Vivarelli et al., 2024; Zarcone et al., 2023). This information available after the issuance of the MRGO raises concerns regarding the carcinogenic potential of MR0000254.PD5 – MR0000254.PD7 aerosols compared to cigarette smoke.

   Although you previously submitted genotoxicity (i.e., an Ames assay, a micronucleus assay, and a mouse lymphoma assay) and carcinogenicity studies in MR0000059.PD1-MR0000061.PD1, these previous studies do not adequately address the concerns raised by information available after the issuance of the MRGO, including your post-market computational toxicology study and recently published studies that identified in vivo or in vitro genotoxic effects of *IQOS* aerosols.

   Specifically:

   - Genotoxicity for MR0000059.PD1 and MR0000061.PD1 aerosol fractions occurred at higher concentrations than with cigarette smoke fractions in the mouse lymphoma assay you submitted; however, there is no currently validated method to determine carcinogen potency from in vitro genotoxicity assay results.
   - Methodological concerns limited conclusions that could be drawn from the micronucleus assay that you submitted.
   - Although the Ames assay data you submitted found that total particulate matter and gas/vapor phase fractions from *IQOS* aerosols did not demonstrate mutagenic potential under the tested conditions, MR0000059.PD1-MR0000061.PD1 aerosols contain compounds with mutagenic activity.

[26] Concentrations of 3-hydroxy tyrosine concentrations were not reported in MR0000059 or MR0000060 because levels were below the level detected in 3R4F cigarette smoke.

- You also previously submitted results from a carcinogenicity study in A/J mice. However, this study was uninterpretable because A/J mice develop spontaneous tumors, limiting the ability to detect exposure-related effects.

Provide scientific evidence to demonstrate that the carcinogenic risk of MR0000254.PD5 – MR0000254.PD7 aerosols is lower than the carcinogenic risk of 3R4F smoke. With the exception of furfural in MR0000060.PD1 and MR0000061.PD1, the Non-Targeted Differential Screening data that you previously submitted in MR0000059.PD1-MR0000061.PD1 did not provide reliable absolute quantities per HeatStick for the chemicals found to be higher in MR0000059.PD1- MR0000061.PD1 aerosols than 3R4F smoke. Therefore, in your response, take into consideration the potential genotoxicity/carcinogenicity of the compounds that were found to be higher in MR0000059.PD1-MR0000061.PD1 aerosols and their metabolites (Appendix C, Table 4), the lack of reliable absolute quantitative data for the levels of these chemicals in MR0000059.PD1-MR0000061.PD1 aerosols, the limitations in your previously submitted studies, and the lack of a validated method to determine toxicant potency from in vitro genotoxicity assays.

PMIGSI RESPONSE

As part of the PMSS, CTP requested a report including hazard identification (genotoxicity and carcinogenicity potential) for the 80 identified compounds from the NTDS study that were new or increased in the aerosol of *IQOS* (THS 2.2) (all *HeatSticks* products combined) compared to the smoke of 3R4F reference cigarette. Even though not all 80 reported constituents revealed a potential genotoxic/carcinogenic concern, the PMSS – THS 2.2 Computational Toxicology Study conducted a hazard identification prediction on all constituents, in accordance with CTP's request, regardless of availability of toxicological data. Results of the PMSS – THS 2.2 Computational Toxicology Study have been shared with CTP[27] and additional analysis of our NTDS study is in the response to Request #3 above. In summary:

- Our NTDS analysis reported 80 constituents as increased or new in *IQOS* (THS 2.2) aerosols compared to the smoke of 3R4F reference cigarette.
- CTP reported 58 constituents in Table 4 in Appendix C of the A/I Request as an outcome of the PMSS – THS 2.2 Computational Toxicology Study and additional CTP concerns.
- From the list of 58 aerosol constituents, the conducted literature review found available scientific expert groups[28] conclusions on the genotoxic and/or carcinogenic potential of these compounds.
- After hazard identification refinement, 18 constituents have been further ruled out based on expert groups conclusions (see Q5a1_Constituents_Listing).
- In total, 40 constituents have been predicted to have genotoxic and/or carcinogenic potential.
- The 40 remaining constituents translates to an average total yield of 137.5 µg/stick for *IQOS* aerosols (combining the 3 *HeatSticks* products together, see Q5a2_ELCR_Methodology) compared to 57.8 µg/cigarette for 3R4F reference cigarette smoke. Considering the total difference of 79.7 µg/*HeatStick*s for an average total particulate matter of 54.14 mg/*HeatStick*s,

[27] See the final report in the referenced (b) (4) /MRTP Renewal/Computational Toxicology/Computational Toxicology/Computational Toxicology Report.pdf

[28] Expert groups such as the United States Environmental Protection Agency (US EPA), the European Food Safety Authority (EFSA), the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA), or the International Agency for Research on Cancer (IARC).

the average portion of reported increased or new constituents in *IQOS* (THS 2.2) aerosols compared to the smoke of 3R4F reference cigarette represents 0.15% of the total *IQOS* aerosol.

Newly Published Literature

The literature cited in this request has been reviewed according to the guidelines listed in the response to Request #3. Compared to our submitted studies, the selected papers from Vivarelli et al., (2021, 2024) exhibit major methodological deficiencies and errors, including the following:

- Non-standardized *IQOS* aerosol generation protocol
- Exaggerated aerosol exposure level
- Uncharacterized samples for genotoxicity testing
- No cigarette group comparator

The authors did not put the animal exposure levels into perspective with real human consumption, affecting the relevance of their exposure levels. The authors also did not include a cigarette smoke-exposed group as a comparator. Therefore, it is difficult to judge the reliability and relevance of Vivarelli et al., (2021, 2024) study results. Additionally, because the main objective of our studies is to conduct comparative evaluations between products, a direct comparison with our study findings cannot be made.

In our original MRTPAs, the *IQOS* aerosol was concluded to have genotoxic potential, as suggested in the Mouse Lymphoma Assay and Micronucleus assay studies, but with a substantially reduced activity compared to 3R4F reference cigarette smoke. Additionally, our study findings align with those of Zarcone et *al.*, (2023), who ranked electronic cigarettes, Heated Tobacco Products (HTPs) (i.e., *IQOS*), and conventional cigarettes. The authors concluded HTPs elicit a biological response similar to those of cigarette smoke, but only after more intensive (i.e., 10-fold) exposure. The conclusion from Zarcone et *al.*, (2023) provides evidence *IQOS* aerosol has a reduced genotoxic potential compared with cigarette smoke.

The interpretability of the results from the carcinogenicity study in A/J mice is addressed in our response to Request #3 above.

We acknowledge every genotoxicity assay has its own limitations. For example, differences between bacterial and mammalian DNA repair mechanisms may affect the conclusions drawn from any given *in vitro* test (e.g., Ames test), and these should not be evaluated in isolation. The strength of our *in vitro* program lies in the convergence of data from multiple, independent *in vitro* studies conducted in accordance with OECD guidelines (Ames test, Mouse Lymphoma assay (MLA), and the *in vitro* micronucleus test), which collectively suggest the *IQOS* aerosol has a lower genotoxic activity than the 3R4F cigarette smoke. This finding aligns with the reduction of the HPHCs in *IQOS* aerosol compared to 3R4F smoke. We emphasize the *in vitro* genotoxicity test battery was not intended to define acceptable human exposure levels or to predict cancer potency or risk. Rather, it was designed to investigate the genotoxic potential of tobacco products and compare and rank the mutagenic/genotoxic activities of 3R4F smoke and *IQOS* aerosols *in vitro*.

Excess Lifetime Cancer Risk (ELCR)

Only long-term epidemiological studies can definitively demonstrate the relative cancer risk of *IQOS* aerosol compared with cigarette smoke, but such data will not be available for several decades. However, because you have applied the approach to other inhaled smokefree product risk assessments,

we estimated the excess lifetime cancer risk cumulated (ELCRc) according to the approach outlined in the recently published FDA memorandum on Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Application (2024)[24]. See Q5a2_ELCR_Methodology for methodological summary. While these values should not be considered final until epidemiological data has been collected, this assessment should only serve as a comparative tool to differentiate the cancer risks potential associated with different tobacco products.

We calculated ELCRc for *IQOS* aerosol and 3R4F reference cigarette smoke and then extrapolated to the ELCRc for 1R6F reference cigarette smoke because that is the reference cigarette that you cite in your memorandum. The calculated ELCRc from the *IQOS* aerosol is determined to be 2,683 excess cancer cases per 100,000 users. The calculated ELCRc from the 3R4F reference cigarette smoke is determined to be 12,243 excess cancer cases per 100,000 smokers. The calculated ELCRc for 3R4F reference cigarette smoke aligns with the estimated ELCRc probability from 1R6F reference cigarette smoke cited in your memorandum, which is 1 in 10, and allows us to validate our calculations. Thus, using the methods laid out in your memorandum, **there is an estimated 78% reduction in cancer risk for *IQOS* aerosol compared to 3R4F reference cigarette smoke**.

While these measurements demonstrate an almost 80% reduction in relative cancer risk from *IQOS* aerosol compared to the 3R4F reference cigarette smoke, we believe the calculated ELCRc is overestimated and, therefore, the reduction in relative cancer risk is underestimated. Our ELCRc calculation for *IQOS* included genotoxic/carcinogenic constituents measured in the targeted aerosol chemistry characterization studies (i.e., PMI-58 list) and potential genotoxic/carcinogenic constituents reported as increased or new in *IQOS* aerosol compared to 3R4F reference cigarette smoke as an outcome of the NTDS studies and subsequent PMSS - THS 2.2 Computational Toxicology Study. However, neither the NTDS nor the PMSS - THS 2.2 Computational Toxicology Study was designed to precisely quantify the levels of potentially genotoxic or carcinogenic compounds identified to calculate the ELCR. The NTDS studies focused only on identifying aerosol constituents with significantly increased per-item yields in *IQOS* aerosols but did not provide information about the number, identities, or concentrations of other compounds present in *IQOS* aerosol or 3R4F reference cigarette smoke. Therefore, basing the ELCRc calculations for *IQOS* aerosol primarily on the NTDS results ignores the toxicological effects of the larger fraction of constituents present at higher levels in cigarette smoke compared to *IQOS* aerosols, resulting in ELCRc calculations that are heavily biased.

Additionally, the methodology laid out in your memorandum has several limitations and assumptions. Accordingly, calculated ELCRc values may be influenced by several parameters:

- Different cancer risk predictions can be calculated based on the identification and selection of reference values Inhalation Unit Risk (IUR) values vs. Threshold of Toxicological Concern (TTC) values) making it difficult to assess what the “true” product-specific value is.
- Constituent specific IUR values are derived to assess the impact of chronic environmental exposure to carcinogens. Therefore, using the TTC as a default value introduces additional uncertainties into the ELCRc calculation.
- Without further guidance, constituent yields determined below the level of quantification (<LOQ) or detection (<LOD) are considered as a worst case scenario to be at defined LOQ or LOD. These values may differ among different laboratories, and it is unclear if these need to be included.
- The choice of chemical aerosol constituents eligible for ELCRc calculation may differ between assessors.

Specific to our calculations, the levels of the 40 constituents reported in the NTDS study predicted to have genotoxic/carcinogenic potential based on the PMSS - THS 2.2 Computational Toxicology Study are based on semi-quantitative yields, which introduce uncertainties in the final ELCRc value. However, this limitation is somewhat mitigated because the same variability applies to constituents detected in 3R4F reference cigarette smoke.[29]

Overall, the PMSS - THS 2.2 Computational Toxicology Study identified additional compounds in *IQOS* aerosol as potentially genotoxic and/or carcinogenic beyond those included in our original MRTPA. CTP raised concerns regarding the carcinogenic potential of *IQOS* aerosol relative to cigarette smoke. However, the ELCRc calculations for *IQOS* aerosol and 3R4F reference cigarette smoke, and the subsequent comparison of the relative cancer risk, demonstrate the carcinogenic risk profile of *IQOS* aerosol is lower than that of cigarette smoke, especially because it is overly cautious in its estimated relative risk compared to cigarette smoke.

FDA Question 6

6. In 7-a06-comp-tox-tables.pdf in MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7, you indicated that a compound previously identified in MR0000060-MR0000061 aerosols as 12,14-Labdadiene-7,8-diol, (7beta,8alpha,12Z) was changed to alpha-cembratriene-diol in MR0000254.PD6 and MR0000254.PD7. Provide a scientific rationale for why this change was made. This information is needed to evaluate whether compounds in MR0000254.PD6 and MR0000254.PD7 aerosols have been correctly identified to evaluate potential toxicological effects associated with chemicals in MR0000254.PD6 and MR0000254.PD7 aerosols.

PMIGSI RESPONSE

The correction from 12,14-Labdadiene-7,8-diol to alpha-cembratriene-diol was documented and explained in Table 25 on page 52 and in the narrative on page 51 of the P1-Characterization Report.[30] As stated in that document, the correction was made after improvements were made to both the aerosol trapping approach and the compound identification process. This particular compound correction occurred after alpha-cembratriene-diol was confirmed by analysis of thermally treated duvatriene standard.

FDA Question 7

7. In 7-a06-comp-tox-tables.pdf in MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7, you provided chemical names and CAS numbers for compounds previously identified in MR0000059.PD1-MR0000061.PD1 aerosols. Some of the CAS numbers that you provided are inconsistent with the chemical names that you provided in both MR0000059.PD1- MR0000061.PD1 and MR0000254.PD5 – MR0000254.PD7, as indicated in Appendix C, Table 5. For the chemicals in Table 5, indicate which chemical names and CAS numbers correctly identify the compounds that you previously detected in MR0000059.PD1-MR0000061.PD1 aerosols. This information is needed to

[29] To obtain a more representative yield value, when a constituent was detected as increased or new in more than one *HeatSticks* variant, the mean value was used for the ELCRc calculation. The same approach was applied to constituents in 3R4F reference cigarette smoke.

[30] The P1-Characterization_Report.pdf is an attachment associated with the April 26, 2018 communication with FDA regarding the P1 Characterization Study for MR0000059-MR0000061.

accurately identify chemicals in MR0000254.PD5 – MR0000254.PD7 aerosols to evaluate potential toxicological effects associated with these chemicals.

PMIGSI RESPONSE

For all chemicals identified in Table 5 of the November 22, 2024, Advice/Information Request, the originally provided CAS numbers are correct, and the compound names provided are either a result of an error or an oversimplification of the compound name based on identified information. A modified version of Table 5 from the Advice/Information Request is provided below **(Table 3)**. The fourth column in the table below has been added to provide our detailed clarification for each compound identification.

Table 3. Corrected version of Table 5 from the November 22, 2024, Advice/Information Request

Chemical name originally provided	CAS number originally provided	FDA Comments	PMI Response
Beta-bourbonene	119903-95-6	The CAS number for beta-bourbonene is 5208-59-3.	The originally provided CAS number corresponds to the "flat" (i.e., no stereo-information) structure for this compound. We report structures without stereo-information when it is not possible to determine the stereochemistry of a compound, due to lack of available reference standards for all stereoisomers. However, beta-bourbonene is the name of the most common stereoisomer, so this name was provided for simplicity. As we cannot provide exact stereochemistry in this case, CAS # 119903-95-6 is the most correct identification.
Trans-4-Hydroxymethyl-2-methyl-1,3dioxolane	3674-21-3	The CAS number you provided is for the cis isomer of this chemical.	The CAS number is correct, but the name of the compound was erroneously listed as the *trans* isomer. The correct identification of the compound is the *cis* isomer, cis-4-hydroxymethyl-2-methyl-1,3-dioxolane.
Pyranone	28564-83-2	The CAS number you provided is for 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-Pyran-4-one.	Pyranone was listed as a synonym in several databases, including CAS SciFinder, for 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-Pyran-4-one and was erroneously included in the NTDS results, rather than the IUPAC name. The CAS number is correct, and the compound should be identified as 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-Pyran-4-one.

FDA Question 8

8. Your 2024 Annual Report (PS0000333) was submitted after FDA received the renewal MRTPA (MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7). Consequently, this Annual Report, PS0000333, is not currently referenced or available to review for FDA's assessment of MR0000254. The 2024 Annual Report includes the most recent Safety Update Report with adverse event reports, and ongoing and completed studies information, among other sources of information needed for review. FDA needs the 2024 Annual Report for review in MR0000254.PD1, MR0000254.PD3, MR0000254.PD5-PD7 so that FDA is using the most up-to- date information to determine whether the products are expected to benefit the health of the population as a whole. We request that MR0000254.PD1, MR0000254.PD3, MR0000254.PD5- PD7 reference PS0000333.

PMIGSI RESPONSE

In addition to all other documents referenced in our claim renewal MRTPA for MR0000254.PD1, MR0000254.PD3, and MR0000254.PD5–PD7, we cross-reference the 2024 Annual Report (PS0000333), submitted on April 29, 2024, as part of our submission package.

FDA Question 9

9. The MRTPA (MR0000254.PD1, MR0000254.PD3, MR0000254.PD5 – MR0000254.PD7) references a Tobacco Product Master File (TPMF) (b) (4) However, upon review, FDA has identified issues in the TPMF for which additional information or clarification will be needed by FDA to perform a complete review. These issues are being conveyed separately to the TPMF owner. If you have questions related to the TPMF, contact the TPMF owner. The TPMF owner's complete and timely response or lack thereof may impact FDA's review of these submissions.

PMIGSI RESPONSE

Responses to requests for additional information or clarification in (b) (4) are in the December 20, 2024, amendment to (b) (4) .

List of Cited Literature

Literature references cited in-text (i.e., not in footnotes) are available in the cross-referenced (b) (4) /literature/references folder.

For example: (Arunachalam, et al., 2010) can be found in (b) (4) /literature/references/ref-arunachalam-2010.pdf

All other references are provided in the footnotes.