FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead Review of MRTPA(s)

Modified Risk Tobacco Product(s) Subject of this Review[1]	
Submission tracking numbers (STNs)	MR0000254.PD1, MR0000254.PD3, MR0000254.PD5 – MR0000254.PD7, see Appendix A
Common Attributes	
Submit date	July 5, 2023
Receipt date	July 5, 2023
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Application type	Renewal
Order Under 911(g)	☐ Risk Modification 911(g)(1) order ☒ Exposure Modification 911(g)(2) order
Product category	Heated Tobacco Products (HTPs)
Product subcategory	HTP Consumable,[2] Open HTP[3]
Modified Risk Claim	AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.
Cross-Referenced Submission(s)	
All STNs	PM0000424 – PM0000426, PM0000479, PM0000634, MR0000059 – MR0000061, MR0000133, MR0000192, (b)(4) (b)(4) PS0000042, PS0000119, PS0000158, PS0000169, PS0000175, PS0000284, PS0000331, PS0000333
Supporting FDA Memoranda Relied Upon in this Review	
All STNS	Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications; signed June 3, 2024 Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications; signed June 3, 2024 Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum; signed July 8, 2025 IQOS heated tobacco products and clarification of the terms "smoke" and "smoking"; signed April 15, 2026
Recommendation	
Issue modified risk granted orders for the products subject of this review.	

[1] Product details, amendments, and dates provided in the Appendix.

[2] For MR0000254.PD5 - MR0000254.PD7, see Appendix A

[3] For MR0000254.PD1 and MR0000254.PD3, see Appendix A

Technical Project Lead (TPL):

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Signatory Decision: Concur with TPL recommendation and basis of recommendation

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Benjamin Apelberg, Ph.D.
Deputy Director
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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 5

2. BACKGROUND 9
2.1. MODIFIED RISK TOBACCO PRODUCTS 9
2.2. MODIFIED RISK CLAIM 10
2.3. REGULATORY ACTIVITY 10
2.4. SCOPE OF REVIEW 14
2.5. TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC) 15
2.6. PUBLIC AVAILABILITY OF MRTPAS 16

3. SCIENTIFIC REVIEW 16
3.1. PRODUCT CHARACTERIZATION 16
Key Findings from Original MRTPA TPL Review 17
Evaluation of New MRTPA Data 17
Product Design, Composition, and Manufacturing 17
Product Stability 18
Section Summary Statement 18
3.2. RELATIVE HEALTH RISKS TO INDIVIDUALS WHO USE TOBACCO 19
Key Findings from Original MRTPA TPL Review 19
Evaluation of New MRTPA Data 21
Toxicant Exposure, Including HPHCs 21
Clinical Assessment 25
Relative Health Risks Conclusion 29
Synthesis and Conclusion of Relative Health Risks 32
3.3. CONSUMER UNDERSTANDING AND PERCEPTIONS 33
Key Findings from Original MRTPA TPL Review 33
Evaluation of New MRTPA Data 33
Understanding Health Risk Relative to Nonuse, Cessation, and Cessation Therapies 35
Understanding How to Use the MRTP to Reduce Exposure 35
Synthesis and Conclusion of Consumer Understanding 35
3.4. TOBACCO USE BEHAVIOR AND IMPACTS TO THE POPULATION AS A WHOLE 36
Key Findings from Original MRTPA TPL Review 36
Evaluation of New MRTPA Data 37
Synthesis and Conclusion about Tobacco Use Behavior 41
3.5. MARKETING AND LABELS, LABELING, AND ADVERTISING (LLA) 42
Evaluation of New MRTPA Data 42

4. ENVIRONMENTAL IMPACT 42
4.1. DISCIPLINE FINDINGS 42
4.2. ENVIRONMENTAL CONCLUSION 43

5. MR0000292 AMENDMENT: CIGARETTE DEFINITION AND SURGEON GENERAL'S WARNINGS 43
5.1. SURGEON GENERAL'S WARNINGS 44

6. CONCLUSIONS AND RECOMMENDATIONS 45
6.1. STATUTORY REQUIREMENTS FOR AUTHORIZATION. 45
6.2. OVERALL CONCLUSIONS: SCIENTIFIC EVIDENCE 46
6.3. RECOMMENDATION FOR THE RENEWAL REQUEST 50
6.4. POSTMARKET SURVEILLANCE AND STUDIES (PMSS) 50

MRTP Consumer Understanding and Perception 50
MRTP Use Behavior 51
Surveillance of Research Study Findings on the MRTPs 51
Conclusion 52
6.5. ENVIRONMENTAL CONSIDERATIONS 52

7. REFERENCES **53**

8. APPENDICES **56**
A. MODIFIED RISK TOBACCO PRODUCT(S) 56
B. AMENDMENTS AND ADDITIONAL SUBMISSIONS 59

LIST OF TABLES

Table 1: List of PMSS studies and adjustments made due to the removal of IQOS from the U.S. market 12
Table 2: Disciplines included in review 14
Table 3: Consultations 14

1. EXECUTIVE SUMMARY

On November 18, 2016, Philip Morris Products (PMP) S.A. submitted modified risk tobacco product applications (MRTPAs) for the IQOS 2.4 System Holder and Charger (MR0000133) and three types of HeatSticks (Marlboro Amber HeatSticks [MR0000059], Marlboro Green Menthol HeatSticks [MR0000060], and Marlboro Blue Menthol HeatSticks [MR0000061]).[4] On March 18, 2021, PMP S.A. submitted an MRTPA for the IQOS 3 System Holder and Charger (MR0000192),[5] an update to the IQOS 2.4 System. PMP S.A. requested authorization under Section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to market the products specified in Appendix A with the following exposure modification claim:

AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

FDA issued modified risk granted orders (MRGOs) for the exposure modification pathway under section 911(g)(2) of the FD&C Act to PMP S.A. for the IQOS 2.4 System Holder and Charger (MR0000133) and three types of HeatSticks (MR0000059-MR0000061) on July 7, 2020. FDA also issued an MRGO for the IQOS 3 System Holder and Charger (MR0000192) on March 11, 2022.

FDA issued these MRGOs after examining the totality of evidence across scientific reviews and determining that the applicant had demonstrated that the products sold or distributed with the proposed modified exposure information met the standard under Section 911(g)(2) of the FD&C Act. Among other things, PMP S.A. demonstrated that the products significantly reduced exposure to harmful and potentially harmful constituents (HPHCs) for individual tobacco users and were expected to 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. The MRGOs specified an order expiration date of July 7, 2024.

On July 5, 2023, PMP S.A. submitted renewal MRTPAs for IQOS 2.4 System Holder and Charger (MR0000254.PD1), IQOS 3.0 System Holder and Charger (MR0000254.PD3), Marlboro Amber HeatSticks (MR0000254.PD5), Marlboro Green Menthol HeatSticks (MR0000254.PD6), and Marlboro Blue Menthol HeatSticks (MR0000254.PD7), requesting renewal authorization under Section 911(g)(2) of the FD&C Act to continue marketing the products specified in Appendix A with the exposure modification claim listed above.

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[4] PMP S.A. refers to the three HeatSticks products submitted in the November 18, 2016, MRTPAs (Marlboro HeatSticks, Marlboro Smooth Menthol HeatSticks, and Marlboro Fresh Menthol HeatSticks) under different names in subsequent submissions to FDA, including the current renewal MRTPAs. PMP S.A. refers to Marlboro HeatSticks as Marlboro Amber HeatSticks and HEETS Amber; to Marlboro Smooth Menthol HeatSticks as Marlboro Green Menthol HeatSticks and HEETS Green; and to Marlboro Fresh Menthol HeatSticks as Marlboro Blue Menthol HeatSticks and HEETS Blue. In the cover letter for the renewal MRTPAs, PMP S.A. referred to the products as Marlboro Amber HeatSticks, Marlboro Green Menthol HeatSticks, and Marlboro Blue Menthol HeatSticks, and we use those names within this review.

[5] IQOS 3.0 System Holder and Charger is also called IQOS 3 Originals.

Under Section 910 of the FD&C Act, the applicant previously requested authorization to market the IQOS 2.4 System Holder and Charger (PM0000479), IQOS 3.0 System Holder and Charger (PM0000634), Marlboro Amber HeatSticks, Marlboro Green Menthol HeatSticks, and Marlboro Blue Menthol HeatSticks (PM0000424-PM0000426) without modified risk claims. FDA authorized the marketing of the products without modified risk claims on April 30, 2019, and December 7, 2020 (for IQOS 3.0 System Holder and Charger). The technical project lead (TPL) review for the accompanying premarket tobacco product applications (PMTAs) provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites.

As TPL, I conducted a thorough scientific review of the information contained in the renewal MRTPAs and amendments received in Appendix B including cross-referenced content (PM0000424 – PM0000426, PM0000479, PM0000634, MR0000059 – MR0000061, MR0000133, MR0000192, (b)(4)) and the postmarket reports submitted under the orders (PS0000119, PS0000175, PS0000284, PS0000333, and their related amendments). I also considered the recommendations from the Tobacco Products Scientific Advisory Committee (TPSAC), relevant comments, data, and information submitted to FDA by interested persons, and scientific information identified by FDA from other sources.

After examining the totality of evidence across scientific reviews, I found that the applicant **has demonstrated** that the products sold or distributed with the modified exposure information continue to meet the standard under Section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely to be demonstrated in subsequent studies, and issuance of an order is expected to 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.

Therefore, as TPL, I recommend MRGOs be issued to PMP S.A. for IQOS 2.4 System Holder and Charger (MR0000254.PD1), IQOS 3.0 System Holder and Charger (MR0000254.PD3), Marlboro Amber HeatSticks (MR0000254.PD5), Marlboro Green Menthol HeatSticks (MR0000254.PD6), and Marlboro Blue Menthol HeatSticks (MR0000254.PD7) subject to the marketing restrictions and postmarket requirements listed in the order letter appendices. Additionally, I recommend a General Correspondence Letter be issued to seek additional evidence on PMP S.A.'s request to remove the Surgeon General's warnings.

The focus of this review of the renewal MRTPAs is on the assessment of the (1) scientific accuracy of the modified exposure claim, (2) relative health risks of the MRTPs to people who use tobacco, (3) consumer understanding and perception of the MRTPs marketed with the claim, and (4) potential impact to the population as a whole, including both users of tobacco products and persons who do not currently use tobacco products, from continuing to market the products with the modified exposure claim.

The modified exposure claim continues to be scientifically accurate:

AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful

chemicals.

In examining the claim's substantiation, as TPL, I relied on the previously submitted information and evaluated a new computational toxicology study and three new studies that assessed biomarkers of exposure (BOE) submitted by the applicant, as well as relevant scientific studies published since the MRGOs. Overall, this evidence suggests that, compared to combusted cigarette (CC) smoking, IQOS use poses lower exposure to harmful or potentially harmful chemicals. This is shown both in the toxicological assessment of the HPHCs in IQOS aerosol and in the reductions demonstrated in the BOE studies. As such, I found that the modified exposure claim continues to be substantiated.

As TPL, my final assessment of the individual health risks of IQOS reflects an evaluation of the health risks *relative* to CC smoking, as this is the comparison made in the claim, and adults who use CC are the applicant's stated intended users of IQOS. Heated tobacco products are a novel type of tobacco product, and as such, long-term health data with which we can evaluate these products remain limited. The applicant did not submit results from observational or clinical studies with follow-up periods that were sufficiently long to evaluate the effects of IQOS on longer term smoking- and tobacco-related health conditions (e.g., cardiovascular disease and cancer). Like in the evaluation of the original MRTPAs (MR0000059-MR0000061, MR0000133, MR0000192), in the absence of long-term health data, my determination about whether a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely is based on the available HPHC and biomarker evidence, along with evidence of the short-term health effects, including adverse events. In the original MRTPAs, while 80 chemicals were found to be higher in IQOS aerosols than in 3R4F reference cigarette smoke (RCS), the comprehensive testing of 108 HPHCs showed that 107 were either below the limit of detection or quantification or present at lower concentrations in IQOS aerosols compared to CC smoke. Overall, these 107 HPHCs were reduced by 47-99.9% in IQOS aerosols on a per stick basis compared to CC smoke and by 20-99.8% when normalized to nicotine levels, with only nicotine and anabasine as exceptions. Some literature published since the issuance of the MRGOs noted certain detrimental effects associated with exposure to IQOS, but these effects are generally less severe than those observed for the CC smoking comparison groups across published toxicological studies (see Section 3.2 below). Although new evidence raises some questions related to individual health risks, the data reviewed do not change the overall conclusions from the original MRTPAs.

As TPL, I find that the totality of evidence – including evidence newly available – suggests the overall level of exposure to HPHCs is lower than that of CC smoke and completely switching from CC to IQOS is reasonably likely to lead to a reduction in morbidity and mortality among individual tobacco users. However, because the health risks of IQOS are not fully known, we continue to monitor and evaluate new evidence about its health harms and risks.

In assessing consumer understanding and perceptions of IQOS, as TPL, I relied on the previously submitted information and evaluated data from one new study submitted by the applicant. Data suggest that the applicant continues to demonstrate that consumers perceive IQOS use to have moderate risk of tobacco-related health effects but to have lower risk than using CC, which is in line with the relative health risks of the product that are reasonably likely. The results also demonstrate that the majority of consumers understood that people who use CC would need to switch completely to IQOS use to receive the benefits conveyed by the modified exposure claim. Overall, the evidence supports the conclusion that the advertising and labeling concerning the MRTPs enable the public to comprehend the information concerning modified exposure and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and

health-related conditions associated with the use of tobacco products.

As TPL, I also examined population-level effects of marketing IQOS as an MRTP, including patterns of IQOS use since the issuance of the MRGOs. As described in Section 2.3 below, IQOS was not available in the U.S. market for much of the MRGO authorization period. Therefore, there is limited use data specific to the U.S. population available. The available data show that IQOS is being used by the applicant's stated intended users--adults who used CC before initiating IQOS. Demographic information suggests that current established IQOS users tend to be middle-aged men with relatively high socioeconomic status. There is no evidence that marketing IQOS as an MRTP has led to an increased likelihood for youth initiation of IQOS.

In one of PMP S.A.'s postmarket studies, almost all current IQOS users reported some prior history of tobacco use, with 91.6% reporting current CC use in the 30 days prior to IQOS initiation. Among current IQOS users, 50.6% reported they were former smokers at the time of the survey which, on average, was completed approximately 11 months after their initiation of IQOS, suggesting that about half of the former CC smokers quit smoking CCs after initiating IQOS. Additionally, 83.1% of current IQOS users who also used CC reported using fewer CC at the time of the survey than before they tried IQOS, although the number of CC per day was not reported. In total, 35% of current established IQOS users reported using IQOS exclusively. These findings suggest the retrospectively reported rates of quitting CC were higher among IQOS users in this study than they are in the overall population of people who smoke CC (e.g., only about 7.5% of all people who smoked CC reported having quit for 6 months or more in the past year in a study by Creamer et al., 2019).

Dual use of IQOS and other tobacco products continues to be a concern. Among current established IQOS users, 64.9% report using IQOS with one or more other tobacco products, with 48.8% using CC. However, if IQOS continues to be marketed as an MRTP, now that it has returned to the U.S. marketplace, repeated exposure to the modified exposure claim as part of the IQOS products' labels, labeling, and advertising (LLA) would provide tobacco users with basic, substantiated information and instructions to switch completely from CC to IQOS.

Overall, the evidence suggests there is a low likelihood of IQOS initiation among youth and people who do not use tobacco products, and the postmarket evidence indicates some potential for IQOS to be used by people who smoke CC to switch completely to IQOS, which reduces their exposure to HPHCs. Given the current evidence of limited influence on youth of marketing IQOS as an MRTP, any complete switching from CC to the MRTPs by adults can likely provide a benefit to population health.

PMP S.A. also requested three Surgeon General's warnings be removed,[6] asserting that IQOS does not meet the statutory definition of a cigarette and that, even if the products do meet that definition, the warnings are scientifically inaccurate and misleading to consumers about the risks of IQOS products. Assessing whether IQOS meets the definition of a cigarette for the purposes of the Surgeon

[6] The April 3, 2019, PMTA authorization for the IQOS System Holder and Charger explained that as cigarettes, if authorized, IQOS would be required to bear the rotating Surgeon General's warnings. However, PMP S.A. provided evidence demonstrating that although the use of Heatsticks in the IQOS device does produce CO, the exposure to CO from IQOS use is comparable to environmental exposure to CO. Therefore, the TPL determined that the required CO warning was misleading and should be removed from the rotation.

General's warnings[7] does not fall within the scope of MRTPA review under section 911. IQOS meets the definition of a cigarette and the term "smoking" in the Surgeon General's warnings applies to use of IQOS.[8] Therefore, the applicant's current request to remove the Surgeon General's warnings is an implied modified risk claim that the products cannot cause the health outcomes in the warnings that FDA would consider in a new MRTPA. Additional evidence would need to be provided by the applicant to establish that removal of the Surgeon General's warnings meets the standard set forth in section 911(g)(1), as well as evidence to establish that the updated advertising and labeling enable the public to comprehend the information concerning modified risk and understand the relative significance of the information in the context of total health under section 911(h)(1). The application that includes such new evidence would also be required to be referred to the Tobacco Products Scientific Advisory Committee (TPSAC) under section 911(f). To provide additional information to the applicant on the process of removing the Surgeon General's warnings, FDA intends to send a separate General Correspondence Letter to PMP S.A.

At this time, I recommend the MRTPs be authorized without removal of the three Surgeon General's Warnings on the proposed product labeling and advertising for IQOS:

- "**SURGEON GENERAL'S WARNING**: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy."
- **"SURGEON GENERAL'S WARNING**: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health."
- **"SURGEON GENERAL'S WARNING**: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight."

In summary, the available scientific evidence is generally consistent with the evidence reviewed in the original MRTPAs and continues to support the original conclusions that, among other things, the MRTPs are expected to benefit the health of the population as a whole. Thus, the products sold or distributed with the modified exposure information continue to meet the standards under Section 911(g)(2) of the FD&C Act.

2. BACKGROUND

2.1. MODIFIED RISK TOBACCO PRODUCTS

The applicant submitted information for the MRTPs listed on the cover page, and with more detail in Appendix A, sold under the brand names IQOS 2.4 System Holder and Charger (MR0000254.PD1), IQOS 3.0 System Holder and Charger (MR0000254.PD3), Marlboro Amber HeatSticks (MR0000254.PD5, previously Marlboro HeatSticks), Marlboro Green Menthol HeatSticks (MR0000254.PD6, previously Marlboro Smooth Menthol HeatSticks), and Marlboro Blue Menthol HeatSticks (MR0000254.PD7, previously Marlboro Fresh Menthol HeatSticks). According to the applicant, the proposed MRTPs are Heated Tobacco Product (HTP)

[7] Section 3(1) of the Federal Cigarette Labeling and Advertising Act (FCLAA) defines cigarette as "(A) any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (B) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette." Contrary to PMP S.A.'s assertion, IQOS also meets the definition of a "cigarette" at section 900(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[8] See the Memorandum "IQOS heated tobacco products and clarification of the terms "smoke" and "smoking",'" signed April 15, 2026, for the assessment of the applicability of "smoking" to IQOS products.

consumables and open HTPs. The MRTPs also meet the definitions of cigarette in section 900(3) of the FD&C Act and components and parts in 21 CFR 1100.3 and 1141.3.

The applicant describes the IQOS System as a "heat-not-burn tobacco product," consisting of three main components:

- IQOS HeatSticks**:** The HeatSticks consumable contains a tobacco plug consisting of crimped cast tobacco sheet made from ground tobacco powder. It is designed to function with the IQOS Holder to produce an aerosol when the plug is heated. It is a filtered non-combusted cigarette.
- IQOS Holder: The HeatSticks consumable is inserted into the Holder, which heats the tobacco material by means of an electronically controlled heating blade. The Holder is activated by the user by pressing the activation button for a set period until the Holder light begins to blink, signaling that the product may be used. The Holder is designed to function for a maximum of six minutes or 14 puffs, whichever comes first, after which it must be recharged and a new HeatStick must be inserted.
- IQOS Charger: The Charger is used to recharge the Holder after each use. The Charger stores sufficient energy for the use of approximately 20 HeatSticks and can be recharged from household power.

The two versions of the IQOS System Holder and Charger (MR0000254.PD1, MR0000254.PD3) and the three varieties of the HeatSticks consumables (MR0000254.PD5-MR0000254.PD7) are collectively referred to as "IQOS" in this document.

2.2. MODIFIED RISK CLAIM

The applicant has requested renewal of their exposure modification orders under section 911(g)(2) of the FD&C Act to continue to market the products specified in Appendix A with the following claim:

AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

2.3. REGULATORY ACTIVITY

Original MRTPAs

On November 18, 2016, PMP S.A. submitted MRTPAs for the IQOS 2.4 System Holder and Charger (MR0000133) and three types of HeatSticks: Marlboro HeatSticks, Marlboro Smooth Menthol HeatSticks, and Marlboro Fresh Menthol HeatSticks (MR0000059-MR0000061), which were received by FDA on December 5, 2016. FDA issued an Acceptance Letter to the applicant on February 16, 2017, and issued a Filing Letter to the applicant on May 23, 2017. FDA issued MRGOs for the exposure modification pathway under Section 911(g)(2) of the FD&C Act for these four products on July 7, 2020. These MRGOs were for four years (July 2020-July 2024). On March 18, 2021, PMP S.A. submitted, and FDA received, an MRTPA for the IQOS 3 System Holder and Charger (MR0000192), an update to the IQOS 2.4 System. FDA issued an Acceptance Letter to the applicant on April 15, 2021, and issued a Filing Letter to the applicant on May 13, 2021. FDA issued an MRGO for the exposure modification pathway under Section 911(g)(2) of

the FD&C Act for the IQOS 3 System on March 11, 2022, for a period that coincided with the first MRGOs (until July 7, 2024).

Postmarket Annual Report Submissions

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies (PMSS) in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]." FDA communicated the PMSS requirements to the applicant in the MRGO letters.

A summary of the PMSS requirements in the MRGO letters included the following:

1. Monitoring adult (ages 21+) use of the IQOS products that were authorized to be marketed with the reduced exposure claim in terms of uptake, dual use, and complete switching; and monitoring awareness and use of IQOS among youth (ages <18) and young adults (ages 18-20) who are below the legal age to purchase tobacco products.
2. An assessment of consumer perceptions of the products and understanding of the claim, particularly that:
    a. to reduce their exposure to harmful or potentially harmful chemicals[9] relative to CC, users of CC must use IQOS products exclusively and cutting down on CC per day while using IQOS products is not sufficient, and
    b. users of other tobacco products who switch to IQOS products understand that the reduction in exposure to harmful or potentially harmful chemicals is relative to CC use and not to other types of tobacco use.
3. Surveillance of MRTP sales and distribution in the U.S., adverse experiences, and new research study findings on the MRTPs and consumer perceptions, behavior, or health.
4. Computational toxicology studies utilizing a battery of genotoxicity and carcinogenicity models to assess the chemicals that were higher in HeatSticks aerosols than in CC smoke in order to predict potential adverse effects in users before toxicity may be evident.
5. Postmarket computational modeling of the impact of the MRTPs on population health, including information on acute and long-term health effects of using IQOS relative to CC use, in order to assess the short- and long-term population health impacts of the marketing.

In accordance with sections 911(g)(2)(C)(ii) - (iii), PMP S.A. received FDA approval in February 2021 of all study protocols for its planned PMSS activities and then submitted four annual reports[10] outlining its progress on the approved PMSS activities.

- Annual Report for PM0000424-PM0000426, PM0000479, PM0000634, MR0000059-MR0000061 and MR0000133, April 30, 2021 (PS0000119)
- Annual Report for PM0000424-PM0000426, PM0000479, PM0000634, MR0000059-MR0000061 and MR0000133, April 30, 2022 (PS0000175)

[9] In the applicant's claim and in the original PMSS requirements for the MRGOs, the term "chemical" was used rather than "constituent," which is retained here for accuracy.

[10] The applicant submitted four annual reports over the MRGO authorization period, and each reporting period covered March 1 - February 28 for the previous year.

- Annual Report for PM0000424-PM0000426, PM0000479, PM0000634, MR0000059-MR0000061 and MR0000133, April 28, 2023 (PS0000284)
- Annual Report for PM0000424-PM0000426, PM0000479, PM0000634, MR0000059-MR0000061 MR0000133, and MR0000192, April 29, 2024 (PS0000333)

The annual reports included information from consumer surveys, a three-phase computational toxicology study, a population health model, surveillance of MRTP U.S. sales and distribution, adverse experiences, and new research findings (see Table 1). The applicant submitted periodic reports relating to the advertising and promotion of the products every 3 months to FDA.

United States International Trade Commission Cease-and-Desist Order

The MRGO authorization period was for four years (July 2020 – July 2024). However, on September 29, 2021, the U.S. International Trade Commission issued a Cease-and-Desist Order (CDO) that prohibited the importation, marketing, sale, and distribution of IQOS products in the U.S. To comply with the CDO, PMP S.A. stopped marketing and selling IQOS products in the U.S. by November 28, 2021.

This market removal affected the ongoing PMSS, and PMP S.A. submitted an updated plan for PMSS data collection in January 2022. Table 1 below lists PMP S.A.'s PMSS and adjustments made due to the removal of IQOS products from the U.S. market.

Philip Morris International announced on February 2, 2024, that a global settlement was reached that allowed the reintroduction of IQOS products to the U.S. However, these products were not re-launched in the U.S. until March 2025. This limited the sales and marketing of IQOS products in the U.S. to approximately 17 months during the MRGO authorization period.

Table 1: List of PMSS studies and adjustments made due to the removal of IQOS from the U.S. market

Study name	Original plan for the study	Adjustments
IQOS with Marlboro HeatSticks Cross-Sectional Postmarket Adult Consumer Study (PACS)	Online, cross-sectional survey administered annually over four years beginning in 2021.	The applicant fielded the first wave from September to November 2021. Subsequent data collection was not completed.
IQOS with Marlboro HeatSticks Cohort Postmarket Adult Consumer Study	Prospective longitudinal cohort study among adult established users of IQOS and a reference group of adult established users of CC over a closed 24-month period.	Study was not conducted.
Secondary Analysis: Estimation of Prevalence of IQOS Use Adult Tobacco Consumer Tracker (ATCT)	Ongoing nationally representative cross-sectional computer assisted random-digit dialing telephone interview survey. Questions about HTPs were added in October 2019.	The removal of IQOS from the market did not make adjustments to this data collection or secondary analysis necessary.
Reporting from the U.S. IQOS Owners Panel	Longitudinal consumer panel recruiting IQOS users from the IQOS consumer database.	IQOS Owners Panel data collection ceased as of November 29, 2021, when IQOS

	Planned recruitment wave every 2 weeks on an ongoing basis with participants surveyed weekly for the first 3 months after recruitment and then monthly thereafter.	became unavailable in the U.S. market. The applicant reported data collected between April 2020 and November 29, 2021.
Secondary Analysis: Estimation of Awareness and Use of IQOS among Underage Individuals using the Underage Tobacco Use Survey (UTUS)	Ongoing nationally representative cross-sectional survey of youth and young adults (ages 13-20) in the U.S., which launched in May 2020 with plans to conduct regular quarterly surveys. This survey planned to oversample youth and young adults in Atlanta, GA, Charlotte, NC, and Richmond, VA, where IQOS was originally marketed.	The applicant halted the oversampling of youth respondents in Atlanta, GA, Charlotte, NC, and Richmond, VA, starting in the second quarter of 2022 because IQOS was no longer available in those markets. The secondary analysis was otherwise unchanged.
Population Health Impact Model (PHIM)	Update to the PHIM submitted in the original MRTPAs using data from PMSS studies as inputs.	The applicant was unable to utilize PMSS estimates for an updated PHIM and instead utilized publicly available estimates.
Computational toxicology study	Three-phase computational toxicology study. The first phase evaluated the potential genotoxicity/carcinogenicity of the 80 chemicals found to be higher in HeatSticks aerosols than in 3R4F RCS in the original MRTPAs. The second phase identified known and potential metabolites of these 80 parent chemicals. The third phase evaluated the potential genotoxicity/carcinogenicity of certain metabolites.	Removal of IQOS from the market did not make adjustments to this study necessary.

Current Renewal MRTPAs

On July 5, 2023, FDA received five renewal MRTPAs from the applicant for the following products:

- IQOS 2.4 System Holder and Charger (MR0000254.PD1)
- IQOS 3.0 System Holder and Charger (MR0000254.PD3)
- Marlboro Amber HeatSticks (MR0000254.PD5)
- Marlboro Green Menthol HeatSticks (MR0000254.PD6)
- Marlboro Blue Menthol HeatSticks (MR0000254.PD7)

FDA issued an Acceptance Letter to the applicant on September 5, 2023. FDA issued a Filing Letter to the applicant on May 9, 2024. During the MRTPA review process, FDA contacted the applicant to request additional information and clarification on the applications in an Advice/Information Request Letter on November 22, 2024. The applicant provided additional information in response to the information request on December 20, 2024. Refer to Appendix B for a complete list of amendments received by FDA related to these renewal MRTPAs.

2.4. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the MRTPs subject of this review. Specifically, this review considered all available evidence, including peer-reviewed scientific literature and new information that the applicant submitted to FDA since the issuance of their MRGOs, including PMSS status updates, periodic reports, and other information submitted as part of their annual reports.

Table 2: Disciplines included in review

Discipline		
	Reviewer(s)	**Review Date**
Engineering	Ramune Meskyte	4/15/2026
Chemistry	Jason Schaff	4/15/2026
Microbiology	Cynthia Zmich	4/15/2026
Toxicology	Sagie Wagage	4/15/2026
Behavioral Clinical Pharmacology	Kia Jackson	4/15/2026
Medical	Anna-Sophie Weidner	4/15/2026
Epidemiology	Mia Peng	4/15/2026
Social Science	Michael Halenar	4/15/2026
OCE – BIMO	Farabi Alam	4/14/2026
OCE – Manufacturing/ Lab	Elaine Gilfillan	4/15/2026
Environmental Science	William Brenner	4/15/2026

Table 3: Consultations

Discipline or Office		
	Consultant(s)	**Review Date**
Statistics for Epidemiology	Christopher Ellison	4/9/2026
Statistics for Medical	Christopher Ellison	4/8/2026
OCE – DPAL	Gina Sutedja & Jaikishan Kakar	4/14/2026
OHCE	Emily Talbert	4/15/2026
Evaluation	Jonathan Hannings	4/14/2026

2.5. TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC)

Pursuant to section 911(f) of the FD&C Act, FDA referred the renewal MRTPAs to TPSAC,[11] and TPSAC reported its recommendations on the renewal applications during an open public committee meeting held on October 7, 2025. The committee included three additional expert consultants with expertise in toxicology. At the meeting, the committee discussed the renewal MRTPAs, including the adequacy of the scientific evidence to support the marketing of these products as MRTPs. Information about the meeting, including the complete transcript, is available on FDA's website.

FDA shared its preliminary assessment of the renewal applications with the committee, focusing on relative health risks of the products in clinical and nonclinical studies, as well as product use behavior since authorization, and consumer understanding and perceptions of the modified exposure claim. TPSAC was asked to discuss the nonclinical toxicology evidence about these MRTPs and any implications for long-term disease risk, as well as the likely patterns of MRTP use behavior.

A summary of TPSAC's discussions on these topics is presented here. FDA's assessment of these discussions is included in the relevant portions of section 3 of this review, as well as in individual discipline reviews.

Regarding toxicological studies published in the scientific literature since the issuance of the MRGOs, TPSAC members discussed the methodological limitations of the studies while further discussing the plausible health effects of IQOS in humans based on the study results. When discussing whether the data still support the reduced exposure claim, some members discussed the biological potency of constituents, public health implications of the studies, and population variations that complicate conclusions about exposure and harm reduction. While some participants interpreted the presented data as demonstrating that IQOS still shows markedly lower toxicant exposures than CC, others cautioned that reduced exposure does not always equal reduced biological harm. Overall, the committee agreed that more rigorous, standardized, and human-relevant studies are needed to clarify the toxicological risks and public health implications of IQOS use. These topics are taken into consideration elsewhere in this review and in the toxicology review.

TPSAC members discussed the totality of the toxicological evidence and implications for long-term disease risk of IQOS aerosols exposure relative to CC smoke exposure, generally agreeing that IQOS likely poses less harm than CC. Members who agreed the reduced exposure claim was substantiated cited the significant reduction in exposure to harmful chemicals compared to CC. Some members noted that biomarkers of potential harm (BOPH) in long-term IQOS users remain comparable to people who smoke CC, suggesting reduced exposure does not automatically translate to reduced disease risk. In addition, some stated that short-term or acute exposure studies cannot reliably predict long-term effects and emphasized the need for sub-chronic and chronic exposure research to understand delayed or persistent health impacts. These topics are taken into consideration elsewhere in this review and in the toxicology review.

Regarding IQOS use behaviors, TPSAC members agreed that due to incomplete postmarket studies, evidence of U.S. consumer behavior remains limited. Members noted that data from

[11] Tobacco Products Scientific Advisory Committee; Notice of Meeting, 90 FR 35894 (July 30, 2025).

international studies indicate high and sustained levels of dual use of IQOS and CC. Multiple members discussed that dual use likely does not reduce harm and may even increase health risks compared with CC smoking alone. Members further noted the difficulty of defining and measuring dual use, as it can include a wide range of behaviors and frequency of use. Members discussed independent studies that have found complete switching from CC to alternative products uncommon. TPSAC members also noted that the U.S. tobacco marketplace has shifted since IQOS was first authorized as an MRTP, and older people who smoke CC have shown limited interest in CC alternatives, which seem to appeal more to younger adults and individuals who do not smoke CC. These topics are addressed elsewhere in this review and in the epidemiology review.

TPSAC members also discussed whether consumers may misinterpret the reduced exposure claim to mean reduced risk. Some members recommended revising MRTP labeling to explicitly state that unique or unknown risks may still exist. These topics are addressed elsewhere in this review and in the social science review.

Throughout the TPSAC discussion, TPSAC members gave suggestions about how to improve PMSS requirements for IQOS, including thoughts about study design, measurement, and sample replenishment. FDA considered these suggestions when making future PMSS requirements discussed in section 5.4.

2.6. PUBLIC AVAILABILITY OF MRTPAS

Pursuant to Section 911(e) of the FD&C Act, FDA made the applicant's renewal MRTPAs available to the public. FDA redacted trade secrets, and confidential and commercial information. The docket for public comment on these renewal MRTPAs was open from May 3, 2024, to December 8, 2025. During this period, FDA received 26 submissions from individuals, academia, and other organizations. The 26 submissions included comments on consumer understanding and perceptions; critiques of the applicant's study methods, measures, and findings; and support for renewal of the MRTP orders to improve access to alternative tobacco products for consumers. One comment expressed concerns that the modified exposure claim could lead consumers to think IQOS is lower risk than CC. One comment shared a personal experience with IQOS use. One comment did not support the renewal of the MRTP orders until there is clear, independent, long-term evidence showing real health benefits for the public. This comment listed issues with the relationship between fewer chemical exposures not equaling less harm, the existence of toxic chemicals that have not been studied long enough to make conclusions, and the issues with dual use and the potential for youth uptake. We assessed the topics of concern expressed in this comment in the toxicology and epidemiology reviews but also note that all eight citations included as scientific support for this comment are not real and the corresponding articles do not exist in the scientific literature. Overall, the issues and concerns raised in the public comments were also identified during FDA's scientific review of the applications and are discussed throughout this review. FDA considered all relevant comments when making the final determination. Specific comments are addressed in the epidemiology, social science, and toxicology reviews.

3. SCIENTIFIC REVIEW

3.1. PRODUCT CHARACTERIZATION

This section describes the product characterization, which includes product design and

composition and examines whether the applications sufficiently describe the products, how they are made, and the consistency of the manufacturing of the products. This information is necessary to fully understand the product science, which, in turn, influences the potential health risks of the products.

Key Findings from Original MRTPA TPL Review

In the July 6, 2020, TPL review, the TPL referred to the product characterization information included in the PMTAs which provided details on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites. No issues with product characterization were identified.

Evaluation of New MRTPA Data

The renewal MRTPAs cross-reference scientific evidence and product characterization information related to the product description and formulation which were provided with the original MRTPAs and PMTAs for the authorized IQOS 2.4 System Holder and Charger (PM0000479 and MR0000133), HeatSticks consumables (PM0000424 - PM0000426 and MR0000059 - MR0000061), and the IQOS 3.0 System Holder and Charger (PM0000634 and MR0000192). Engineering, microbiology, and chemistry disciplines conducted independent literature reviews (2020 – 2025) and did not find any relevant literature related to product characterization.

Product Design, Composition, and Manufacturing

The microbiology, engineering, and chemistry reviews assessed scientific literature submitted by the applicant and concluded that the literature in the combined PMTA/MRTPA annual reports for 2021 (PS0000119), 2022 (PS0000175), 2023 (PS0000284), and 2024 (PS0000333) do not contain relevant product design or product characterization studies.

In the renewal applications, the applicant reported that scientific evidence and information related to product design, composition, or manufacturing remained valid and did not require reanalysis. However, in combined PMTA/MRTPA annual reports for the products subject to this review, PMP S.A. submitted logs of changes to manufacturing processes, facilities, controls, and product components. In the first combined PMTA/MRTPA annual report (PS0000119), PMP S.A. reported two changes to the HeatStick consumables: 1) [redacted] and 2) (b)(4) [redacted] On June 24, 2022, a general correspondence letter was sent to PMP S.A. in which the applicant was informed that these two changes may cause the products subject to the annual report to be new products as a change in design, any component, any part, or any constituent of the authorized products. (b)(4) [redacted]. In the 2024 combined PMTA/MRTPA annual report (PS0000333), PMP S.A. provided more details about these two changes and argued that these changes did not change the products' performance, composition, constituents, or characteristics, and therefore did not cause the products to be new products. FDA held a teleconference with PMP S.A. in which clarification and additional information was requested about the products to which the manufacturing changes applied. In response, PMP S.A. replied to this information request (PS0000390), stating that, "Furthermore, we will not implement either of these modifications for products that are in the scope of our renewal and which received Modified Risk Granted Orders, as

listed in the table below" and supplied a table listing the original HeatSticks products that are the subject of this MRTPA TPL review (MR0000059-MR0000061). Consequently, this MRTPA TPL review, and the supporting discipline reviews and consults, are for the HeatSticks products and for the IQOS System Holders and Chargers listed in Appendix A (MR0000254.PD1, MR0000254.PD3, MR0000254.PD5, MR0000254.PD6, and MR0000254.PD7).

While PMP S.A. stated that changes were not applied to the products that are the subject of these renewal applications, the discipline reviewers evaluated the change logs provided by PMP S.A. to determine whether the studies that included products with these component changes could be bridged to the authorized products identified in the original MRGOs. Engineering and microbiology assessed the information on manufacturing provided by the applicant and concluded it is sufficient from their discipline's perspectives for bridging, and no additional information is needed to determine that bridging is appropriate. As a part of chemistry's assessment of reported component changes, the reviewer assessed whether the studies utilizing products with these component changes could be bridged to the authorized products identified in the original MRGOs. Chemistry also determined that the component changes could be bridged to the original products subject to this review.

Because no changes were identified that raised concerns about manufacturing the products subject to this review, the Office of Compliance and Enforcement (OCE) Division of Product Compliance (DPC) and OCE Bioresearch Monitoring (BIMO) did not inspect any facilities.

Product Stability

The original MRTPAs provided stability studies to establish a (b)(4) shelf life; however, in the original MRTPAs the applicant did not include any microbiological parameters (water activity (a_w), moisture content, microbial counts) as part of the stability testing. Postmarket a_w stability data was submitted in the 2021 annual report (PS0000119) with defined microbiological parameters. The microbiology review concluded that the applicant provided adequate microbiology-related information for the products to demonstrate product stability over the established(b)(4) shelf life and to address factors that can potentially affect the microbial stability of the product.

Section Summary Statement

The original TPL review relied upon the associated PMTA reviews for adequate product design and composition, manufacturing, and product stability information. In the present renewal MRTPAs, the engineering, microbiology, and chemistry reviews conclude that no new scientific information alters their original conclusions.

While the applicant reported in the renewal applications that scientific evidence and information related to product design, composition, or manufacturing remained valid and did not require reanalysis, the chemistry review identifies several component replacements in IQOS HeatSticks since 2020. Information provided by the applicant clarified that these component changes do not apply to the tobacco products authorized in the original MRGOs and subject to this review. The chemistry review of the component changes concluded that studies utilizing these products with the component changes could be bridged for review of the original MRTPA products.

As TPL, I agree with the engineering, microbiology, and chemistry review conclusions that the new information does not change the assessment of product design and composition, manufacturing, and product stability information that would result in a change to FDA's original conclusions on product characterization. I also agree with the chemistry review conclusion that studies utilizing these products with component changes could be bridged to the authorized products identified in the original MRGOs.

3.2. RELATIVE HEALTH RISKS TO INDIVIDUALS WHO USE TOBACCO

Key Findings from Original MRTPA TPL Review

The 2020 MRTPA TPL review provided a comprehensive evaluation of the evidence related to the health risks to individuals who use IQOS products, focusing on substantiation of the proposed modified exposure claim. The review focused on several main topics:

- The lack of combustion with IQOS products;
- The production of HPHCs in IQOS aerosols;
- The nonclinical toxicological assessment of IQOS, including in vitro studies, in vivo studies, systems toxicology studies, and other constituents in IQOS; and
- The clinical assessment of IQOS, including BOE and BOPH.

Combustion

Review of data on combustion in IQOS found that the low temperature in the IQOS System (~350°C), the lack of an exothermic process, the similar levels of HPHCs in the presence and absence of oxygen, and the low level of nitrogen oxides in the aerosol of the IQOS System with HeatSticks suggested that combustion does not occur in the IQOS System with HeatSticks when it is used as intended. The 2020 MRTPA TPL review concluded that there was sufficient evidence to support the following statement: "The IQOS system heats tobacco but does not burn it."

HPHCs

The comprehensive testing of 108 HPHCs showed that 107 were either below the level of detection or quantification or present at lower concentrations in IQOS aerosols compared to CC smoke. Overall, HPHCs were reduced by 47-99.9% in IQOS aerosols on a per stick basis compared to CC smoke and 20-99.8% when normalized to nicotine levels, with only nicotine and anabasine as exceptions. While some compounds like menthol-related constituents, alkaloids, and flavors were found exclusively or in higher quantities in IQOS aerosols, the yields of potential carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower than in CC smoke. Based on this substantial reduction in harmful chemicals, the 2020 MRTPA TPL review concluded that there was sufficient evidence to support the modified exposure claim that heating tobacco without burning it "significantly reduces the production of harmful and potentially harmful chemicals."

Nonclinical toxicological assessment

The nonclinical evidence demonstrated that IQOS HeatSticks aerosols had reduced toxic potential compared to 3R4F RCS across multiple testing methods. Evidence from in vitro studies indicated that HeatSticks aerosols had reduced cytotoxic and mutagenic potential compared to RCS. Evidence from in vivo rat studies revealed that exposure to HeatSticks aerosols produced fewer or less severe histopathological changes compared

to exposure to RCS. Evidence from human organotypic tissue studies had two general outcomes: 1) fewer pathophysiological changes and adverse effects from HeatSticks aerosols compared to exposure to RCS, or 2) similar pathophysiological changes and adverse effects but only when IQOS aerosol exposure is at higher concentrations than exposure to RCS. The overall yields of carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower in HeatSticks aerosols than in RCS. However, while the overall data suggested IQOS aerosols had lower toxic potential than CC smoke, systematic differences in collection methods created some uncertainty in interpreting results, and significant study limitations identified in the toxicology review prevented drawing stronger conclusions about the relative health risks of using the IQOS System. In addition, the applicant included only a limited toxicological evaluation of the 80 chemicals found exclusively or at higher concentrations in HeatSticks aerosols than in RCS.

Clinical assessment

The clinical studies provided evidence that completely switching from CC to IQOS significantly reduced exposure to HPHCs. Four 5-day studies showed that complete switching from CC to IQOS resulted in reduced HPHC exposure with a magnitude similar to complete smoking abstinence. Two 90-day studies in Japan and the U.S. demonstrated reductions in BOE to 15 HPHCs among individuals who switched completely from CC to IQOS. The reduced BOE spanned multiple chemical and toxicity classes. The 2020 MRTPA TPL review concluded that the exposure reduction evidence supported substantiation of the claim that switching completely to IQOS from CC "significantly reduces your body's exposure to harmful or potentially harmful chemicals."

The 2020 MRTPA TPL review noted several important limitations of the clinical studies. The applicant did not assess BOE for HPHCs found to be elevated in IQOS aerosols compared to RCS. More critically, the clinical studies measured BOPH rather than actual disease endpoints, and currently there are clear limitations in the utility of biomarkers as surrogates of disease. The studies showed only minor improvements in some BOPH with unclear clinical significance. Since the predictive value of the chosen biomarkers for long-term tobacco-related disease risk remains unclear, the TPL concluded that longer-term studies were needed to evaluate the overall health impact of switching to IQOS, despite the demonstrated reduction in harmful chemical exposure.

Original MRTPAs Conclusion

Using available, indirect evidence, the 2020 MRTPA TPL review assessed whether the reduction in exposure to harmful or potentially harmful chemicals observed with complete switching from CC to the IQOS System was likely to translate into a measurable and substantial reduction in morbidity and mortality among individual tobacco users. Although the use of the IQOS System does still expose users to HPHCs and would be expected to cause harm, the level of exposure was expected to be lower relative to CC and, thus, reasonably likely to, in general, translate to lower risk of tobacco-related morbidity and mortality relative to CC. Although reduced risk was not demonstrated, the totality of evidence presented suggested that a measurable and substantial reduction in morbidity or mortality among individual tobacco users was reasonably likely in subsequent studies.

Evaluation of New MRTPA Data

Toxicant Exposure, Including HPHCs

In this renewal application, the toxicology review identified new information regarding the toxicant exposure of IQOS. As part of the original MRGO PMSS requirements, the applicant submitted a postmarket computational toxicology study consisting of three phases.

- The first phase evaluated the potential genotoxicity/carcinogenicity of the 80 parent chemicals found to be higher in HeatSticks aerosols than in 3R4F RCS that were identified in the original MRTPAs.
- The second phase identified known and potential metabolites of these 80 parent chemicals.
- The third phase evaluated the potential genotoxicity/carcinogenicity of metabolites identified in Phase 2.

Compared to information submitted in the original MRTPAs, the postmarket computational toxicology study identified additional HPHCs, including metabolites of the parent chemicals on the list of 80 chemicals identified in the original MRTPAs, as being potentially genotoxic/carcinogenic.

Before assessing the 3-phase computational toxicology study results, toxicology evaluated the underlying aerosol constituent data that went into the computational toxicology study. In the original MRTPAs, the applicant submitted aerosol constituent data for IQOS products showing that most HPHCs were reduced by 13-99% compared to 3R4F RCS. However, a non-targeted differential screening identified 80 chemicals present at higher levels in IQOS aerosols than in CC smoke, and it was these chemicals that were further assessed in the computational toxicology study. In the renewal MRTPAs, chemistry consultations clarified that the semi-quantitative data from the original non-targeted differential screening is valid for relative comparisons between IQOS aerosol and CC smoke, but that there are significant limitations in the reliability of the semi-quantitative data for absolute comparisons. Only 10 of the 80 identified chemicals have semi-quantitative yields that can reasonably be expected to be within a factor of five of true yields, indicating that the yields provided by the applicant in the original MRTPAs for the constituent data are not fully reliable for absolute comparisons, which has implications for the reliability of the postmarket computational toxicology results, as described in the subsequent sections of this review. The applicant acknowledges that their non-targeted screening approach is not fully quantitative and can differ from true values by more than 4-fold, limiting the utility and reliability of these data for comprehensive quantitatively based toxicological risk assessment.

Genotoxic and Carcinogenic Hazards

The required postmarket computational toxicology study identifies 36 HPHCs in IQOS aerosols with potential genotoxic/carcinogenic properties (increased from 23 identified in the original MRTPA review), and some non-genotoxic parent chemicals have metabolites with carcinogenic potential, suggesting IQOS may pose higher genotoxic risks than originally assessed. Using a tiering approach based on genotoxicity hazard identification (Division of Nonclinical Science Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in

ENDS Premarket Tobacco Product Applications; signed 6/3/2024), constituents are classified into various risk tiers. Some higher-tier constituents are found at elevated levels in IQOS compared to CC.

New information from the applicant's computational toxicology study raises toxicology's level of uncertainty regarding the carcinogenic risk of IQOS aerosols. In response to an information request from FDA, the applicant notes that only long-term epidemiological studies can definitively demonstrate the relative cancer risks of IQOS compared to CC. The applicant also states that the increase in the level of constituents identified in the non-targeted differential screening that were predicted to have genotoxic/carcinogenic potential in IQOS aerosols compared to CC smoke constitutes 0.15% of the total particulate matter from IQOS aerosols. As discussed previously, the applicant's non-targeted screening approach is not fully quantitative and can differ from true values by more than 4-fold, limiting the utility and reliability of these data for comprehensive quantitative toxicological risk assessment.

Both the applicant and FDA calculated Excess Lifetime Cancer Risk (ELCR) estimates that suggest reductions in cancer risk for IQOS versus CC, but the applicant's calculations had limitations including reliance on unreliable constituent data that did not establish true quantitative values, inappropriate exposure assumptions, and exclusion of relevant carcinogenic chemicals, resulting in uncertainty about actual cancer risk. Because toxicology had to rely on the same unreliable constituent data submitted by the applicant, their ELCR was also limited. Based on the limitations in available data, there is a high level of uncertainty regarding the extent to which the ELCR calculations reflect the carcinogenic risk of IQOS aerosols, and these limitations could result in either an overestimation or underestimation of calculated ELCRs.

Noncarcinogenic hazards

To address noncarcinogenic hazards of IQOS, the toxicology review evaluates noncancer toxic effects associated with chemicals found at higher levels in IQOS aerosols compared to RCS. Several chemicals that were found to be higher in IQOS aerosols in the original MRTPAs have the potential to induce respiratory toxicity, produce toxic effects on male reproductive organs, affect the central nervous system, and cause cardiovascular toxicity. Although these chemicals have the potential to induce toxic effects, limited toxicity information was available for many of these chemicals, and, similar to the issues outlined above, the data on the chemicals found at higher levels in IQOS aerosol than CC smoke are not sufficiently quantitative and reliable. In addition, there is limited inhalation exposure data available to assess the specific effects of these chemicals in IQOS aerosol.

Published Literature

To further evaluate IQOS aerosol exposure, the toxicology review identifies literature published after the issuance of the MRGOs focused on noncancer outcomes. Toxicology reviewed 71 studies published since the issuance of the MRGOs, including systematic reviews, in vitro studies, and in vivo studies, that focus on the effects of IQOS and HTPs on toxicological outcomes, including respiratory,

cardiovascular, reproductive, and metabolic effects. Of these 71 studies, 58 studies do not change toxicology's conclusions from the original MRTPAs. The remaining 13 studies, which assessed a range of health-related outcomes, found that IQOS aerosols had equivalent or worse adverse toxicological effects on the specified outcome compared to CC, and in some cases, the study identified toxicities or adverse outcomes that were found in IQOS and not in CC. Other studies reported toxic effects of IQOS aerosol exposures in vivo, including effects on the liver, lungs, or brain, but did not include experimental groups exposed to CC for comparison.

Respiratory Effects

Of the studies that focused on respiratory toxicity, the toxicology review generally concluded that subacute toxicity studies (1-8 weeks) showed that both IQOS aerosols and CC smoke caused lung inflammation and immune infiltration. In Bhat et al. (2021), mice were exposed to IQOS aerosols or CC smoke for two weeks. Lung immune infiltrates were significantly increased following exposure to IQOS aerosols or CC smoke, and the levels of lung immune infiltrates were similar between mice exposed to IQOS aerosols or CC smoke. Additionally, exposure to IQOS aerosols or CC smoke led to increases in the levels of multiple cytokines or chemokines associated with inflammation in bronchoalveolar lavage fluid. The levels of most of these cytokines and chemokines were not significantly different between mice exposed to IQOS aerosols or CC smoke. In addition, exposure to IQOS aerosols or CC smoke led to significantly increased levels of albumin in bronchoalveolar lavage fluid, indicating increased lung vascular permeability which is associated with lung injury. However, mice exposed to CC smoke had significantly higher levels of albumin in bronchoalveolar lavage fluid than mice exposed to IQOS aerosols.

In a similar study from the same research group, mice were exposed to IQOS aerosols or CC smoke for 8 weeks (Bhat et al., 2023). Lung immune infiltrates were significantly increased following exposure to either IQOS aerosols or CC smoke. Mice exposed to IQOS aerosols or CC smoke had significantly increased levels of pro-inflammatory chemokines and cytokines in bronchoalveolar lavage fluid. Some of these proteins were found at similar levels in bronchoalveolar lavage fluid following IQOS aerosol or CC smoke exposure, while other cytokines or chemokines were found at significantly higher levels in bronchoalveolar lavage fluid from mice exposed to CC smoke when compared to IQOS aerosol-exposed mice. IQOS aerosol or CC smoke exposure also led to increased myeloperoxidase activity and neutrophil elastase levels, both additional measures of inflammation, in bronchoalveolar lavage fluid in comparison to air-exposed controls. Compared to mice exposed to CC smoke, mice exposed to IQOS aerosols had significantly lower levels of myeloperoxidase activity and levels of neutrophil elastase that were not significantly different. Exposure to CC smoke or IQOS aerosols also led to increased lung vascular permeability, a cause of pulmonary edema which is a sign of acute lung injury.

Two independent chronic toxicity studies with durations lasting at least 6 months (Gu et al., 2023; Nitta et al., 2022) demonstrate that mice exposed to IQOS aerosols for 6 months developed emphysematous changes comparable to those seen with CC smoke exposure, including airspace enlargement and alveolar wall destruction.

Both Gu et al. (2023) and Nitta et al. (2022) had numerous limitations in the

methodology they used, including the use of a small number of images for quantification, no information on whether images were analyzed in a blinded manner, and no information on whether the histopathological analysis was performed by a veterinary pathologist. As an additional limitation, Nitta et al. (2022) did not provide statistical evaluations of differences in the measured endpoints between mice exposed to IQOS aerosols and mice exposed to CC smoke. Moreover, statistical analyses of multiple groups in Gu et al. (2023) were based on Student's t-tests that did not adjust for multiple comparisons. Not adjusting for multiple comparisons increases the probability of obtaining a false positive result in which the study detected an effect that is not truly present. Gu et al. (2023) also lacked data for BOE in exposed mice, which would provide relevant information for evaluation of comparisons of exposure levels between mice exposed to IQOS aerosols or CC smoke; however, mice in Gu et al. (2023) were exposed to smoke or aerosols from 5 HeatSticks or 5 CC, which may have led to comparable exposures but the data was not provided to verify this assumption. Despite these limitations, these findings suggest that exposure to IQOS aerosols or CC smoke may have similar effects on the development of emphysema in mouse models.

Overall, the toxicology review concludes that the new evidence for the effects of IQOS aerosol exposures on respiratory toxicity demonstrates that IQOS has detrimental respiratory effects, with some being comparable to CC smoke exposure. Several studies indicated that exposure to IQOS aerosols led to lung inflammation and increased lung vascular permeability (Bhat et al., 2023; Bhat et al., 2021; Gu et al., 2023; Nitta et al., 2022), and two of these studies provided evidence that exposure to IQOS aerosols led to outcomes indicative of emphysema. Results of the chronic exposure studies (Gu et al., 2023; Nitta et al., 2022) demonstrate more severe effects than results of the acute studies, which only look at short-term exposure.

Cardiovascular Effects

Some studies published after the MRGOs and reviewed by toxicology found cardiovascular effects from IQOS aerosol exposure that are similar to CC smoke exposure. Rao et al. (2022) demonstrated that IQOS aerosols impaired flow-mediated dilation in rats to a similar degree as CC smoke, with rats exposed to IQOS aerosols showing higher serum nicotine levels. More comprehensively, Qiu et al. (2023) found that 2-month exposures to IQOS aerosols or CC smoke led to similar cardiac dysfunction, including increased blood pressure, impaired left ventricular function, cardiac fibrosis, and altered heart rhythm patterns. Moreover, a review of literature by Alarabi et al. (2022) found that HTP aerosol exposure may lead to similar cardiovascular outcomes as CC smoke exposure.

According to the toxicology review, the results from these three studies published since the MRGOs run contrary to the studies conducted by PMP S. A. and submitted in support of the original MRTPAs. Studies submitted to support the MRGOs found that CC smoke exposure was worse than IQOS aerosol exposure for cardiovascular toxicity outcomes. For example, applicant-submitted studies in support of the original MRTPAs using ApoE-/- mice showed less severe cardiovascular effects from IQOS aerosol exposure (Phillips et al., 2019; Phillips et al., 2016; Szostak et al., 2017; Szostak et al., 2020). Overall, taking into account the studies published since the

MRGOs, evidence related to the relative effects of IQOS aerosol exposure and CC smoke exposure on cardiovascular toxicity is currently more mixed than at the time of the original MRGO issuance.

Reproductive Effects

Only one animal study (Yoshida et al., 2020) published since the issuance of the MRGOs and reviewed by toxicology focused on the reproductive effects of IQOS aerosol exposure, and it raises questions about the potential effect of IQOS relative to CC on development of the male reproductive system. Yoshida et al. (2020) evaluated the effects of in utero exposure to IQOS aerosols or CC smoke on testicular function. Results demonstrated no differential effects on litter size or fertility between IQOS aerosol exposure and CC smoke exposure, nor were there differences in body weight or testicular weights of offspring. However, 5-week-old male mice exposed to IQOS aerosols in utero had statistically significant higher levels of seminiferous tubule damage and reduced daily sperm production compared to mice exposed in utero to filtered air as a control. In contrast, exposure to CC smoke in utero did not lead to statistically significant changes in seminiferous tubule damage or daily sperm production compared to mice exposed in utero to filtered air as a control. These effects were transient, and at age 15 weeks these outcomes were comparable between mice that had been exposed in utero to filtered air, IQOS aerosols, or CC smoke. The authors concluded that in utero IQOS aerosol exposure delayed male sexual maturation or impaired testicular function more than CC exposure (Yoshida et al., 2020).

As only one study was identified that focused on reproductive effects of IQOS aerosol exposure and the reproductive effects observed were transient, a definitive conclusion by toxicology regarding the relative reproductive effects of IQOS aerosol exposure and CC smoke exposure cannot be made.

Metabolic Effects

Toxicology reviewed studies examining cellular metabolic responses and found that IQOS aerosol exposure created unique biochemical fingerprints distinct from CC smoke exposure. Curley et al. (2024) and Lenski et al. (2024) both identified unique metabolites and dysregulated pathways following IQOS aerosol exposure, though the toxicological significance of these changes remains unclear due to methodological limitations.

Clinical Assessment

Relative Individual Health Risks to Tobacco Users

To assess relative individual health risks of IQOS to tobacco users, the behavioral and clinical pharmacology (BCP), medical, and epidemiology reviews evaluate applicant-submitted clinical studies and include reviews of the scientific literature. Scientific literature was identified two ways. First, as part of its PMSS requirements, the applicant submitted annual reports from 2020-2024 that included new literature published since the MRGOs regarding relative individual health risks to tobacco users, including product-specific and HTP-relevant studies on BOE, BOPH, and other health outcomes. Second, BCP, medical, and epidemiology reviewed these studies

and also conducted their own searches and reviews of product-specific individual health risk studies.

Biomarkers of Exposure (BOE)
The BCP review summarizes three new relevant studies submitted by the applicant that assessed BOE:

1. A 6-month extension of a 6-month U.S. study submitted in the original MRTPAs that measured reductions in exposure to HPHCs among individuals who switched from CC to IQOS and individuals who continued to smoke CC.
2. A 6-month study in Japan that evaluated the effects of switching from CC smoking to using IQOS or continuing to smoke CC on the response of pocket depth, a sign of gum health, to mechanical periodontal therapy among individuals with generalized chronic periodontitis.
3. A 12-week study in Germany that evaluated the effect of switching from CC smoking to using IQOS or continuing to smoke CC on exercise tolerance among individuals who smoke CC.

The findings from the new studies support that switching completely from CC to IQOS significantly reduces exposure to selected HPHCs. In the extension study, BOE to selected HPHCs (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), total N'-nitrosonornicotine (NNN), carboxyhemoglobin (COHb), cyanoethyl mercapturic acid (CEMA)) at Month 12 were significantly lower in IQOS users than in CC users. However, there was no statistical difference in any measured BOE between CC users and dual users of IQOS and CC. In the Japan study, BOE to selected HPHCs (total NNAL, CEMA) at Month 6 were lower in IQOS users than in CC users. In the Germany study, BOE to selected HPHCs (total NNAL, CEMA) at Month 3 were reduced from baseline in IQOS users but not in CC users.

The submitted studies are consistent in study design and population to those submitted in the original MRTPAs (i.e., randomized controlled trials of CC smokers switching to IQOS, conducted in the U.S., Japan, and Europe). Of note, none of the new studies measured the array of BOE collected in the studies in the original MRTPAs and only the U.S. extension study had a primary goal of evaluating reductions in exposure to HPHCs in smokers who switched from CC to IQOS. Two studies evaluated HPHC exposure as secondary objectives. Nonetheless, the evidence presented in the new studies is of similar quality as that presented in the original MRTPAs, and the results and conclusions are consistent with those of the original MRTPAs, that switching completely from CC to the IQOS System significantly reduces exposure to selected HPHCs.

The epidemiology review summarizes a new post-hoc analysis submitted by the applicant that assessed BOE. The analysis compared BOE among people who predominantly used IQOS (“IQOS group”), people who predominantly used CC (“CC group”), and people who were smoking abstinent (“SA group”) over 12 months. Data for the IQOS and CC groups were from selected participants who completed the 6-month U.S. study submitted in the original MRTPAs and its 6-month extension (see study 1 outlined above). Data for the SA group were from selected participants who quit smoking and maintained smoking abstinence for 12 months in a smoking cessation study (described in the BOPH section below). Epidemiology found that,

compared to people who predominantly used CC, people who predominantly used IQOS had lower blood carboxyhemoglobin levels and lower urinary concentrations of BOE to select tobacco-specific nitrosamines (TSNAs), volatile organic compounds (VOCs), and polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke, but the magnitudes of reductions were smaller than those between people who stopped smoking and who predominantly used CC.

The BCP review finds that, since the issuance of the MRGOs, the literature published on BOE continues to show that people who completely switch from CC to HTPs, including IQOS, are generally exposed to lower levels of selected HPHCs than people who continue to use CC (Drovandi et al., 2020; Nishihara et al., 2024; Tattan-Birch et al., 2022; Yuki et al., 2022). In addition, the epidemiology review identifies a Cochrane Review (Tattan-Birch et al., 2022) that found moderate-certainty evidence of lower exposure to some toxicants and carcinogens in HTP users (including IQOS) relative to CC smokers, and very low- to moderate-certainty evidence of higher exposure in HTP users relative to those attempting abstinence from all tobacco products.

Biomarkers of Potential Harm (BOPH)
The medical review summarizes four new relevant studies conducted and submitted by the applicant:

1. The 6-month U.S. extension study described in the section above.
2. A 12-month lab-based smoking cessation study conducted in the U.S., Japan, and Europe designed to document biological and functional changes related to smoking cessation in healthy smokers who are continuously abstinent from smoking for a year; no IQOS condition was included.
3. The 6-month study in Japan described above.
4. The 12-week study in Germany described above.

The changes in BOPH in IQOS users as compared with CC users in the 6-month extension study are similar to those reported at 6 months in the study submitted for the original MRTPAs. The changes in BOPH in the extension study at Month 12 are generally minor and of uncertain clinical significance. The BOPH data are insufficient to determine whether it is reasonably likely that future studies will show a measurable and substantial reduction in morbidity and mortality among individual tobacco users. Longer term follow-up is needed to determine if any further changes occur in BOPH over the long-term and if they correlate with any clinically meaningful outcomes.

The post-hoc analysis epidemiology reviewed for BOE above also assessed BOPH. Epidemiology concluded that there were few differences in BOPH between people who predominantly used IQOS and people who predominantly used CC. In contrast, the levels of most BOPH were more favorable at all timepoints among people who stopped smoking CC compared to those who predominantly used CC.

The medical review summarizes literature published since the original MRGOs assessing IQOS's effects on BOPH. Since the issuance of the MRGOs, the literature published regarding BOPH is mixed. In a recent systematic review of the impact of HTPs on BOPH, analysis of data on 143 BOPH indicated that short-term use of HTPs

had mixed effects compared with CC use, CC use abstinence, and ENDS use (Braznell et al., 2025). A small cross-over trial with 40 young adults who used CC examined changes in leukocyte count after a single trial use of CC or IQOS. Participants who used CC and those who used IQOS both had significant increases in leukocytes (Belkin et al., 2023). Another study that examined BOPH related to HTP use not specific to IQOS found that, compared to CC use, HTP use was associated with favorable levels of six biomarkers (TG, sICAM-1, WBC, 1-DHTXB2, 2,3-d-TXB2, and 8-epi-PGF2α) but unfavorable levels of four biomarkers (HDL-C, FEV1, %FEV1, and FEF25-75) (Sakaguchi et al., 2021).

In their own literature review, epidemiology identifies product-specific studies on the health effects of IQOS use focused mainly on acute cardiovascular and respiratory effects in a clinical setting. These studies found that brief IQOS use led to acute adverse effects on multiple cardiovascular and respiratory parameters (Belkin et al., 2023, Franzen et al., 2020; Goebel et al., 2023; Lyytinen et al., 2024; Pataka et al., 2020; Yaman et al., 2021), with the effects similar in direction and often in magnitude to CC use (Belkin et al., 2023, Franzen et al., 2020; Goebel et al., 2023; Yaman et al., 2021). In one of these studies (Goebel et al., 2023), increases in several measures of small airway obstruction were numerically greater after using IQOS than CC. However, these studies had small sample sizes. Consistent with these product-specific studies and as described above from the medical review, a recent systematic review on the effects of HTPs (including IQOS) on 143 BOPH and adverse events concluded that “short-term HTP use had mixed effects compared with cigarettes, e-cigarettes, and smoking abstinence” and “the rate of adverse event reporting was not significantly different between HTP and any comparator group” (Braznell et al., 2025).

Likelihood and Effects of Product Misuse

The BCP review states no new information was submitted about the likelihood and effects of product misuse from a BCP perspective, and BCP did not find any new information in the published literature.

The medical review states that clinical data in the published literature and adverse event (AE) reports indicate that HTP use can result in adverse health effects, including acute eosinophilic pneumonia and hypersensitivity reactions, and that there is a risk of accidental child exposure. Specifically, aggregated data from the postmarket experience from the medical review found that the most frequently reported serious adverse events were angina pectoris and hypersensitivity, and that accidental exposure by a child and pneumonia were the next most reported serious adverse events, but these reported events are not substantively different either in type of risk or prevalence of risk than those reported about CC. The available clinical data do not indicate that short-term use of IQOS alone presents a greater health risk than short-term use of CC; however, it should be noted that most of the randomized clinical trials with safety data were not conducted in the U.S. and have relatively short periods of follow-up. The long-term health effects of IQOS use are unknown. Additionally, the medical review included a search of the Safety Reporting Portal for Tobacco Products that identified eight reports pertaining to IQOS, none that indicated the affected person lived in the U.S.

Relative Health Risks Conclusion

The toxicology, BCP, medical, and epidemiology reviews find that HPHC exposure is reduced in IQOS aerosols relative to CC smoke. This is shown both in the toxicological assessment of the HPHCs in IQOS aerosols and in the reductions demonstrated in BOE studies. Specifically, the comprehensive testing of 108 HPHCs revealed that 107 were either below the limit of detection or quantification or present at lower concentrations in IQOS aerosols compared to CC smoke.

The toxicology review of IQOS identifies new considerations through assessment of postmarket computational toxicology studies and published scientific literature. A postmarket three-phase computational toxicology study identified 36 chemicals in IQOS aerosols with potential genotoxic/carcinogenic properties (increased from 23 in the original MRTPA review). In addition, the review of chemicals higher in IQOS than in CC indicates the potential for noncancer toxic effects. Some of the parent chemicals that were not predicted to be genotoxic or carcinogenic have metabolites with potential genotoxic or carcinogenic effects and may act as pro-carcinogens.

This information raises toxicology's level of uncertainty regarding the genotoxic and carcinogenic potential of IQOS aerosols compared to CC smoke. However, as TPL, in this case, I find that the increased number of chemicals identified in IQOS aerosols with potential genotoxic and carcinogenic properties do not preclude my overall MRTPA determination that is based on the totality of the evidence. The aerosol yields of these potentially genotoxic and carcinogenic chemicals are semi-quantitative and indicate which of the two products, CC or IQOS, has a higher level of a given chemical. The aerosol yield data for constituents evaluated in the computational toxicology study do not provide an appropriate measure of the absolute quantities in the two products (see Chemistry consultations completed to support the Advice/Information request letter). Therefore, while we know the 80 chemicals that are higher in IQOS than CC, we do not know the absolute value of the difference in the levels of these chemicals, and therefore are unable to determine from these studies whether their levels are clinically meaningful and matter for overall disease risk. In addition, out of the 80 chemicals found to be higher in IQOS than CC smoke, only 10 have semi-quantitative yields that are somewhat reliable. This further limits our ability to make any clear conclusion about the genotoxic and carcinogenic potential of these chemicals and their potential effect, if any, that would differ from FDA's previous findings. I find that, in this case, because the aerosol yields for chemicals evaluated in the computational toxicology study results are semi-quantitative and involve a high degree of uncertainty, our ability to draw clear conclusions at this time about the genotoxic and carcinogenic potential of these products are limited, and therefore these toxicological findings do not preclude my overall assessment that there continues to be substantial reduction in known cigarette-related chemicals, as articulated in the original MRTPA review

Both FDA and the applicant calculated estimated lifetime cancer risk (ELCR) estimates for IQOS versus CC and found reduced risk relative to CC. The applicant's calculations had limitations including reliance on unreliable constituent data that did not establish true quantitative values, inappropriate exposure assumptions, and exclusion of relevant carcinogenic chemicals, resulting in uncertainty about actual cancer risk. Because toxicology had to rely on the same constituent data submitted by the applicant, their ELCR was also limited. While the overall data suggests IQOS aerosols have lower toxic potential than CC

smoke, constituent data and study limitations currently limit my drawing stronger conclusions about the long-term cancer risks of using IQOS.

Overall, toxicological studies published since the MRGOs found that while short-term studies (1-8 weeks) generally indicated that CC smoke produced more severe respiratory effects than IQOS, two chronic exposure studies (6+ months) demonstrated that IQOS aerosols were associated with lung changes comparable to CC in animal models. Toxicology reviewed 71 scientific studies and identified 13 studies, which assessed a range of health-related outcomes, that found that IQOS aerosols had equivalent or worse adverse toxicological effects on the specified outcome compared to CC, and in some cases, the study identified toxicities or adverse outcomes that were found in IQOS and not in CC. These published studies raise toxicology's level of uncertainty regarding the toxicological effects of IQOS aerosols compared to CC smoke.

Of issue to toxicology were the outcomes of three studies. Specifically, toxicology stated PMP S.A. did not adequately address two studies related to respiratory toxicity (Gu et al., and Nitta et al.) and one related to cardiovascular toxicity (Qiu et al.) in their response to FDA's Advice/Information request letter. Although these three studies have limitations, the findings raise toxicology's uncertainty regarding whether the noncancer toxic effects of exposure to IQOS aerosols are reasonably likely to be substantially lower than the effects of CC smoke exposure. As TPL, in this case, I find that these studies *do* raise questions that require continued observation and assessment but that these observed outcomes do not preclude the issuance of an exposure modification MRTPA renewal at this time. Consumers who use IQOS are inhaling multiple heated constituents into their lungs over time. It is reasonable to conclude that this exposure can lead to negative health effects but in general those effects may be reduced in comparison to CC use.

As a reminder from the beginning of Section 3.2, the 2020 MRTPA TPL review provided a comprehensive evaluation of the health risks associated with IQOS products, with particular focus on substantiating the proposed modified exposure claims. The review examined four main areas: combustion, production of HPHCs, nonclinical toxicological assessment, and clinical assessment.

The analysis of HPHCs revealed substantial reductions compared to CC smoke. Of the 108 chemicals tested, 107 were either undetectable or present at lower concentrations in IQOS aerosols versus CC smoke. Overall, chemicals were reduced by 47-99.9% on a per stick basis and by 20-99.8% when normalized to nicotine levels, with only nicotine and anabasine as exceptions. While some compounds—including menthol-related constituents, alkaloids, and flavors—were found exclusively or at higher levels in IQOS aerosols, the yields of carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower than in CC smoke. Based on these substantial reductions, the 2020 review concluded there was sufficient evidence to support the modified exposure claim that heating tobacco without burning it "significantly reduces the production of harmful and potentially harmful chemicals."

The nonclinical toxicological assessment in 2020 demonstrated that IQOS HeatSticks aerosols had reduced toxic potential compared to CC smoke across multiple testing methods. In vitro studies showed reduced cytotoxic and mutagenic potential, while in vivo rat studies revealed fewer or less severe histopathological changes with HeatSticks aerosol

exposure. Human organotypic tissue studies yielded two general outcomes: either fewer pathophysiological changes and adverse effects from HeatSticks aerosols compared to RCS, or similar changes and effects but only when IQOS aerosol exposure occurred at higher concentrations than RCS exposure. However, the 2020 review identified important limitations that prevented drawing more definitive conclusions about relative health risks that would have been required to support the applicant's then-proposed (g)(1) reduced risk claims. Systematic differences in collection methods created uncertainty in interpreting results, and the applicant provided only limited toxicological evaluation of the 80 potentially harmful chemicals found exclusively or at higher concentrations in HeatSticks aerosols compared to CC smoke.

The clinical studies likewise provided evidence that completely switching from CC to IQOS significantly reduced exposure to HPHCs. Four 5-day studies demonstrated that complete switching resulted in reduced HPHC exposure with a magnitude similar to complete smoking abstinence. Two 90-day studies conducted in Japan and the United States showed reductions in BOE to 15 chemicals among individuals who switched completely from CCs to IQOS, with these reductions spanning multiple chemical and toxicity classes. The 2020 review stated that, "While the predictive value of the chosen BOE for long-term tobacco-related disease risk remains unclear and longer-term studies are needed to confirm the overall health impact of switching to IQOS…" the exposure reduction evidence supported the claim that switching completely to IQOS from CC "significantly reduces your body's exposure to harmful or potentially harmful chemicals."

Overall, the 2020 MRTPA TPL review used available indirect evidence to evaluate whether the observed reduction in exposure to chemicals with complete switching from CCs to IQOS was likely to translate into a "measurable and substantial reduction in morbidity and mortality among individual tobacco users," one of the statutory requirements for authorizing the marketing of modified risk products with reduced exposure claims. While IQOS use still exposes users to HPHCs and would be expected to cause harm, the level of exposure was expected to be lower relative to CCs and thus a measurable and substantial reduction in morbidity or mortality among individual tobacco users was reasonably likely in subsequent studies.

When considering the totality of the data about IQOS both in this renewal and the data included to support the original MRTPAs, including the levels of HPHCs and other chemicals in the aerosol, toxicological outcomes, BOE data, and BOPH data, I find a measurable and substantial reduction in tobacco-related morbidity and mortality outcomes among individual tobacco users is reasonably likely when comparing IQOS to CC.

The studies that are of issue to toxicology rely on animal models. Currently, the applicability of results from these animal models to conclusions about long-term human health outcomes for IQOS aerosols does not outweigh the totality of the evidence from all disciplines. The limitations of translating animal models to human health outcomes in general, paired with the specific limitations of these studies reviewed by toxicology, underscore the importance of considering many lines of evidence when evaluating health risks and what the totality of evidence indicates (Bell, 2019; Mak et al., 2014; Marshall et al., 2023; Seok et al., 2013).

Undeniably, several HPHCs present in IQOS should receive further scientific scrutiny, and

questions about toxicity and human health risk need to be monitored postmarket. Nevertheless, I find that, in this case, the toxicological assessment of IQOS aerosols in these animal models do not preclude my assessment that it is appropriate to renew the exposure modification orders for these MRTP renewals at this time and that the MRTPs 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.

To evaluate clinical assessments of individual health effects, the BCP, medical, and epidemiology reviews examined BOE data, BOPH data, and other health effects outcomes. Applicant-submitted BOE studies and the scientific literature both showed that there is lower HPHC exposure in IQOS users compared to CC smokers, but higher exposure than those abstaining from tobacco products. Applicant-submitted BOPH studies and the scientific literature both had mixed effects, with some favorable BOPH changes but also some minor BOPH changes or BOPH with no improvement when switching from CC to IQOS. Assessment at multiple time points can facilitate the evaluation of clinical relevance of these changes. The published scientific literature on the relative health effects for users of IQOS and other HTPs has been generally limited to acute or short-term outcomes, leaving the long-term health effects of IQOS and HTPs as a class generally unknown. Limited published evidence indicates that, like exposure to CC, exposure to IQOS can have acute detrimental effects on the respiratory and cardiovascular systems. Overall, conclusions from the applicant-submitted studies and the scientific literature are in line with conclusions from the original MRTPAs that longer-term studies are needed to evaluate the overall health impact of switching to IQOS. Although the use of the IQOS system clearly still exposes users to HPHCs and would be expected to cause harm, the demonstrated reductions in exposure relative to CC are reasonably likely to, in general, translate to lower risk of tobacco-related morbidity and mortality. While new evidence raises some questions related to individual health risks, the data reviewed does not change the overall conclusions from the original MRTPAs that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Synthesis and Conclusion of Relative Health Risks

The toxicology, BCP, medical, and epidemiology reviews conclude that no new information, including the published scientific literature, changes the original FDA assessment regarding claim substantiation. Overall, they found that HPHC exposure is reduced in IQOS relative to CC smoke. This is shown both in the toxicological assessment of the HPHCs in IQOS aerosol and in the reductions demonstrated in BOE studies.

As with the original MRTPA assessment, questions about the health effects of long-term IQOS use remain, demonstrated by the uncertainty in the toxicological assessment of additional constituents in IQOS, the new toxicological studies related to health effects in animal models, and the lack of compelling evidence to date related to reductions in BOPH for IQOS relative to CC use. These limitations underscore the importance of considering many lines of evidence when evaluating health risks and what the totality of evidence indicates. As with the original MRTPA assessment, in the absence of long-term health data, determinations about the likely effects on morbidity and mortality were based on constituent data, mainly that the totality of the evidence demonstrated a substantial reduction in HPHCs in IQOS aerosols relative to CC smoke. The unresolved uncertainty about additional constituents in IQOS, the publications utilizing animal models, and the lack of BOPH reduction in IQOS relative to CC is not sufficient to change conclusions drawn in the

original MRGOs given the reduction in HPHCs. That is, the new evidence is not enough to override the findings in the original MRGOs that "there is an overall reduction in exposure to respiratory as well as reproductive and developmental toxicants" from IQOS aerosols relative to CC smoke. Further supporting this conclusion, committee members in TPSAC drew similar conclusions that IQOS is reasonably likely to pose less risk of harm than CC.

The applicant-submitted scientific evidence and the new evidence in the published literature continues to substantiate that relative to CC smoking, exclusive use of IQOS reduces exposure to HPHCs. Accordingly, as TPL, I find that the available scientific evidence demonstrates that exclusive use of IQOS products will significantly reduce exposure to HPHCs and that the claim continues to be scientifically accurate:
"AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."

3.3. CONSUMER UNDERSTANDING AND PERCEPTIONS

Key Findings from Original MRTPA TPL Review

The 2020 MRTPA TPL review found that consumer perception studies demonstrated that after viewing labeling and advertising materials with the reduced exposure claim, consumers perceived IQOS as presenting moderate risks for tobacco-related diseases and health effects, with risks lower than CC but higher than quitting smoking or using nicotine replacement therapy. These perceptions aligned with the reasonably likely relative health risks of the product, and similar patterns were observed even without the modified exposure claim, suggesting product features beyond the labeling contributed to risk perceptions. The evidence supported that consumers comprehended the modified exposure information in the context of total health, understanding that IQOS is not risk-free and is more harmful than smoking cessation.

The 2020 MRTPA TPL review noted some considerations regarding consumer understanding, including misperceptions that IQOS is less addictive than CC despite similar abuse liability, which was addressed through required nicotine addiction warnings on packaging and advertising. A gap existed in consumer understanding of the difference between exclusive IQOS use versus dual use with other tobacco products. The applicant did not assess consumer perceptions of partial switching risks, so the TPL required that the applicant's postmarket surveillance assess whether consumers understand that continued smoking CC alongside IQOS use negates the reduced exposure benefits described in the modified exposure claim.

Evaluation of New MRTPA Data

The applicant's PMSS requirements included an assessment of consumer perceptions of the products and understanding of the claim, particularly that:

- To reduce their exposure to HPHCs relative to CC, users of CC must use IQOS products exclusively and cutting down on CC per day while using IQOS products is not sufficient, and

- Users of other tobacco products who switch to IQOS products understand that the reduction in exposure to HPHCs is relative to CC use and not to other types of tobacco use.

The social science review evaluated one new relevant study submitted by the applicant that assessed consumer understanding, the *IQOS Cross-sectional Postmarket Adult Consumer Study (PACS)*, an online, cross-sectional survey administered annually over four years beginning in 2021. Risk perceptions and understanding were assessed via questions asked to "ever established IQOS users" (defined as having used at least 100 Marlboro HeatSticks in their lifetime) in the U.S. There were 463 participants, of whom 439 were "current established IQOS users" and 24 were former IQOS users. "Current established IQOS users" were defined by self-report as an IQOS user who now uses IQOS "every day" or "some days."

The median age of the current established IQOS users was 44 years. Approximately 60% of them were male; 72.9% were non-Hispanic White and 14.4% were non-Hispanic Asian. Approximately 61% of current established IQOS users had a household income of $60,000 or more; 78.8% had some college or more education and 80.6% were employed. These data suggest that current established IQOS users in the study tended to be middle-aged men with relatively high socioeconomic status. These characteristics of the sample population are different than the population of U.S. adults who smoke CC (Cornelius et al., 2022), suggesting that consumer understanding outcomes from the PACS may not be generalizable to the U.S. population of adults who smoke CC.

The social science review identified several study limitations of the PACS. Notably, the survey did not include the modified exposure claim and did not ask participants about whether they had seen the modified exposure claim, so it is unknown how much influence the claim itself had on consumer perceptions. In addition, the number of former established IQOS users in the sample (n=24) was too low for some statistical analyses, limiting conclusions that could be made about former IQOS users' understanding.

Understanding of the Exposure Reduction Described in the Claim

The findings from the PACS support that IQOS users (overall and broken down by CC use status) rated the risk of CC smoking as higher than the risk of using IQOS but still believed that IQOS use carried some amount of risk.

To assess how current established IQOS users perceive HPHC exposure if CC users switch completely from CC to IQOS, participants were asked "Based on what you know or believe, please complete the following: Smokers who switch completely from cigarettes to IQOS:" and then participants could respond in one of five ways, "Have more exposure to harmful or potentially harmful chemicals," "Have the same exposure to harmful or potentially harmful chemicals," "Have less exposure to harmful or potentially harmful chemicals," "Have no exposure to harmful or potentially harmful chemicals," or "Don't know." A total of 80.9% of current established IQOS users responded that smokers who switch completely from cigarettes to IQOS "have less exposure to harmful or potentially harmful chemicals." Of those who did not choose the less exposure option when asked about completely switching, 8.9% of individuals responded that switching completely to IQOS would lead to the same HPHC exposure and 0.7% of individuals responded that switching completely to IQOS would lead to more HPHC exposure. In addition, 4.8% of

participants responded that switching completely to IQOS would lead to "No exposure" to HPHCs. An additional 4.8% responded "Don't know." These results are consistent with findings submitted in the original MRTPAs and suggest that most current established IQOS users understand that switching completely to IQOS from CC reduces their exposure to HPHCs.

Social science could not compare the postmarket findings with consumers' understanding of the exposure reduction claim in the original MRTPAs, as the applicant did not ask the same question about switching in its premarket research.

Understanding Health Risk Relative to Nonuse, Cessation, and Cessation Therapies

Though the applicant did not submit data comparing risk perceptions of IQOS relative to cessation therapies, nonuse, or cessation, the applicant did assess absolute risk perceptions of health outcomes related to IQOS use. Comparing risk perceptions of IQOS in the PACS to the applicant's data from the original MRTPAs, the social science review concluded that consumers continue to understand that IQOS use presents more risk than using cessation therapies or quitting tobacco use altogether.

Understanding How to Use the MRTP to Reduce Exposure

The PACS asked participants what CC users need to do in order to reduce their body's exposure to HPHCs. This question was only asked of participants who correctly answered "less exposure" to the question about perceptions of HPHC exposure when switching completely from CC to IQOS. Results showed that 85.4% of participants responded that people who use CC would need to completely stop smoking and only use IQOS to get the conveyed benefits. Among the 14.6% who did not understand or misunderstood how to reduce exposure to HPHCs, the most common responses were "Smoke fewer cigarettes and also use IQOS" (7.9%) and "Don't know" (5.9%).

Synthesis and Conclusion of Consumer Understanding

The social science review concluded that the applicant demonstrated that most study participants understood that "switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."

The social science review also concluded the evidence submitted in the renewal is consistent with the conclusions in the 2020 MRTPA TPL review and shows that consumers understand the reasonably likely risks of using IQOS. In addition, the review concluded that participants understood that people who use CC must completely switch from CC to IQOS to get reduced HPHC exposure. Though social science noted study limitations of the PACS, such as the small sample recruited from the applicant's IQOS user database, the results from the PACS mirror the studies submitted for the original MRTPAs, and do not indicate any large changes in consumer understanding from the initial MRTPA review.

Overall, the evidence supports the conclusion that the advertising and labeling concerning the MRTPs enable the public to comprehend the information concerning modified exposure and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.

3.4. TOBACCO USE BEHAVIOR AND IMPACTS TO THE POPULATION AS A WHOLE

Key Findings from Original MRTPA TPL Review

The 2020 MRTPA TPL review assessed abuse liability of IQOS, patterns of IQOS use, the likelihood of use after exposure to the MRTP claim, impacts to non-users of tobacco, and a population health impact model.

Abuse Liability

Clinical studies demonstrated that IQOS delivers systemic nicotine exposure similar to CC for both menthol and non-menthol products, with sufficient levels to provide user satisfaction that may facilitate complete switching from CC. Self-reported measures of craving, withdrawal, dependence, and reinforcing effects were comparable between IQOS and CC, leading to the conclusion that IQOS will likely have similar addictive potential and abuse liability. While this supported IQOS as a viable replacement product for current CC users seeking reduced exposure benefits through complete switching, the similar abuse liability also creates addiction risks for non-users, particularly youth, underscoring the importance of preventing youth access and exposure to both the product and its marketing.

Likelihood of Use

Observational studies showed that dual use with CC was the predominant pattern of IQOS use, with exclusive use ranging widely from 7.5% in the U.S. to 65% in Japan, which did not provide strong support for population-level benefits because exclusive use is required for exposure reduction. However, U.S. studies were conducted over short time frames without marketing with the modified exposure claim, making it unclear whether dual use represents sustained behavior or a transition state, and whether marketing with the claim was likely to change these patterns of use.

Studies summarized in the 2020 MRTPA TPL review assessed adult CC smokers' intentions to try IQOS. Results showed substantial interest among current CC smokers, with 40-44% of all CC smokers with no intention to quit CC smoking expressing they would "definitely" or "very likely" try IQOS when exposed to LLA that did not include the modified exposure claim. Importantly, adding the reduced exposure claim to LLA materials did not significantly increase CC smokers' intentions to use IQOS compared to materials without claims, though the high interest in the product supported the conclusion that authorization with the reduced exposure claim would positively impact population health.

Impacts to Non-users of Tobacco

Studies summarized in the 2020 MRTPA TPL review found that adding the proposed exposure claim to LLA materials did not appear to increase adult or young adult never smokers’ or former smokers’ intentions to use IQOS. The applicant did not directly study whether modified exposure claims would increase youth uptake of IQOS, though published studies from Italy and Japan suggested low youth use in those countries, and the applicant found no evidence that adding claims increased young adult never CC smokers' intentions to use IQOS.

Evaluation of New MRTPA Data

Impacts to Users of Tobacco Products

Abuse Liability

BCP reviewed new nicotine BOE and subjective effects data from three postmarket studies to evaluate the abuse liability of IQOS (studies described in Section 3.2).

In the applicant's U.S.-based extension study, product use did not change significantly from baseline in either the IQOS or CC product use groups demonstrating that abuse liability did not change across the study period. Exposure to nicotine was comparable among the IQOS-use, Dual-use, and CC-use groups, based on urinary nicotine equivalents (Neq) levels and on plasma nicotine and cotinine concentrations at Month 12, consistent with what was observed in the 3- and 6-month results that were reviewed as part of the original MRTPAs. In addition, subjects' self-reported scores for subjective effects were similar between IQOS and CC users for aversion, psychological reward, craving reduction, enjoyment of respiratory tract sensation, and smoking satisfaction throughout the study. However, a slightly lower psychological reward score in the IQOS-use group compared to the CC use group was observed at Month 12. Overall, findings from this study support that the nicotine exposure and subjective effects following exclusive use of IQOS are comparable to CC at Month 12, suggesting comparable abuse liability to CC for IQOS.

Two international postmarket studies were submitted and reviewed by BCP. The results of these studies should be interpreted with caution as it is unclear whether the products used have the same characteristics as those subject to the current MRTPA renewal. In one postmarket study conducted in Japan, switching from CC to IQOS resulted in comparable daily self-reported tobacco consumption (CC and HeatSticks) at follow-up compared to baseline levels of self-reported consumption (CC only). No significant differences were found in Neq levels at Month 6 follow-up among CC users, dual users, or IQOS users compared to baseline, suggesting comparable nicotine exposure and abuse liability between IQOS and CC. Additionally, in a separate study from sites in Europe, at Month 3 follow-up, Neq was slightly, but not significantly, decreased from baseline in the CC and IQOS groups while Neq was significantly decreased from baseline in the CC smoking abstinent product use group (-90.5%). Although it is unclear whether the products in these studies have the same characteristics as those subject to the MRTPA renewal, the findings are similar to the U.S.-based extension study and further suggest comparable nicotine exposure and abuse liability between IQOS and CC.

The cross-sectional PACS was conducted to provide survey data from U.S. adult established IQOS users to assess use and perceptions of the products. The Heaviness of Smoking Index (HSI) was used to measure dependence among established IQOS users who were either dual users of IQOS and CC or current

exclusive IQOS users. Most current IQOS users had a moderate addiction level, as indicated by a median HSI score of 3, while the subset of dual users of IQOS and CC had a slightly lower median HSI score of 2. These data support the nicotine exposure findings that dependence is comparable between exclusive and dual users of IQOS.

BCP also conducted a literature search of studies published after the MRGOs and found that nicotine is not reduced following switching from CC to IQOS and the abuse liability of IQOS is comparable to CC, supporting the conclusions from the original MRTPA (Rabenstein et al., 2023; Yuce et al., 2025, and Yingst et al., 2024). For example, one study conducted with experienced IQOS users reported no statistically significant difference in nicotine exposure between IQOS and CC after 90 minutes of ad libitum use of the products (Rabenstein et al., 2023).

Patterns of Use

IQOS Cross-Sectional PACS

Epidemiology reviewed patterns of use data submitted about IQOS from the IQOS Cross-Sectional PACS (described in Section 3.3). The IQOS Cross-sectional PACS included U.S. adult (21 years or older) ever established IQOS users, which the applicant defined as having used at least 100 Marlboro HeatSticks in their lifetime. The analytical sample consists of 463 individuals, including 439 current established and 24 former established IQOS users.

Retrospectively recalling their history of tobacco use, in the 30 days prior to trying IQOS, 93.4% of the 439 IQOS users reported being ever established CC smokers and 91.6% reported being current CC smokers. At the time the survey was completed, 99.3% of current established IQOS users reported ever trying CCs, and only 0.7% reported never trying CCs. Additionally, 96.6% of the current established IQOS users were ever established CC smokers, 50.6% of participants were former CC smokers, and 48.8% were current CC smokers. Note that these final percentages of former and current CC smokers include participants who never smoked enough to be considered established CC smokers. Overall, these results suggest that the vast majority of current established IQOS users in the study were ever established CC smokers, many of whom were smoking CC when they initiated IQOS use.

Current established IQOS users had used IQOS for a median of 0.9 years. Approximately 70% of them used IQOS daily in the past 30 days. On the days they used IQOS, the median number of HeatSticks used per day was 15. These data suggest that current established IQOS users in the study used IQOS frequently.

Approximately 35.0% of the current established IQOS users used IQOS exclusively. The majority (64.9%) of current established IQOS users used IQOS with one or more other tobacco products: 29.2% dual used IQOS and CC, and 19.6% used IQOS, CC, and one or more other tobacco products. This means that 48.8% of all current established IQOS users also used CC, with many reporting

daily CC use. These data suggest concurrent use of IQOS and CC is a common pattern of use.

Because IQOS was removed from the market in the U.S. due to the CDO issued by the U.S. International Trade Commission on September 29, 2021, the applicant did not examine the incidence of complete switching prospectively. Instead, they reported participants' recall of past behaviors and calculated complete switching retrospectively using the percentage of current established IQOS users who reported having "completely switched" from CC to IQOS in the IQOS Cross-sectional PACS. The cross-sectional study design among IQOS users cannot assess the relationship between IQOS use and completely switching temporally among CC users but does give us some ideas about self-reported switching upon initial introduction to IQOS among IQOS users.

The applicant stated that, among the 439 current established IQOS users, 31.2% had switched completely from CCs to IQOS after first trying IQOS. As for smoking reduction, they stated that "most IQOS users who currently smoked cigarettes at the time of the survey (83.1%) stated that they used fewer cigarettes now than before they tried IQOS." Because of the cross-sectional nature of the study, it is unclear whether this reduction in CC smoking is a transitional behavior that could lead to completely switching or whether this dual use of CCs and IQOS is a more entrenched behavior pattern.

Impacts to Nonusers of Tobacco Products Including Youth

Epidemiology reviewed two studies that addressed impacts to nonusers of tobacco. The applicant planned to conduct two surveys, the Underage Tobacco Use Survey (UTUS) and the Adult Tobacco Consumer Tracking (ATCT) study to assess IQOS use among the general youth and adult populations.

- The UTUS was an ongoing, quarterly repeated cross-sectional survey of tobacco use behaviors in youth and young adults aged 13-20 years in the U. S. The study reported the awareness of IQOS and the prevalence of ever and past 30-day IQOS use for youth.
- The ATCT Study was an ongoing, monthly repeated cross-sectional survey of tobacco use behaviors in U.S. adults aged 21 years or over.

In both studies, the number of IQOS users was very low at each survey time point, understandably so as these data were collected mostly while IQOS was not in the U.S. marketplace. Among the approximately 19,000- 28,000 individuals in each pooled annual sample of the ATCT, few current IQOS users were identified (0 in 2020/2021; 3 in 2021/2022; 3 in 2022/2023; and 4 in 2023/2024). Because these data were collected when IQOS was not on the market, the ability to make conclusions about the uptake of IQOS in the general adult population in the U.S. is limited.

The epidemiology review notes the prevalence of ever and past 30-day IQOS use among youth and young adults in UTUS was also extremely low. Overall, in samples of over 5,000 participants each year, no more than 36 youth and young adults

reported ever use of IQOS in a given reporting year, and no more than 8 reported past 30-day IQOS use.

Youth and Young Adult Awareness

Social science also reviewed UTUS results regarding awareness of IQOS among youth and young adults. The applicant's 2024 annual report included IQOS-related analyses with 4,565 individuals. Approximately 5.5% (weighted; n=255) of the analytic sample had seen or heard of IQOS between March 2023 and April 2024. However, of those 255 participants, only about 16% (weighted; n=41) correctly identified the best description of IQOS. Among those who had seen or heard of IQOS, the most common source of awareness was friends, peers, or classmates (39%) followed by seeing advertisements at gas stations, convenience stores, or other retail (20%). Overall, findings from this study suggests low awareness of IQOS among youth and young adults, understandable given that IQOS was not marketed in the U.S. due to the CDO.

Population Health Modeling

The applicant developed a Population Health Impact Model (PHIM) v8.2 to estimate the health impact of introducing IQOS to the market on the total population. The model projected the number of smoking-attributed deaths between ages 30-79 from lung cancer, chronic obstructive pulmonary disease, ischemic heart disease, and stroke for people aged 10-79 years from 2010 to 2080, assuming an introduction of IQOS in 2024, and found a reduction in deaths of 15,519. This model has several limitations, such that key aspects of the model's structure, assumptions, and inputs were not clearly described or justified. Had it been possible, it would have been preferable to use estimates from the applicant's PMSS as inputs for IQOS-related transition probabilities. However, this was not feasible due to the removal of IQOS from the U.S. market. Consequently, the PHIM was not informative for epidemiology's review.

Sales Data

Generally speaking, IQOS was not sold in the U.S. outside of Georgia, Virginia, North Carolina, and South Carolina during the MRGO authorization period.

On September 29, 2021, in relation to a patent-infringement case, the U.S. International Trade Commission issued a CDO which prohibited the importation, sale, and distribution of imported IQOS products (including their components) in the U.S. beginning November 29, 2021. The applicant has stated that the products specified in Appendix A were removed from the market on November 28, 2021, pursuant to this order. Philip Morris International announced on February 2, 2024, that a global settlement was reached that allowed the reintroduction of IQOS products to the U.S. However, these products were not re-launched in the U.S. until March 2025. This means that IQOS products were only available in the U.S. for approximately 17 months during the MRGO authorization period.

In summary, these products were only available in select geographies and only for a limited amount of time. This limited availability makes it difficult to draw

conclusions about sales at a national level and about the impact of the original MRGOs based on sales data.

Synthesis and Conclusion about Tobacco Use Behavior

The original MRTPA TPL review found that IQOS has similar abuse liability and addictive potential to CC, delivering comparable nicotine exposure and a level of user satisfaction that supports complete switching for current CC smokers but creates addiction risks for non-users, particularly youth. Observational studies showed dual use with CC was the predominant pattern of use, with exclusive use varying widely by region (7.5% in the U.S. to 65% in Japan), though short study timeframes made it unclear whether this represents sustained behavior or a transition state. Adult CC smokers reported interest in trying IQOS, but adding the reduced exposure claim did not significantly increase intentions to use it. There was little to no interest in trying IQOS among former and never CC users, and the applicant did not submit youth-specific evidence.

In the current MRTPA review, BCP utilized new nicotine BOE and subjective effects data to evaluate IQOS abuse liability, finding that nicotine exposure remained comparable between IQOS users, dual users, and CC users across multiple studies. Self-reported subjective effects (e.g., craving reduction and smoking satisfaction) were also similar between IQOS and CC users. The cross-sectional study of established IQOS users showed that most had moderate addiction levels regardless of whether they were dual users with CC or exclusive IQOS users. Additionally, BCP's literature search of post-MRGO studies confirmed that nicotine is not reduced when switching from CC to IQOS and that IQOS abuse liability remains comparable to CC, supporting the original MRTPA conclusions regarding abuse liability.

Regarding patterns of IQOS use in users of tobacco products, the epidemiology review reported that current established IQOS users in PACS were predominantly middle-aged men with relatively high socioeconomic status. These users had been using IQOS for a median of 0.9 years, with approximately 70% using it daily and consuming a median of 15 HeatSticks per day when using IQOS. The vast majority (96.6%) of current IQOS users were ever established CC smokers, with 91.6% being current CC smokers in the 30 days prior to trying IQOS.

Only 35.0% of current established IQOS users used the product exclusively, whereas 64.9% used IQOS with one or more other tobacco products. While 31.2% of current established IQOS users reported having "completely switched" from CCs to IQOS after first trying the product, the implication of this finding on the likelihood of switching from CC to IQOS among CC users is unclear. The IQOS cross-sectional PACS included only ever established IQOS users and its cross-sectional study design cannot assess the temporal relationship between IQOS use and switching behavior. Additionally, 83.1% of current dual users reported using fewer CC than before trying IQOS, though it is unclear whether this reduction in CC smoking is a transitional behavior that could lead to completely switching or whether dual use of CC and IQOS is a more entrenched behavior pattern.

Regarding nonusers of tobacco products, due to low numbers of IQOS users identified in postmarket surveys, the applicant could only report basic counts and prevalence data. Results indicated very low prevalence of ever and current IQOS use, but this data was collected mainly when IQOS was not in the U.S. marketplace, making it difficult to make conclusions about uptake of IQOS in the general U.S. population. Awareness of IQOS among

youth was low; only 0.9% of youth surveyed (N = 4,565) had heard of IQOS and were able to correctly identify it.

3.5. MARKETING AND LABELS, LABELING, AND ADVERTISING (LLA)

Evaluation of New MRTPA Data

We consulted the Office of Health Communication and Education (OHCE) to review the applicant's marketing materials and LLA. The OHCE review noted that, prior to the CDO requiring removal of the products from the U.S. market, the applicant advertised the products via company-owned retail stores, email, direct mail, print media, digital paid media, branded social media pages, point-of-sale signage at third-party retailers, brochures, guides, face-to-face interactions, paid affiliate activities, consumer engagements, and branded websites.

To minimize youth exposure to the products' advertising, the applicant employed measures such as requiring age- and identity-verification at the first point of access to its branded websites and using only social media platforms with age-restriction controls. The applicant also conducted ongoing media tracking and optimization, including developing procedures to take corrective or preventative measures to address delivery of advertising to youth. OHCE concluded that the applicant's advertising and marketing plan implementation appears reasonably targeted to its intended audience and that the applicant has taken appropriate actions to limit youth exposure to the products' advertising and marketing.

The social science review did not identify potential implied modified risk claims or additional express modified risk claims that were outside the scope of the MRGOs in the marketing materials and LLA submitted by the applicant since the MRTP authorization. The review did identify LLA reported in PMSS reports that included additional language added to the claim and extrapolating from the claim. Social science concluded some of the identified statements are rewordings of the authorized claim but convey the intended message of the authorized language. The OCE Division of Promotion, Advertising, and Labeling (DPAL) reviewed the same LLA submitted by the applicant in PMSS reports and concluded that the labeling and advertising contained in the submission is compliant with the applicable provisions of the FD&C Act and the marketing and modified risk granted orders.

Further, OCE DPAL reviewed the proposed and current marketing materials and LLA and concluded there is no evidence to suggest the labeling samples submitted in the renewal MRTPAs are false or misleading or outside of the scope of the initial MRGOs.

4. ENVIRONMENTAL IMPACT

4.1. DISCIPLINE FINDINGS

The following key findings were provided in the environmental science review.

The products subject to this exposure modification renewal review are those products identified in the original MRGOs. The applicant's cross referenced environmental assessments (EAs) and FDA's prepared EA for the original PMTAs MGO and the original MRTPAs MRGOs showed no changes in the environmental effects. Therefore, the manufacture, use, and disposal of the products are not expected to contribute to any significant new or additional environmental impacts.

Potential Environmental Impacts from Product Manufacturing and Alternatives
The applicant stated that information related to the environmental effects as submitted with the initial MRTPAs and PMTAs with related appendices and data, remains valid and does not require reanalysis for these renewal MRTPAs. Consequently, environmental science does not expect the continued marketing of the new products with the modified exposure claims would affect the environmental effects associated with the manufacturing of the MRTPs.

Potential Environmental Impacts from Product Use and Alternatives
The applicant stated that information related to the environmental effects as submitted with the initial MRTPAs and PMTAs with related appendices and data, remains valid and does not require reanalysis for these renewal MRTPAs. Consequently, environmental science does not expect the continued marketing of the new products with the modified exposure claims would result in the direct introduction or changes in the ingredients due to the use of the MRTPs.

Potential Environmental Impacts from Product Disposal and Alternatives
The applicant stated that information related to the environmental effects as submitted with the initial MRTPAs and PMTAs with related appendices and data, remains valid and does not require reanalysis for these renewal MRTPAs. Furthermore, the MRTPs and any associated waste will be disposed of in the same manner as the IQOS products without a modified exposure claim. Therefore, no new environmental effects are anticipated from disposal of these products being marketed as MRTPs.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Hans Rosenfeldt on April 17, 2026. The FONSI was supported by an EA prepared by FDA on April 16, 2026.

5. MR0000292 AMENDMENT: CIGARETTE DEFINITION AND SURGEON GENERAL'S WARNINGS

On August 4, 2025, PMP S.A. submitted an amendment, MR0000292, asserting that IQOS does not meet the statutory definition of a cigarette and therefore should not be required to bear the following three required Surgeon General's warnings on their product labeling and advertising:

- "**SURGEON GENERAL'S WARNING**: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy."
- **"SURGEON GENERAL'S WARNING**: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health."
- **"SURGEON GENERAL'S WARNING**: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight."

Additionally, PMP S.A. argues that the Surgeon General's warnings are scientifically inaccurate and misleading to consumers as applied to IQOS, and that the agency lacks substantial evidence to support the requirement of including the Surgeon General's warnings. As noted above, assessing whether IQOS meetings the definition of a cigarette for the purposes of the Surgeon General's warnings does not fall within the scope of MRTPA review under section 911.[12] The term "smoking" in

[12] Section 3(1) of the Federal Cigarette Labeling and Advertising Act (FCLAA) defines cigarette as "(A) any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (B) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette." Contrary to PMP S.A.'s assertion, IQOS also meets the definition of a "cigarette" at section 900(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

the Surgeon General's warnings applies to use of IQOS.[13] Therefore, the applicant's current request to remove the Surgeon General's warnings is an implied modified risk claim that the products cannot cause the health outcomes in the warnings that we would consider in a new MRTPA. Additional evidence would need to be provided by the applicant to establish that removal of the Surgeon General's warnings meets the standard set forth in section 911(g)(1), as well as evidence to establish that the updated advertising and labeling enable the public to comprehend the information concerning modified risk and understand the relative significance of the information in the context of total health under section 911(h)(1). The application that includes such new evidence would also be required to be referred to the Tobacco Products Scientific Advisory Committee (TPSAC) under section 911(f). To provide additional information to the applicant on the process of removing the Surgeon General's warnings, FDA intends to send a separate General Correspondence Letter to PMP S.A.

5.1. SURGEON GENERAL'S WARNINGS

As noted above, three Surgeon General's warnings are currently required for these MRTPs as stated in the MGOs for PM0000424-PM0000426 and PM0000479. FDA considers this request for the removal of required health warnings to be implied modified risk claims that, unlike other products that meet the definition of a cigarette, IQOS cannot cause the health outcomes named in the warnings.

The proposed removal of the remaining three warnings is not supported by this MRTPA renewal application, even when considering information in the prior PMTAs and prior MRTPAs. These three warnings focus on health risks including cancer, other tobacco-related diseases, and pregnancy complications. The evidence PMP S.A. submitted to substantiate their MRTPA claim demonstrates reduced exposure to harmful chemicals but does not demonstrate reduced health risk. PMP S.A., in their original MRTPAs, requested claim authorization under section 911(g)(1) for risk reduction and section 911(g)(2) for exposure reduction. The authorization was made only for the exposure reduction claim following FDA review of both claims. Specifically, the original MRTPA TPL review stated, "Although the available scientific evidence shows that the IQOS system produces lower concentrations of many harmful and potentially harmful constituents (HPHCs) compared to cigarette smoke and the non-clinical data suggests a favorable toxicological profile of the IQOS system compared to combusted cigarettes, the overall body of evidence was not sufficient to demonstrate that completely switching from combusted cigarettes to the IQOS system reduces the risk of tobacco-related disease or harm. Relatedly, there is no direct clinical or epidemiological evidence of risk reduction, and the available evidence is insufficient to demonstrate that the product, as actually used by consumers, will significantly reduce harm and risk to individual users and benefit the health of the population as a whole."

Similarly, the additional data submitted by PMP S.A. for renewal of their section 911(g)(2) claim does not support removal of the warnings.[14] As concluded below in Section 6.2, "Heated

[13] See the Memorandum "IQOS heated tobacco products and clarification of the terms "smoke" and "smoking"," signed April 15, 2026, for the assessment of the applicability of "smoke" to IQOS products.

[14] As part of the amendment, PMP S.A. included a consumer perception study. Details of the methodology of the consumer perception study were not included in the amendment provided by the applicant (MR0000292), and were instead included in the TPMF(b)(4), an amendment to (b)(4). The amendment (MR0000292) did include a brief summary of the study. Based on the information provided, the study focuses on product categorization and does not assess consumer

tobacco products are a novel type of tobacco product, and as such, long-term health data with which we can evaluate these products remain limited. The applicant did not submit any observational or clinical studies to support claims related to long-term health outcomes associated with IQOS." IQOS still exposes users to many of the same HPHCs as CCs, just at lower levels, and the toxicological evidence demonstrates that IQOS aerosol has many of the same toxicological effects as CCs. At this time, PMP S.A. has not substantiated that their products cannot cause the health outcomes in the warnings, and consequently the applicant has not demonstrated that the warnings are not accurate or appropriate for IQOS. To provide additional information to the applicant on the process of removing the Surgeon General's warnings, FDA intends to send a separate General Correspondence Letter to PMP S.A.

6. CONCLUSIONS AND RECOMMENDATIONS

6.1. Statutory Requirements for Authorization.

The applicant requested authorization under Section 911(g)(2) of the FD&C Act to continue to market the products specified in Appendix A with the following exposure modification claim:

AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the "special rule") if it determines, under Section 911(g)(2)(A) of the FD&C Act, that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and

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understanding of the removal of the Surgeon General's warnings. FDA intends to send a General Correspondence Letter to PMP S.A. to provide additional information on the process to submit evidence to support their request to remove the Surgeon General's warnings. With regard to the exposure reduction claim that is the subject of this renewal request under section 911(g)(2), PMP S.A.'s consumer perception data submitted to support the original MRTPAs and this renewal demonstrate that consumers are able to accurately answer questions about complete switching and risk of IQOS relative to CC. The information outlined in the social science review continues to support that consumers do have accurate comprehension of the modified risk information provided by the advertising or labeling of IQOS, including understanding that consumers must switch completely to reduce exposure to HPHCs, and that consumers understand that IQOS is reasonably likely to be less risky than CC but not risk-free.

- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must find, under Section 911(g)(2)(B) of the FD&C Act, that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to 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.

In making the determination under section 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the tobacco product that is the subject of the application;
- The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to using the tobacco product that is the subject of the application;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application;
- The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence; and
- Comments, data, and information submitted by interested persons.

Under Section 911(h)(1) of the FD&C Act, FDA also must ensure that the advertising and labeling concerning the MRTPs enable the public to comprehend the information concerning modified exposure and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health conditions associated with the use of tobacco products.

6.2. Overall Conclusions: Scientific Evidence

As TPL, my review of the scientific evidence integrated various lines of evidence regarding the MRTPs and their potential effects on health and tobacco use behavior. I undertook this assessment to determine whether the MRTPAs met the statutory requirements listed above.

The claim (below) continues to be scientifically accurate.
AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

In examining the claim's substantiation, as TPL, I relied on the previously submitted information and evaluated a new computational toxicology study and three new studies that assessed biomarkers of exposure (BOE) submitted by the applicant, as well as relevant scientific studies published since the MRGOs. Overall, this evidence suggests that, compared to CC smoking, IQOS use poses lower exposure to HPHCs. This is shown both in the toxicological assessment of the HPHCs in IQOS aerosol and in the reductions demonstrated in the BOE studies. As such, I found that the modified exposure claim continues to be substantiated.

As TPL, my final assessment of the individual health risks of IQOS reflects an evaluation of the health risks *relative* to CC smoking, as this is the comparison made in the claim, and adults who use CC are the applicant's stated intended users of IQOS. Heated tobacco products are a novel type of tobacco product, and as such, long-term health data with which we can evaluate these products remain limited. The applicant did not submit results from observational or clinical studies with follow-up periods that were sufficiently long to evaluate the effects of IQOS on longer term smoking- and tobacco-related health conditions (e.g., cardiovascular disease and cancer). Like in the evaluation of the original MRTPAs (MR0000059-MR0000061, MR0000133, MR0000192), in the absence of long-term health data, my determination about whether a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely is based on the available HPHC and biomarker evidence, along with evidence of the short-term health effects, including adverse events. In the original MRTPAs, while 80 chemicals were found to be higher in IQOS aerosols than in 3R4F RCS, the comprehensive testing of 108 HPHCs showed that 107 were either below the limit of detection or quantification or present at lower concentrations in IQOS aerosols compared to CC smoke. Overall, these 107 HPHCs were reduced by 47-99.9% in IQOS aerosols on a per stick basis compared to CC smoke and by 20-99.8% when normalized to nicotine levels, with only nicotine and anabasine as exceptions. Some literature published since the issuance of the MRGOs noted certain detrimental effects associated with exposure to IQOS, but these effects are generally less severe than those observed for the CC smoking comparison groups across published toxicological studies (see Section 3.2 below). Although new evidence raises some questions related to individual health risks, the data reviewed do not change the overall conclusions from the original MRTPAs.

As TPL, I find that the totality of evidence – including evidence newly available – suggests the overall level of exposure to HPHCs is lower than that of CC smoke and completely switching from CC to IQOS is reasonably likely to lead to a reduction in morbidity and mortality among individual tobacco users. However, because the health risks of IQOS are not fully known, we continue to monitor and evaluate new evidence about its health harms and risks.

In assessing consumer understanding and perceptions of IQOS, as TPL, I relied on the previously

submitted information and evaluated data from one new study submitted by the applicant. Data suggest that the applicant continues to demonstrate that consumers perceive IQOS use to have moderate risk of tobacco-related health effects but to have lower risk than using CC, which is in line with the relative health risks of the product that are reasonably likely. The results also demonstrate that the majority of consumers understood that people who use CC would need to switch completely to IQOS use to receive the benefits conveyed by the modified exposure claim. Overall, the evidence supports the conclusion that the advertising and labeling concerning the MRTPs enable the public to comprehend the information concerning modified exposure and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.

As TPL, I also examined population-level effects of marketing IQOS as an MRTP, including patterns of IQOS use since the issuance of the MRGOs. As described in Section 2.3 below, IQOS was not available in the U.S. market for much of the MRGO authorization period. Therefore, there is limited use data specific to the U.S. population available. The available data show that IQOS is being used by the applicant's stated intended users--adults who used CC before initiating IQOS. Demographic information suggests that current established IQOS users tend to be middle-aged men with relatively high socioeconomic status. There is no evidence that marketing IQOS as an MRTP has led to an increased likelihood of youth initiation of IQOS.

In one of PMP S.A.'s postmarket studies, almost all current IQOS users reported some prior history of tobacco use, with 91.6% reporting current CC use in the 30 days prior to IQOS initiation. Among current IQOS users, 50.6% reported they were former smokers at the time of the survey which, on average, was completed approximately 11 months after their initiation of IQOS, suggesting that about half of the former CC smokers quit smoking CCs after initiating IQOS. Additionally, 83.1% of current IQOS users who also used CC reported using fewer CC at the time of the survey than before they tried IQOS, although the number of CC per day was not reported. In total, 35% of current established IQOS users reported using IQOS exclusively. These findings suggest the retrospectively reported rates of quitting CC were higher among IQOS users in this study than they are in the overall population of people who smoke CC (e.g., only about 7.5% of all people who smoked CC reported having quit for 6 months or more in the past year in a study by Creamer et al., 2019).

Dual use of IQOS and other tobacco products continues to be a concern. Among current established IQOS users, 64.9% report using IQOS with one or more other tobacco products, with 48.8% using CC. However, if IQOS continues to be marketed as an MRTP, now that it has returned to the U.S. marketplace, repeated exposure to the modified exposure claim as part of the IQOS products' LLA would provide tobacco users with basic, substantiated information and instructions to switch completely from CC to IQOS.

Overall, the evidence suggests there is a low likelihood of IQOS initiation among youth and people who do not use tobacco products, and the postmarket evidence indicates some potential for IQOS to be used by people who smoke CC to switch completely to IQOS, which reduces their exposure to HPHCs. Given the current evidence of limited influence on youth of marketing IQOS as an MRTP, any complete switching from CC to the MRTPs by adults can likely provide a benefit to population health.

PMP S.A. also requested three Surgeon General's warnings be removed,[15] asserting that IQOS does not meet the statutory definition of a cigarette and that, even if the products do meet that definition, the warnings are scientifically inaccurate and misleading to consumers about the risks of IQOS products. Assessing whether IQOS meets the definition of a cigarette for the purposes of the Surgeon General's warnings[16] does not fall within the scope of MRTPA review under section 911. IQOS meets the definition of a cigarette and the term "smoking" in the Surgeon General's warnings applies to use of IQOS.[17] Therefore, the applicant's current request to remove the Surgeon General's warnings is an implied modified risk claim that the products cannot cause the health outcomes in the warnings that FDA would consider in a new MRTPA. Additional evidence would need to be provided by the applicant to establish that removal of the Surgeon General's warnings meets the standard set forth in section 911(g)(1), as well as evidence to establish that the updated advertising and labeling enable the public to comprehend the information concerning modified risk and understand the relative significance of the information in the context of total health under section 911(h)(1). The application that includes such new evidence would also be required to be referred to the Tobacco Products Scientific Advisory Committee (TPSAC) under section 911(f). To provide additional information to the applicant on the process of removing the Surgeon General's warnings, FDA intends to send a separate General Correspondence Letter to PMP S.A.

At this time, I recommend the MRTPs be authorized without removal of the three Surgeon General's Warnings on the proposed product labeling and advertising for IQOS:

- "**SURGEON GENERAL'S WARNING**: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy."
- **"SURGEON GENERAL'S WARNING**: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health."
- **"SURGEON GENERAL'S WARNING**: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight."

In summary, the available scientific evidence is generally consistent with the evidence reviewed in the original MRTPAs and continues to support the original conclusions that, among other things, the MRTPs are expected to benefit the health of the population as a whole. Thus, the products sold or distributed with the modified exposure information continue to meet the standards under Section 911(g)(2) of the FD&C Act.

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[15] The April 3, 2019, PMTA authorization for the IQOS System Holder and Charger explained that as cigarettes, if authorized, IQOS would be required to bear the rotating Surgeon General's warnings. However, PMP S.A. provided evidence demonstrating that although the use of Heatsticks in the IQOS device does produce CO, the exposure to CO from IQOS use is comparable to environmental exposure to CO. Therefore, the TPL determined that the required CO warning was misleading and should be removed from the rotation.

[16] Section 3(1) of the Federal Cigarette Labeling and Advertising Act (FCLAA) defines cigarette as "(A) any roll of tobacco wrapped in paper or in any substance not containing tobacco, and (B) any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette." Contrary to PMP S.A.'s assertion, IQOS also meets the definition of a "cigarette" at section 900(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[17] See the Memorandum "IQOS heated tobacco products and clarification of the terms "smoke" and "smoking,"' signed April 15, 2026, for the assessment of the applicability of "smoking" to IQOS products.

6.3. Recommendation for the Renewal Request

As TPL, I reviewed the scientific evidence regarding the MRTPs and their potential effects on health and tobacco use behavior. I undertook this assessment to determine whether the MRTPs met the statutory requirements listed above. After conducting a thorough scientific review of the information contained in the MRTPAs, the recommendations from the Tobacco Products Scientific Advisory Committee, comments, data, and information submitted to FDA by interested persons, and other scientific information identified by the Agency from other sources, I conclude that with respect to the exposure modification order renewal request, the applicant **has demonstrated** that the products sold or distributed with the modified exposure information continue to meet the standard under Section 911(g)(2) of the FD&C Act, including that issuance of renewal orders is expected to 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.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited to a term of not more than 5 years. I recommend authorization for a period of 5 years. Although this review has found that an exposure modification order for the products would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, that determination may change over time with new evidence or as a function of how the products are actually used by consumers. Therefore, monitoring use of the MRTPs in terms of initiation, dual use with other tobacco products, and complete switching should be required, including the potential for initiation among youth. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and claim understanding at multiple time points. In this case, a 5-year period is a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate data on behavior in postmarket surveillance and studies to assess whether the standard continues to be met and whether the orders should be renewed.

6.4. POSTMARKET SURVEILLANCE AND STUDIES (PMSS)

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]."

MRTP Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco products that are the subject of this order continue to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by consumers' understanding of the claim and perceptions of the MRTPs. In particular, PMSS must assess the extent to which users of these products understand that reducing their exposure to HPHCs is relative to smoking CC as described in the modified exposure information, and that adults who currently smoke CC must use the MRTPs exclusively and stop smoking CC. Thus, adults who currently smoke CC who start using the MRTPs must understand that they should switch completely to the MRTPs and stop smoking CC, and that cutting down on CC per day while using the MRTPs is not sufficient to reduce their exposure to HPHCs. People who use tobacco products other than CC must understand that the reduction in HPHCs from use of the MRTPs is relative to smoking CC and not to

other types of tobacco use. In addition, PMSS must include an assessment of exposure to, and awareness of, the reduced exposure claim to help elucidate the impact of real-world and repeated claim exposure on consumer understanding and perceptions.

MRTP Use Behavior

An assessment of tobacco use behaviors is necessary to monitor whether the applicant's intended users (adults who use CC) are the consumers using the MRTPs and to ensure that unintended users are not using the MRTPs. As such, monitoring the use of the MRTPs among adults who smoke CC in terms of initiation, dual use with other tobacco products, and complete switching at multiple time points continues to be a PMSS requirement. Specifically, PMSS must assess the current tobacco use behavior among people who use the MRTPs, including whether people exclusively use or dual use the MRTPs with CC or other tobacco products. The PMSS must also assess the tobacco use history of people who use the MRTPs (e.g., never, formerly, or currently smoke CC; use of other tobacco products at time of initiating the MRTPs).

Adults who smoke CC must not only use the MRTPs, but switch to exclusive use of them and cease CC smoking, as instructed by the claim, in order to realize the potential population health benefit of these MRTPs, including whether it is reasonably likely there will be a measurable and substantial reduction in morbidity or mortality in future studies. Data from studies of BOE suggest that reduced HPHC exposure does not apply to dual users of IQOS and CC. This makes an assessment of dual use within the U.S. an important component of PMSS requirements.

To adequately assess these impacts, PMSS must include assessments of behavior and consumer understanding among people who use the MRTPs at multiple time points. Conducting a longitudinal cohort study, like the one planned for the original modified risk orders (but not conducted due to the CDO), may produce robust and reliable evidence to demonstrate the impact of the MRTPs in terms of uptake, dual use with other tobacco products, and complete switching over time. If the applicant is unable to conduct such a longitudinal study, a repeated cross-sectional study that collects valid information on recalled history of tobacco use may also provide evidence across multiple time points to determine whether people who use the MRTPs used them to switch completely from CC smoking.

Surveillance of Research Study Findings on the MRTPs

In order for FDA to determine whether these MRTPs continue to benefit the health of the population as a whole, the applicant must report any previously unreported findings from any internal and unpublished research studies conducted by them or on their behalf, regardless of whether such studies were specifically required as part of PMSS.

Submitting all available internal or unpublished research on youth awareness and use of the MRTPs is particularly important. Given the novelty of these products and the continued uncertainty related to the impact of modified risk information on youth, the applicant must report any unpublished data about individuals under the age of 18 related to: (a) youth awareness of the MRTPs in order to evaluate how effectively any marketing is limiting unintended exposure to youth, and (b) youth use of the MRTPs, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. This

unpublished data may also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20).

Additionally, these MRTP applications continued to demonstrate that switching completely from CC to the MRTPs would, in general, significantly reduce exposure to HPHCs. New information from the applicant's computational toxicology study in these applications suggests that the genotoxic potential of IQOS aerosols may be higher than initially indicated from information available during the original MRTPA review. Therefore, PMSS must also include a literature review of all nonclinical studies published after the issuance of these orders that evaluate the toxicity of IQOS, with discussion of study results as they relate to IQOS aerosol toxicity relative to CC.

A literature search and published scientific articles are not required for other topics.

Conclusion

Modified risk granted orders should be issued for the products that are the subject of this review, as identified on the cover page.

6.5. Environmental Considerations

FDA has examined the environmental effects of continued marketing of the products with the modified risk claim and made a Finding of No Significant Impact (FONSI).

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8. APPENDICES

A. MODIFIED RISK TOBACCO PRODUCT(S)

Common Attributes[18,19,20,21]	
Submit date	July 5, 2023
Receipt date	July 5, 2023
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Product category	Heated Tobacco Products (HTPs)
Product order under 911(g)	911(g)(2) Exposure Modification Order
Modified Risk Claim	AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

[18] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[19] Product name is brand/sub-brand or other commercial name used in commercial distribution.
[20] Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. Therefore, nicotine source should be included in future submissions.
[21] Attributes in Appendix A may display converted values.

Attributes	Tobacco Product
STN	**MR0000254.PD1**
Previously authorized STN	MR0000133
Product name[22]	IQOS 2.4 System Holder and Charger
Product subcategory	Open HTP
Package type	Box
Product quantity	1 Holder, 1 Charger
Characterizing flavor (CF)	Unflavored
Length	93.60 millimeters (mm) (Holder) 112.50 mm (Charger)
Diameter	15.04 mm (Holder)
Nicotine Source	None
Wattage	6 W (Charger)
Battery Capacity	120-130 mAh (Holder) 2900-3200 mAh (Charger)
Additional property	Source of Energy: Electric (rechargeable battery) Depth: 21.86 mm (Charger) Width: 51.20 mm (Charger)
STN	**MR0000254.PD3**
Previously authorized STN	MR0000192
Product name[23]	IQOS 3.0 System Holder and Charger
Product subcategory	Open HTP
Package type	Box
Product quantity	1 Holder, 1 Charger
Characterizing flavor (CF)	Unflavored
Length	92.25 mm (Holder) 114.80 mm (Charger)
Diameter	14.40 mm (Holder) (smallest) 14.90 mm (Holder) (largest area with protruding button)
Nicotine Source	None
Wattage	Not provided
Battery Capacity	> 110 mAh (Holder) > 2600 mAh (Charger)
Additional property	Source of Energy: Electric (rechargeable battery) Thickness: 23.00 mm (Charger) Width: 46.35 mm (Charger)

[22] The product is originally known as IQOS System Holder and Charger.
[23] The product is also known as IQOS Originals.

Attributes	Tobacco Product
STN	**MR0000254.PD5**
Previously authorized STN	MR0000059
Product name[24]	Marlboro Amber HeatSticks
Product subcategory	HTP Consumable
Package type	Box
Product quantity	20 HeatSticks
Characterizing flavor (CF)[25]	Tobacco
Length	45 mm
Diameter	7.42 mm
Ventilation[26]	Not provided
Nicotine Source	Tobacco
Additional property	Source of Energy: Electric (rechargeable battery)
STN	**MR0000254.PD6**
Previously authorized STN	MR0000060
Product name[27]	Marlboro Green Menthol HeatSticks
Product subcategory	HTP Consumable
Package type	Box
Product quantity	20 HeatSticks
Characterizing flavor (CF)	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation[26]	Not provided
Nicotine Source	Tobacco
Additional property	Source of Energy: Electric (rechargeable battery)
STN	**MR0000254.PD7**
Previously authorized STN	MR0000061
Product name[28]	Marlboro Blue Menthol HeatSticks
Product subcategory	HTP Consumable
Package type	Box
Product quantity	20 HeatSticks
Characterizing flavor (CF)	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation[26]	Not provided
Nicotine Source	Tobacco
Additional property	Source of Energy: Electric (rechargeable battery)

[24] The product is also known as HEETS Amber and originally known as Marlboro HeatSticks.
[25] The characterizing flavor previously identified as "None" has been updated to "Tobacco" to accurately reflect that the product provides a tobacco characterizing flavor from the filler. As such, this product does not have any change in characterizing flavor.
[26] Filter efficiency or ventilation are not used to control aerosol deliveries.
[27] The product is also known as HEETS Green and originally known as Marlboro Smooth Menthol HeatSticks.
[28] The product is also known as HEETS Blue and originally known as Marlboro Fresh Menthol HeatSticks.

B. AMENDMENTS AND ADDITIONAL SUBMISSIONS

Amendments Received for These Applications

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
April 24, 2024	April 24, 2024	All	Yes	Additional information for study report documents, data, and analysis
June 6, 2024	June 6, 2024	All	Yes	Additional information for study report documents, data, and analysis
October 3, 2024	October 3, 2024	All	Yes	Additional information for study report documents, data, and analysis
November 25, 2024	November 25, 2024	All	Yes	Extension request to respond to A/I letter dated November 22, 2024
December 5, 2024	December 5, 2024	All	Yes	Response to General Correspondence letter dated October 30, 2024
December 20, 2024	December 20, 2024	All	Yes	Response to A/I Letter dated November 22, 2024
July 11, 2025	July 11, 2025	All	No	Amendment withdrawn by applicant
August 4, 2025	August 4, 2025	All	Yes	Request to withdraw amendment received on July 11, 2025
August 4, 2025	August 4, 2025	All	Yes	Information on statutory definition and request to remove required warnings

Additional Submissions Received for These Applications

Submit Date	Receipt Date	Reviewed	Brief Description
March 18, 2024	March 18, 2024	Yes	Prioritization information
February 24, 2025	February 24, 2025	Yes	Update US Agent and Point of Contacts