U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead Review of MRTPA

Modified Risk Tobacco Product Subject of this Review[1]	
STN[2]	MR0000192
Attributes	
Submission date	March 18, 2021
Receipt date	March 18, 2021
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Product category	Heated Tobacco Product (HTP)
Product subcategory	Open HTP
Purpose	☐ Risk Modification 911(g)(1) order ☒ Exposure Modification 911(g)(2) order
Proposed Claims	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 Submissions	
MR0000192	(b) (4), MR000059-61, MR0000133, PM0000634, PM0000479
Recommendation	
Issue a modified risk granted order for the product subject of this review.	

Technical Project Lead (TPL): /S/

CAPT Robin L. Toblin, Ph.D., M.P.H.
Associate Director
Division of Population Health Science, Office of Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

/S/

Matthew R. Holman, Ph.D.
Director
Office of Science

[1] Product details, amendments, and dates provided in the Appendix. MRTPA means modified risk tobacco product application.

[2] Submission tracking number

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1. EXECUTIVE SUMMARY

This modified risk tobacco product application (MRTPA) is a request for authorization to market the IQOS 3 System Holder and Charger[3] (IQOS 3 device) under a Section 911(g)(2) (exposure modification) order, which was granted a Marketing Granted Order (MGO) under Section 910 of the FD&C Act on December 07, 2020 (PM0000634). The IQOS 3 device is an update to their previous device, the IQOS 2.4 Holder and Charger (IQOS 2.4 device, PM0000479), that was granted a MGO on April 30, 2019 and a Modified Risk Granted Order under Section 911(g)(2) as an MRTP on July 07, 2020 (MR0000133).

The table below summarizes the regulatory history of these two products.

	IQOS 2.4 System Holder and Charger	IQOS 3 System Holder and Charger
PMTA	Authorized for marketing in PM0000479	Authorized for marketing in sPMTA[4] PM0000634
MRTPA	Authorized as a MRTP[5] in MR0000133	Subject of this TPL review

This MRTPA utilizes the same claims as in the MRTPA for the IQOS 2.4 System Holder and Charger (i.e., MR0000133), requests the same order that was requested and issued for MR0000133 (i.e., a reduced exposure order under Section 911(g)(2)) of the FD&C Act), and plans to utilize the same postmarket surveillance studies. In addition, the IQOS 2.4 device and IQOS 3 device are comparable products as the IQOS 3 device is similar in design to IQOS 2.4 device (with mainly aesthetic physical modifications) and uses the same tobacco source (Marlboro Heatsticks). As such, this review relies on the TPL review for the IQOS 3 device (PM0000634) and the TPL review for the MRTPA for the IQOS 2.4 device (MR000059-61, MR0000133) to examine the relative health risks of the proposed MRTP to individual tobacco users, consumer understanding and perceptions of the proposed modified risk claim, and tobacco use behavior and impacts to the population as a whole.

After conducting a thorough scientific review of the information contained in the MRTPA, comments, data, and information submitted to FDA by interested persons and other scientific information, I conclude that the proposed MRTP, as actually used, reduces a user's exposure to harmful and potentially harmful constituents (HPHCs) if they switch completely from combusted cigarettes to the IQOS 3 System Holder and Charger when using Marlboro Heatsticks. A measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. Further, the applicant has demonstrated that the modified risk labeling and advertising enable the public to understand the proposed MRTP to be a product with likely moderate risks of a range of tobacco-related diseases and a considerably greater risk than quitting smoking or using nicotine replacement therapies (NRT). As the two devices have similar operating procedures, use the same tobacco sources, and produce comparable aerosols, FDA has no reason to believe the IQOS 3 device will result in different nicotine exposure, use patterns, user populations, or abuse liability.

As such, the IQOS 3 device has been found to be appropriate to promote public health and 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. I conclude that the current application meets the statutory requirements for an exposure modification order under Section 911(g)(2) of the FD&C Act. A finding of no significant impact (FONSI) has been established for the proposed MRTP. I recommend that the order be issued through July 07, 2024.

[3] The MRTPA does not contain any modifications to the previously authorized Heatsticks (MR0000059-MR0000061).

[4] Supplemental premarket tobacco product application.

[5] Modified risk tobacco product.

2. BACKGROUND

2.1. MODIFIED RISK TOBACCO PRODUCT

The applicant submitted information for the proposed modified risk tobacco product listed on the cover page and with more detail in Appendix A.

2.2. PROPOSED CLAIMS

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

On March 18, 2021, FDA received an MRTPA from Philip Morris Products S.A. FDA issued an Acceptance letter to the applicant on April 15, 2021. FDA issued a Filing letter to the applicant on May 13, 2021.

Refer to the Appendix B for a complete list of amendments received by FDA.

2.4. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the modified risk tobacco product subject of this review.

Table 1. Disciplines reviewed

Discipline	Cycle 1	
	Reviewers	Review Date
Regulatory	Donna Cheung	4/15/2021
Environmental Science	Carla Figueroa	11/8/2021

Table 2. Consultations

Discipline or Office	Cycle 1	
	Reviewers	Review Date
Chemistry/Engineering	Yuan-Wei Nei/ Nashaat Rasheed	March 8, 2022

2.5. TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC)

The MRTPAs for the IQOS 2.4 System Holder and Charger, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks (MR0000059-61, MR0000133) were referred to TPSAC and TPSAC reported its recommendations on the applications during an open public committee meeting held on January 24-25, 2018. The current MRTPA is for the IQOS 3 device, which contains mainly aesthetic physical modifications to the Holder and Charger. FDA authorized the marketing of the IQOS 3 device without modified risk claims on December 07, 2020 (PM0000634). The MRTPA largely cross-references the previously submitted and authorized MRTPAs for the IQOS 2.4 System (MR0000059-61, MR0000133) and does not involve any new modified risk claims. FDA obtained TPSAC's recommendations during the January 24-25, 2018 meeting on the modified risk claims that accompany IQOS 2.4 and which would not change on IQOS 3; therefore, the current application did not raise any new scientific matters that would require an

additional TPSAC meeting.

2.6. PUBLIC AVAILABILITY OF MRTPAS

Pursuant to Section 911(e) of the FD&C Act, FDA made the subject MRTPA available to the public (except matters in the applications that are trade secrets or are otherwise confidential, commercial information). The docket for public comment of the current MRTPA was opened May 14, 2021, extended on July 20, 2021 due to missing cross-referenced files in PM0000634 and closed on December 10, 2021. FDA received 33 public comments from individuals, academia, and other organizations. The comments included advocacy concerns and clinical concerns. FDA considered all significant comments when making our final determination on this MRTPA.

3. SCIENTIFIC REVIEW

3.1. RELATIVE HEALTH RISKS OF THE PROPOSED MRTPs TO INDIVIDUAL TOBACCO USERS

3.1.1. Discipline key finding

There are no new data specifically related to relative health risks to individual tobacco users in this MRTPA. I relied on the TPL review for the sPMTA (PM0000634) to examine the toxicant exposure and health effects of the IQOS 3 device. That TPL review found that "the aerosol generated with the IQOS 3 device when using Marlboro Heatsticks is comparable to that generated with the IQOS 2.4 device using the same Heatsticks" and the "overall health risks appear to be similar for IQOS 2.4 and 3." Further, to ensure that the changes to the device itself and the aerosols and related harmful and potentially harmful constituents (HPHCs) emitted would not alter claim substantiation (and thus, whether the proposed MRTP is appropriate to promote the public health and is expected to benefit the health of the population as a whole), Chemistry and Engineering provided a combined consultation. The consultation concluded, "This consultation has not identified any issues from a chemistry and engineering perspective in this MRTPA submission (MR0000192) that would alter our conclusions on the currently authorized MRTPA (MR0000133)." There was a public comment that disputed the substantiation of the claims noting that their concerns about individual health risks related to IQOS 2.4 still stood. However, because those risks have not changed since the original MRTPA, these comments do not impact the current assessment.

I relied on the TPL review for the original MRTPA (MR000059-61, MR0000133) for the scientific basis for claim substantiation. That review found that all three claims submitted for 911(g)(2) exposure modification, the same claims submitted in this MRTPA under review, were substantiated.

3.1.2. Synthesis

Based on the key findings in the cross-referenced sPMTA, original MRTPA and the consultation with Engineering and Chemistry, I conclude that all claims proposed are supported from the perspective of relative health risks to individual users. Further, the proposed MRTP, as actually used, reduces a user's exposure to harmful and potentially harmful constituents (HPHCs) if they switch completely from combusted cigarettes to the IQOS 3 System Holder and Charger when using Marlboro Heatsticks. A measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

3.2. CONSUMER UNDERSTANDING AND PERCEPTIONS

3.2.1. Discipline key findings

There are no new data specifically related to consumer understanding and perceptions in this MRTPA. The MRTPA noted that labeling used will be the same as authorized in PM0000634 and will be nominally different from that used in MR0000133 such that the proposed MRTP will note updated user instructions and safety warnings "to reflect learnings from the global in-market experience with *IQOS."* Differences included additional information on battery risk, a new hot aerosol risk section, formatting for enhanced consumer comprehension, and clarified instructions for safe use as relates to Marlboro Heatsticks. After reviewing these changes, I conclude that they provide greater clarity regarding instructions for use and safety than prior versions, and thus, do not change my assessment. Due to these similarities with the labels authorized in PM0000634 and in MR0000133, I relied on the TPL review for MR000059-61 and MR0000133 on consumer understanding and perceptions. That review found sufficient consumer understanding of (a) the exposure reduction described in the proposed claims, (b) the health risks relative to non-use, cessation or nicotine replacement therapies (NRT), and (c) the conditions of use to reduce exposure (i.e., switching completely from combustible cigarettes).

3.2.2. Synthesis

Based on the key findings in the reviews for the cross-referenced sPMTA, original MRTPA and my review of the differences in labeling as noted above, I find that the applicant has demonstrated that the modified risk labeling and advertising enable the public to understand the proposed MRTP to be a product with likely moderate risks of a range of tobacco-related diseases and a considerably greater risk than quitting smoking or using NRT. This supports comprehension of the proposed modified risk claims in the context of total health.

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

3.3.1. Discipline key findings

There are no new data specifically related to tobacco use behavior and impacts to the population as a whole in this MRTPA.

3.3.1.1. Impacts to Tobacco Users

- ***Abuse Liability***
  The applicant did not provide new data specific to abuse liability for this application or in the sPMTA. Because the product designs and operating procedures are similar between IQOS 2.4 and IQOS 3 and use the same Heatsticks, FDA has no reason to believe that the abuse liability will change. This is coupled with the findings from the original MRTPA, which concluded that "the data support the conclusion that IQOS will likely have an addictive potential and abuse liability similar to combusted cigarettes." In addition, the TPL review also noted that due to the abuse liability, youth might also be interested in trying the product and noted the "importance of preventing youth access and exposure to the product and its marketing."
- ***Patterns of Use***
  I relied on the TPL review for the sPMTA, which examined newly submitted use data from international markets (no new U.S. data were provided) that compared users of IQOS 2.4, IQOS 2.4P, and IQOS 3. That review found that data were limited and "may

not reflect the way IQOS 3 would be used in the U.S.," but "IQOS 3 seems to be accepted by tobacco users in other countries and some of the users report switching completely to IQOS (as opposed to dual use with cigarettes)." Because the proposed MRTP will utilize the same marketing plans and the devices operate similarly, FDA has no reason to believe the use patterns in the U.S. for the proposed MRTP will be significantly different from those for the currently marketed version (IQOS 2.4).

- ***Likelihood that Current Users will Start Using the Proposed MRTPs***
  I relied on the TPL review for the original MRTPA which concluded that "these findings are supportive that marketing IQOS with a reduced exposure claim could appeal to current smokers who are most likely to benefit from their use, and this supports a likely benefit to population health." Because the MRTP will utilize the same claims and marketing plans, and the devices operate similarly, FDA has no reason to believe the impact on current users will be significantly different from those for the currently marketed version (IQOS 2.4).

3.3.1.2. Impacts to Non-Users of Tobacco

I relied on the TPL reviews for the authorized sPMTA and original MRPTA. The sPMTA concluded, "There is no evidence the user population for IQOS 3 will be different from the population who use IQOS 2.4. The survey data also show no evidence of increased youth and young adult initiation of IQOS 3 use in international markets. Given the product similarities, there is no evidence of increased risk for youth initiation and use for IQOS 3 as compared to IQOS 2.4." The original MRTPA TPL review found that there was low interest in trying the product among adult and young adult never smokers with some interest in trying the product among former smokers, but the addition of the claim did not appear to increase interest among any of the non-user groups. Nonetheless, the same care to mitigate youth exposure taken with the original MRTP and the sPMTA also apply to this study, which will be monitored through required post-market surveillance studies.

3.3.1.3. Actions Proposed to Mitigate Risk of Unintended Use

As this application proposes to utilize the same marketing plans as outlined in the cross-referenced sPMTA and seeks to combine the data from the original MRTPA with data collected with the proposed MRTPA, I find the actions to mitigate risk of unintended use acceptable.

3.3.1.4. Population Health Impact Model

I relied on the TPL review for the original MRPTA as no new data were provided in this application that would change the population health impact model. The review found that the data were neither supportive nor unsupportive of a modified exposure order. A public comment to the MRTPA docket thought that the data provided by the applicant underestimated the health impacts and because this has not changed since the previous application, the current product and model assumptions carry the same flaws. Because these data did not change since the original MRTPA, this comment does not impact my assessment.

3.3.2. Synthesis

I concur with the following TPL conclusion from the sPMTA that states, "As the two devices have similar operating procedures, use the same tobacco sources, and produce comparable aerosols, FDA has no reason to believe the IQOS 3 device will result in different nicotine

exposure, use patterns, user populations, or abuse liability." In addition, the applicant is proposing to market the product with the same claims that were authorized for IQOS 2.4. Thus, I find that the proposed MRTP would be expected to promote the public health and 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.

3.4. STATUTORY REQUIREMENTS

3.4.1. Public health conclusion

The applicant has requested an exposure modification order under 911(g)(2) of the FD&C Act to market the product specified in Appendix A for the following claims:

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

As discussed above, as TPL, I find that the MRTPA meets the following statutory requirements.

In making the determination under either section 911(g)(1) or 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

For 911(g)(2) specifically, FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the "special rule") if it determines 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

- 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 (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that 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 the similar types of tobacco products then 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 (section 911(g)(2)(B) of the FD&C Act).

4. ENVIRONMENTAL DECISION

A finding of no significant impact (FONSI) was signed by Luis G. Valerio on November 08, 2021. The FONSI was supported by an environmental assessment prepared by FDA on November 08, 2021.

5. CONCLUSION AND RECOMMENDATION

After conducting a thorough scientific review of the information contained in the MRTPA, the TPL review for the cross-referenced sPMTA for the IQOS 3 device and the TPL review and recommendations from TPSAC for the original MRTPA, and comments, data, and information submitted to FDA by interested persons for the proposed MRTP, I conclude that the applicant has demonstrated that the proposed MRTP meets the statutory requirements for an exposure modification order as described in section 911(g)(2) of the FD&C Act. I recommend that a modified risk order be granted for a period to end on July 07, 2024.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited for a term of not more than 5 years. I recommend authorization for a period to end on July 07, 2024, the date that the authorization ends for the original MRTP, MR0000133. Aligning the authorization period of this MRTPA with the original MRTPA allows for the applicant and the FDA to efficiently submit and review, respectively, renewal applications for all products at the same time. 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 as a function of how the products are actually used by consumers. Therefore, monitoring use of the proposed MRTP in terms of uptake, dual use, 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 understanding over time. The applicant is conducting studies for MR0000133 and can utilize those studies to also collect the required information for the product subject of this review once authorized.

I recommend that the language in Appendix B be included in the marketing authorization for postmarket surveillance and studies (PMSS) and postmarket reporting.

FDA has examined the environmental effects of authorizing the proposed MRTP and made a Finding of No Significant Impact (FONSI).

A Modified Risk Granted Order should be issued for the modified risk product subject of this review, as identified on the cover page of this review.

6. APPENDIX

A. MODIFIED RISK TOBACCO PRODUCT

Attributes of MRTPA	
Submission date	March 18, 2021
Receipt date	March 18, 2021
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Product category	Heated Tobacco Product (HTP) [6,7]
Product subcategory	Open HTP
Order type	911(g)(2) Exposure Modification Order
Proposed Claims	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.
Attributes	**Tobacco Product**
STN	**MR0000192**
Product name	IQOS 3 System Holder and Charger
Package type	Box
Package quantity	1 Holder, 1 Charger
Characterizing flavor	None
Length	92.25 mm (Holder) 114.80 mm (Charger)
Diameter	14.40 mm (Holder) (smallest) 14.90 mm (Holder) (largest area with protruding button)
Wattage	Not provided
Battery capacity	> 110 milliAmpere hour (mAh) (Holder) > 2600 mAh (Charger)
Additional property	Ventilation: Not provided Source of energy: Electric (rechargeable battery) Thickness: 23.00 mm (Charger) Width: 46.35 mm (Charger)

[6] Upon scientific review, the product category and product subcategory were revised.

[7] The IQOS products are also regulated as cigarettes and cigarette components and parts. Cigarettes and their components and parts must be in compliance with the FD&C Act and applicable regulations.

B. MODIFIED RISK GRANTED ORDER APPENDICES

Appendix B

Required 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]."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco product that is the subject of this order continues to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by use behavior. Therefore, monitoring use of the tobacco product that is the subject of this order in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTP and the extent to which new users of the MRTP become exclusive IQOS users, dual users with combusted cigarettes or other tobacco products, or transition to combusted cigarette smoking over time. Relatedly, such surveillance must include an assessment of consumers' understanding of the claim and perceptions of the product. These studies should be designed to observe behavior over a sufficient period of time to examine, for instance, the extent to which dual use of IQOS and combusted cigarettes is a transitional versus stable pattern of use.

Given the novelty of these products and the uncertainty related to the impact of modified risk information on youth, your studies must also be designed to monitor individuals under the age of 18 to assess: (a) youth awareness of IQOS, to evaluate how effectively your marketing is limiting unintended exposure to youth, and (b) youth use of the IQOS system, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. Your surveys must also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20).

Your studies must also include an assessment of consumers' understanding of the claim and perceptions of the products. In particular, your PMSS must assess the extent to which users of the product understand that reducing their exposure to harmful and potentially harmful chemicals is relative to smoking, as described in the modified risk information, and that current smokers must use the IQOS system exclusively and stop smoking. Thus, current smokers who take up IQOS, must understand that they should switch completely to IQOS and stop smoking and that cutting down on combusted cigarettes per day while using IQOS is not sufficient. Other tobacco users who switch to IQOS must understand that the reduction in harmful and potentially harmful chemicals is relative to combusted cigarette smoking and not to other types of tobacco use.

Your studies must have clear research objectives, including assessing whether the modified risk tobacco product leads to changes in product use behaviors that are expected to benefit population health. Your protocol must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives.

In addition, FDA has determined that assessing the impact of your MRTP order on uptake of the product requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the product is sold (e.g., IQOS stores and kiosks, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the tobacco product by quarter since the date of issuance of your modified risk granted order (for the initial reporting period) or the previous reporting period (for all reports that follow), including total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold during the reporting period (e.g., IQOS stores, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).
- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly growth rate (percent change) in total U.S. sales and distribution of the tobacco product, post-MRTP authorization.

MRTP Use and Health Risk – Toxicology

Although your applications demonstrated that switching completely from combusted cigarettes to the IQOS system would, in general, significantly reduce exposure to harmful or potentially harmful chemicals, there were some chemicals that were higher in Heatstick aerosol than in combusted cigarette smoke. Additional research must be conducted to better characterize the potential impact of these exposures. In your applications, you reported computational toxicology predictions on chemicals found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke. However, your applications lacked details of the quantitative structure-activity relationship (QSAR) modeling prediction results including, information to judge reliability of the modeling results, information on how you made interpretations of the model predictions, and a description of the training sets used in the models and why they are appropriate for tobacco constituents to predict adverse effects at the endpoints that were tested. An adequate computational toxicology assessment of Heatstick aerosols must be conducted in order to predict potential adverse effects in users before toxicity may be evident.

Given that the chemicals analyzed by QSAR are found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke and that Heatsticks are novel tobacco products for which long term health consequences have not been established, you must conduct a rigorous computational toxicology study using a battery of genotoxicity and carcinogenicity models (modeled endpoints: in vitro bacterial mutagenicity, mammalian cell mutagenicity, clastogenicity, rodent carcinogenicity) that have been validated in the published literature. A well-designed computational toxicology study must use both structure-activity-relationship (SAR), as well as QSAR models, and provide a full explanation of the computational basis for each prediction from the models. This includes probabilistic information of the prediction from a statistical model (i.e., probability of being positive), how the predictions were interpreted, model training set information including structurally similar compounds in the training set to the query compound, information on external validation testing and applicability domain of the models to understand reliability of the results for assessing the tobacco compounds.

MRTP Use and Health Risk – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the modified risk product that is the subject of this order, as actually used by consumers, continues to be appropriate to promote the public health and continues to

be 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)(A-B)), your PMSS must include ongoing surveillance of all adverse experiences including those that are both serious and unexpected associated with the use of the MRTP. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and unexpected adverse experiences for the tobacco product, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list, including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.

In addition, the PMTA order for your tobacco product, issued on December 07, 2020, requires you to report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for this product. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT FOR STNs PM0000424-PM0000426, PM0000419, PM0000634, MR0000059-MR0000061, MR0000133 and MR0000192**.

For purposes of this reporting, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTP and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the tobacco product that is the subject of this order, as actually used by consumers, continues to be appropriate to promote the public health and continues to be expected to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTP and consumer perception, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTP and consumer perception, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco product from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order.
- A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the MRTP and consumer perception, behavior, or health.

Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTPs on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using IQOS; the percentage of current smokers who start using IQOS and become dual users; the percentage of current smokers who switch completely to IQOS; the percentage of youth and young adults below the legal age of purchase who start using IQOS; and the percentage of individuals who start using IQOS and then initiate or re-initiate combusted cigarette smoking. Postmarket modeling must incorporate the latest information on acute and long-term health effects of using IQOS relative to combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

II. Submitting PMSS Protocols and Reports

As required under section 911(g)(2)(C)(ii) of the FD&C Act, your modified risk order is conditioned on your agreement to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of determinations on which the order is

based. Within 30 days of receiving this notice, you must submit your agreement to conduct PMSS and complete protocols for your PMSS. **FDA expects that modifications of previously approved protocols for the original MRTPA (MR0000133) that incorporate the product subject of this order would be appropriate for the PMSS required under this order.** Label your submission clearly as a "PMSS Protocol," and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, submit each protocol as a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA intends to review the protocol(s) and evaluate if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of data or other information that has the potential to enable FDA to accurately determine the impact of the order on consumer perception, behavior and health and to review of accuracy of the determinations upon which the order was based, pursuant to section 911(g)(2)(C)(ii) of the FD&C Act. FDA will notify you of, and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(g)(2)(C)(iii) requires that the results of the PMSS be submitted on an annual basis. As this product will be modifying the previously approved protocol for MR0000133, it should be submitted when the PMSS report is submitted for MR0000133. These reports must be identified as "PMSS Report", and the MRTPA STNs should be referenced for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.