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Module 2: Table of Contents, Glossary, Summary

2.4 Executive Summary

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OVERVIEW OF SECTION 2.4

Section 2.4 presents a summary of this application as recommended in Section VIII (A)(2) of the FDA Draft Guidance for Modified Risk Tobacco Product Applications (MRTPA)[1].

This section describes aspects of the application and summarizes the scientific findings with sufficient detail to enable a general understanding of the data and information contained in the application.

Section 2.4 is organized into five sections:

1. Executive Summary of the Application
2. Proposed Modified Exposure Claim
3. Product Description and Scientific Rationale
4. The Scientific Basis for the Exposure Modification Order for the *IQOS* 3 System
5. Summary of Findings that Support a Modified Risk Tobacco Product Market Order

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Tobacco Products, Guidance for Industry, Modified Risk Tobacco Product Applications, Draft Guidance, March 2012, available at "Modified Risk Tobacco Product Applications (fda.gov): https://www.fda.gov/media/83300/download".

1. EXECUTIVE SUMMARY OF THE APPLICATION

Philip Morris Products S.A. (PMP S.A.) is submitting this application under section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requesting authorization under section 911(g)(2) to make reduced exposure claims for its *IQOS* 3 System Holder and Charger, which received a Marketing Granted Order (MO) (PM0000634) under section 910(c) of the FD&C Act on December 7, 2020.

Following the review of a supplemental Premarket Tobacco Product Application (sPMTA)[2], the FDA determined that marketing of the *IQOS* 3 System Holder and Charger (further referred to as *IQOS* 3 System) is appropriate for the protection of the public health. The issuance of the marketing order confirmed that the product meets the requirements of section 910 of the FD&C Act. Under the relevant provisions of section 910 of the FD&C Act, the *IQOS* 3 System can be introduced or delivered for introduction into interstate commerce, in accordance with the requirements outlined in the marketing order.

The *IQOS* 3 System is a modified version of the *IQOS* 2.4 System Holder and Charger (further referred to as *IQOS* 2.4 System), which was granted a MO on April 30, 2019 (PM0000479) and a Modified Risk Granted Order (MRGO) – Exposure Modification on July 7, 2020. The *IQOS* 3 System, like the *IQOS* 2.4 System, is intended for use with any variant of authorized *HeatSticks*, including, *Marlboro HeatSticks* (MR0000059), *Marlboro* Smooth Menthol *HeatSticks* (MR0000060), and *Marlboro* Fresh Menthol *HeatSticks* (MR0000061), which also received a MRGO – Exposure Modification on July 7, 2020.

The FDA has concluded that the aerosol from the *IQOS* 3 System is comparable to that from the *IQOS* 2.4 System[3]. However, because of the current difference in regulatory status between *IQOS* 2.4 System (authorized as an MRTP with reduced exposure information) and the *IQOS* 3 System (authorized for commercialization under a PMTA marketing order), there is a risk of consumer confusion. Specifically, the simultaneous commercialization of the *IQOS* 2.4 System and *IQOS* 3 System, which are both designed to be utilized with the same *Marlboro HeatSticks* consumables, will be subject to different consumer messages (one with the authorized reduced exposure information and one without). To address this potential confusion, it is important that both versions of the *IQOS* System, which generally perform in

[2] A PMTA under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was submitted on March 30, 2020, and received by FDA on April 1, 2020 (FDA STN: PM0000634). The *IQOS 3* System Holder and Charger was authorized by the Marketing Order of December 7, 2020.

[3] As confirmed in the Marketing Granted Order of December 7, 2020 (STN: PM0000634) and associated Technical Project Lead (TPL) Review of PMTA.

the same manner in terms of sensory experience and emissions, be marketed with the same authorized reduced exposure information.

Therefore, PMP S.A. submits this supplemental MRTPA for the *IQOS* 3 System.

1.1. Application Background

The *IQOS* System Holder and Charger commercialized outside the U.S. continues to evolve. This evolution is based on the learnings from consumer research among adult smokers and adult *IQOS* users and advances in electronic technology over the years. These learnings and technological developments have been incorporated in an improved device, the *IQOS* 3 System, for which PMP S.A. received the December 7, 2020 MO authorizing the marketing of the product in the United States.

Like the *IQOS* 2.4. System, the *IQOS* 3 System delivers substantial reductions in the number and levels of Harmful and Potentially Harmful Constituents (HPHCs) compared to combustible cigarettes. This substantial reduction is similar to that measured with the *IQOS* 2.4 System (the PMI-58 list of HPHCs and the FDA-18 abbreviated list of HPHCs). Furthermore, the *IQOS* use patterns, product consumption, and user profiles, as evidenced by data from countries where the *IQOS* 3 System is sold, closely resemble the data for the *IQOS* 2.4 System. Finally, the design of the *IQOS* 3 System does not contain any features that are anticipated to alter the low level of interest in trial and use among adult never smokers, adult former smokers and young adults that was found with the *IQOS* 2.4 System.

The *IQOS* 3 System, like the *IQOS* 2.4 System, satisfies the requirements of section 911(g)(2), including the requirement that marketing the product is appropriate to promote the 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. Such conclusion is based on the demonstrated comparability of the *IQOS* 3 System to the *IQOS* 2.4 System in performance, use patterns, product consumption, and user profiles, successful switching of adult smokers to this modified-risk tobacco product as well as minimal use among non-users of tobacco products (including youth). As a result, we believe that the authorized reduced exposure claim(s) for the *IQOS* 2.4 System apply equally to the *IQOS* 3 System.

1.2. Supplemental MRTPA (sMRTPA) Pathway

On February 11, 2021, in FDA's written response to PMP S.A.'s pre-submission meeting request related to the planned submission of an MRTPA under section 911(g)(2) of the

FD&C Act for the *IQOS* 3 System, the FDA stated that the sMRTPA pathway may be appropriate in certain circumstances, which FDA described[4].

Applying that description to the *IQOS* 3 System, the submission of an sMRTPA is appropriate considering that:

- The *IQOS* 3 System can be legally marketed, having received a MO under the PMTA pathway (PM0000634),
- The *IQOS* 3 System represents a modified version of an authorized Modified Risk Tobacco Product, *IQOS* 2.4 System, which can be legally marketed and has an MRGO,
- The implemented modifications are not likely to – and based on the demonstrated comparability will not - render the original claims unsubstantiated for the *IQOS* 3 System,
- PMP S.A. will not submit significant new data for review in this sMRTPA for the *IQOS* 3 System (*i.e.*, studies that supported the original MRGO are the same and do not require reanalysis),
- There is no change to the modified risk statements or changes outside the scope of the authorized claims under the original MRTPA, and
- PMP S.A. is seeking an MRGO that reflects the order type, claim language included, that FDA issued under the original MRTPA (*i.e.*, an order under § 911(g)(2)).

1.3. Structure of the Dossier

To facilitate review of the sMRTPA, PMP S.A. utilized cross-referencing to the original MRTPA for the *IQOS* 2.4 System and where relevant to the premarket application (sPMTA) for the *IQOS* 3 System. This application has been structured in the same manner as the original MRTPA for the *IQOS* 2.4 System.

Table 1 below provides an overview of the PMP S.A.'s approach to providing the data and information.

[4] *See* Feb. 11, 2021 letter from Stephanie Durkin to Adam Susser Re: (STN: TC00006573).

Table 1: Structure of the sMRTPA for the *IQOS* 3 System

Module 1 General Information	Updated from MR0000479 and PM0000634 Module content: - Cover Letter
Module 2 Table of Contents	Updated from MR0000479 and PM0000634 Module content: - Table of Contents, - Glossary, - Executive Summary
Module 3 3.1 Product Description 3.2 Product Formulation 3.3 Manufacturing	Cross-referenced to PM0000634
Module 4 Labeling and Advertising	Cross-referenced to PM0000634
Module 5 Environmental Impact	Cross-referenced to PM0000634
Module 6 Summary of all Research Findings	Cross-referenced to MR0000479 and PM0000634
Module 7 Scientific Studies and Analyses	Cross-referenced to MR0000479 and PM0000634
Module 8 Post-Market Assessment	Cross-referenced to MR0000479 and PM0000634
Module 9 References	Cross-referenced to MR0000479 and PM0000634

2. PROPOSED MODIFIED EXPOSURE CLAIM

With this sMRTPA, PMP S.A. is seeking for the *IQOS* 3 System an MRGO that mirrors the order type that FDA issued under the original MRTPA for the *IQOS* 2.4 System (*i.e.*, MRTPA order under section 911(g)(2) of the FD&C Act).

Therefore, there is no change to the modified risk statements or changes outside the scope of the authorized claims under the original MRTPA. Namely, PMP S.A. seeks to use the following claim language:

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. PRODUCT DESCRIPTION AND RATIONALE

3.1. Product Description

The *IQOS* 3 System (Figure 1) is similar to the *IQOS* 2.4 System in its functionality. It consists of two components: holder (electrical heating unit) and charger (power supply to the holder) and these have the same basic operating principles.

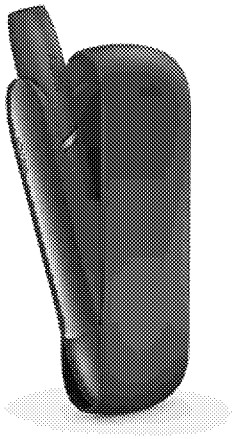


Figure 1: *IQOS* 3 System

3.2. The *IQOS* 3 System is comparable with the *IQOS* 2.4 System

The *IQOS* 3 System retains all the functional elements of the *IQOS* 2.4 System. As a result, the principles of aerosol generation remain unchanged in the *IQOS* 3 System. Therefore, as demonstrated by the data in the sPMTA, the aerosol generated with both *IQOS* Systems is comparable.

The user operates the *IQOS* 3 System in the same manner as the *IQOS* 2.4 System. A *Marlboro HeatStick* (MR0000059 – MR0000061) is inserted into the *IQOS* 3 Holder. Once inserted, the electronically controlled and chemically inert heater blade will heat the *Marlboro HeatStick*, reaching temperatures between 320 – 350 °C. This process generates aerosol that is inhaled by the user during a puff. The duration of a single *HeatStick* and the number of puffs provided by the device remain the same between the *IQOS* 3 System and the *IQOS* 2.4 System.

After use, the used *HeatStick* is to be discarded and the Holder to be recharged by the Charger for the next use.

3.3. Upgrades to the *IQOS* 2.4 System

As described in the sPMTA, modifications based on consumer research and implemented to improve the product use and convenience, involve:

(b) (4)

Also described in the sPMTA, the *IQOS* 3 System includes modifications to incorporate the evolution of electronics technology and aligns the U.S. version of the device more closely with the *IQOS* version currently commercialized outside the U.S.. Examples of these changes include:

(b) (4)

(b) (4)

Comparison of *IQOS* 2.4 Holder and Charger with *IQOS* 3 Holder and Charger is provided in Figures 2 and 3.

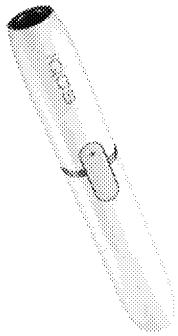
***IQOS* 2.4 Holder**	***IQOS* 3 Holder**
	

Figure 2: Comparison of *IQOS* 2.4 Holder and *IQOS* 3 Holder

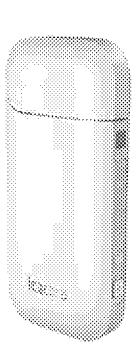
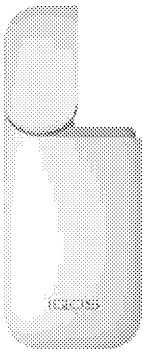
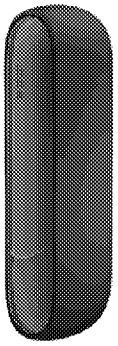
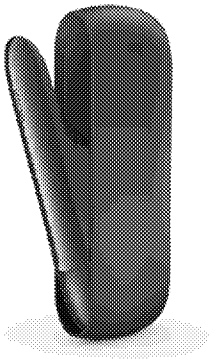
***IQOS* 2.4 Charger**		***IQOS* 3 Charger**	
			

Figure 3: Comparison of *IQOS* 2.4 Charger and *IQOS* 3 Charger

3.4. Manufacturing and Controls

The same contract-manufacturing organization that is used for the *IQOS* 2.4 System - **(b) (4)** oversees *IQOS* 3 System assembly. This organization has extensive experience with manufacturing the *IQOS* 2.4 System and was the subject of an FDA inspection in the context of the original PMTA for the *IQOS* 2.4 System.

Scientific evidence and information concerning manufacturers and manufacturing process supplied with the sPMTA for the *IQOS* 3 System (PM0000634) remains valid. PMP S.A. is not providing any new information or data in the context of this supplemental MRTPA.

3.5. Marketing and Commercialization Plans

As with the *IQOS* 2.4 System, Altria Client Services LLC (ALCS)[5] and an ALCS affiliate are licensed to distribute and sell the *IQOS* 3 System in the United States. The ALCS affiliate that distributes and sells the product in the U.S. is Philip Morris USA Inc. (PM USA).

The marketing plans presented to the Agency in the context of the *IQOS* 2.4 System were also implemented for the *IQOS* 3 System. When commercializing the *IQOS* 3 System, PM USA observes and adheres to the marketing requirements of the *IQOS* 3 System Market Order.

[5] Altria Client Services LLC (ALCS) is a wholly-owned subsidiary of Altria Group, Inc. ALCS provides certain services to the Altria family of companies.

4. SCIENTIFIC BASIS FOR A MODIFIED RISK TOBACCO PRODUCT ORDER FOR THE *IQOS* 3 SYSTEM

Other than studies provided with the sPMTA for the *IQOS* 3 System to demonstrate comparability to the *IQOS* 2.4 System, PMP S.A. did not conduct additional studies with the *IQOS* 3 System specific to this sMRTPA. As demonstrated in the sPMTA, the *IQOS* 3 System is comparable to the *IQOS* 2.4 System as it retains all functional elements of the *IQOS* 2.4 System and preserves critical principles of the System performance, safety and consumer behavior. The *IQOS* 3 System delivers substantial reductions in the number and levels of HPHCs compared to combustible cigarettes. The *IQOS* use patterns, product consumption, and user profiles, as evidenced by data from countries where the *IQOS* 3 System is sold, closely resemble the data for the *IQOS* 2.4 System. Finally, the design of the *IQOS* 3 System does not contain any features that are anticipated to alter the low level of interest in trial and use among adult never smokers, adult former smokers and young adults that was found with the *IQOS* 2.4 System.

The scientific program discussed in this section represents studies that supported the MRGO, presented in the MRTPA for the *IQOS* 2.4 System (MR0000133) with related appendices and data, and with subsequent amendments, as well as additional information specific to the *IQOS* 3 System that was provided and evaluated by the FDA as part of the sPMTA (PM0000634). All studies remain valid and do not require reanalysis.

4.1. Relative Health Risks to Individual Tobacco Users

4.1.1. Aerosol Chemistry and Physics

The *IQOS* 3 System generates an aerosol that is comparable in terms of its physico-chemical properties to the aerosol generated with the *IQOS* 2.4 System. More specifically, the data presented in sPMTA for the *IQOS* 3 System (PM0000634) show that:

- The Droplet Size Distribution (DSD) of aerosols generated with the *IQOS* 3 System is essentially the same as DSD of aerosols generated with the *IQOS* 2.4 System,
- The levels of HPHCs from the PMI-58 list of HPHCs generated with the *IQOS* 3 System, in combination with standard monitor *HeatSticks* under both extreme operating conditions (firmware with warm aerosol mitigation forced "On", and firmware with warm aerosol mitigation forced "Off") are comparable to the levels generated with the *IQOS* 2.4 System with the same standard monitor *HeatSticks*, with all nominal differences within the range of normal method variability,
- The profile and level of reductions of HPHCs from the FDA-18 abbreviated list generated with the *IQOS* 3 System with its commercial firmware configuration and each

of the *HeatSticks* variants commercially available in the U.S. (MR0000059 – MR0000061) are essentially the same as the profile and level of reductions of HPHCs reported in the original MRTPA for MR0000133, with all nominal differences attributable to normal method variability,

- The four additional constituents, which are neither part of the PMI-58 nor of the FDA - 18 list, which were reported at higher levels in the *IQOS* 2.4 System in comparison to the 3R4F reference cigarette, remain at comparable levels whether aerosols are generated with the *IQOS* 3 System or with the *IQOS* 2.4 System.

The lack of an exothermic process and the low level of nitrogen oxides in the aerosol of the *IQOS* 3 System with *Marlboro HeatSticks* confirm that combustion does not occur in the *IQOS* 3 System with *HeatSticks* when it is used as intended. Therefore, like the *IQOS* 2.4 System, there is sufficient evidence to support the statement that: "*The IQOS 3 System heats tobacco but does not burn it*."

The substantial reduction across constituents on FDA's HPHC list (abbreviated list of 18 HPHCs) demonstrates that, on the whole, the process used to heat tobacco in the *IQOS* 3 System, like in the *IQOS* 2.4 System, significantly reduces the production of HPHCs compared to cigarette smoke. Therefore, like the *IQOS* 2.4 System, there is sufficient evidence to support the modified risk claim: "*This* [the process of heating tobacco, but not burning it] *significantly reduces the production of harmful and potentially harmful chemicals*."

4.1.2. Nonclinical and Clinical Assessment

The operating principles of the *IQOS* 3 System are the same as the *IQOS* 2.4 System. Results of the aerosol chemistry and physics assessment demonstrate that the product performance remains unchanged. Aerosol generated with the *IQOS* 3 System is comparable to aerosol generated with the *IQOS* 2.4 System. The design of the *IQOS* 3 System and its usage are also largely similar to what users experience with the *IQOS* 2.4 System. Consequently, the user of the *IQOS* 3 System will be exposed to comparable aerosol as the user of the *IQOS* 2.4 System.

Comparable reductions in levels of HPHCs in the aerosol of the *IQOS* 3 System imply comparable effects observed in nonclinical and clinical models, and guide the conclusion that bridging to the nonclinical and clinical evidence provided with the original MRTPAs, instead of conducting new studies, is appropriate. Therefore the nonclinical and clinical assessments from the original MRTPA for the *IQOS* 2.4 System (MR0000133) remain valid and applicable to the *IQOS* 3 System.

4.1.3. Consumer Understanding and Perceptions

Given the comparability in aerosol of the *IQOS* 3 System to the *IQOS* 2.4 System, and considering that the applicant is not seeking any change to the modified risk statements or changes outside the scope of the authorized claims under the original MRTPA for MR0000133, PMP S.A. did not conduct any additional consumer understanding and perceptions studies.

The labeling for the *IQOS* 3 System will be consistent with the labeling for the *IQOS* 2.4 System but not identical. Differences between the labeling for the *IQOS* 2.4 System and the *IQOS* 3 System are primarily to distinguish the modified *IQOS* 3 System from the *IQOS* 2.4 System and to provide *IQOS* users with updated instructions and safety warnings based on experiences gained from countries where the *IQOS* 3 System has been commercialized. The labeling for the *IQOS* 3 System will continue to bear the brand name "IQOS®" but will be marked so as to distinguished it as a new version of the authorized product.

The marketing plan for the *IQOS* 3 System will be the same as the marketing plan for the *IQOS* 2.4 System. The target audience for the *IQOS* 3 System will continue to be adult smokers age 21+. PM USA will continue to provide adult consumers with a high level of education and guidance. Marketing will continue to be grounded in the existing *IQOS* Brand Book and Good Conversion Practices, and follow the marketing requirements of the marketing order of December 7, 2020

Given that the authorized claims and marketing plans proposed for the *IQOS* 3 System are essentially identical to those for the *IQOS* 2.4 System, the proposed marketing of the *IQOS* 3 System similarly satisfies the requirements of section 911(g)(2).

4.2. Tobacco Use Behavior and Impact to the Population as a Whole

4.2.1. User Behavior

To support authorization of the *IQOS* 3 System under section 910 of FD&C Act, PMP S.A. collected data concerning the ability of *IQOS* to completely switch adult smokers away from cigarettes in the *IQOS* Owner Panel. Those studies were conducted in several countries, including 5 countries (Germany, Japan, Italy, South Korea and Switzerland) where the observational Whole Offer Tests (WOT) premarket studies were conducted (as provided in the original MRTPA for MR0000133).

Those data show that the majority of *IQOS* owners switched completely to *IQOS* and are using *IQOS* exclusively, irrespective of the *IQOS* System version they owned, *i.e.*, *IQOS* 2.4/2.4+ or *IQOS* 3. In all five countries comparable patterns of exclusive *IQOS* use were observed (*i.e.*,

IQOS representing 100% of the daily tobacco consumption, considering both cigarettes and heat-not-burn products) for panelists owning either *IQOS* 2.4/2.4+ or *IQOS* 3 Systems. In addition, data from the same *IQOS* Owner Panels show that the average daily consumption in each of the 5 countries is similar, regardless of the version of *IQOS* System owned. Finally, in each of the 5 countries, the data show that the gender and age profile of *IQOS* owners is, in general, comparable irrespective of the version of the *IQOS* System.

With respect to the likelihood of adult non-smokers starting to use *IQOS*, it can be reasonably expected that the same three major factors that can be considered as limiting conditions for the *IQOS* 2.4 System are also applicable for the *IQOS* 3 System:

1) The *IQOS* 2.4 System and the *IQOS* 3 System, consist of the same main components (*i.e.,* a holder and a charger), with no major differences that could result in a different outcome,
2) Premarket PBA 05 studies conducted in the U.S. with the *IQOS* 2.4 System show low intention to try/use *IQOS* among adult non-smokers. The same product characteristics that likely led to low intention to try/use *IQOS* among adult non-smokers are inherent to the *IQOS* 3 System. Based on what the data show in non U.S. countries where the *IQOS* 3 System is commercialized, the modifications brought to the system in terms of design and features are not likely to alter the low intent to try/use observed through the PBA 05 studies conducted with *IQOS* 2.4 System,
3) The marketing requirements and periodic reporting included in the PMTA Marketing Order for the *IQOS* 2.4 System and the Marketing Granted Order for the *IQOS* 3 System are designed to ensure that the marketing of the product continues to be appropriate for the protection of public health.

In view of the above, it can reasonably be expected that irrespective of the *IQOS* System version, current adult cigarette smokers will represent the segment of the population that is most likely to use *IQOS*. As presented and discussed in the sPMTA for the *IQOS* 3 System (PM0000634), PMI pre-market data gathered in the U.S., international PMI post-market data from different countries, and independent studies from non-U.S. countries show low likelihood of starting using *IQOS* among non-smokers, including former and never smokers, regardless of the *IQOS* System version. Therefore, an increased risk of unintended consequences, *e.g.*, high tobacco use initiation and re-initiation with the *IQOS* 3 System, is not to be expected in the U.S. if the *IQOS* 3 System will be authorized with the MRGO by the Agency. The marketing and advertising restrictions implemented for the *IQOS* 2.4 System will also apply to the *IQOS* 3 System and hence ensure that *IQOS* is only sold to current adult smokers who would otherwise continue smoking and are at least 21 years old.

4.2.2. Product Safety

Based on PMP S.A.'s experience with the *IQOS* 3 System from the countries where it has been commercialized since 2018, there are no meaningful differences in the safety profile of the *IQOS* 3 System and the *IQOS* 2.4 System. The analysis of available data shows that the *IQOS* 2.4 System and *IQOS* 3 System have similar safety profiles. Therefore, introducing the *IQOS* 3 System to the market is not expected to affect the user's safety.

These observations further confirm comparability of the *IQOS* 3 System to the *IQOS* 2.4 System.

4.2.3. 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.*"

Upon issuance by FDA of the MRGO – Exposure Modification, the *IQOS* 3 System will be incorporated into the PMSS program implemented for the *IQOS* 2.4 System, which was accepted by the FDA on February 24, 2021[6].

Like the PMSS for the *IQOS* 2.4 System, the PMSS for the *IQOS* 3 System will generally comprise the following activities:

(1) Assessment of Behavior and Perceptions.

A combination of new studies and analyses of data from existing studies to assess adult (age 21+) consumer uptake, dual use and switching associated with *IQOS* use. The studies assess tobacco user status (never, former, current) prior to first *IQOS* use. Further, the research evaluates exclusive and dual/poly use with *IQOS* and transitions to/away from combustible cigarettes, and it includes observations of these behaviors over time. In addition, the program will assess adult consumer perceptions of risk associated with *IQOS* use. It will as well assess awareness of the modified risk message and, among those aware, comprehension of the modified risk information.

[6] Letter of February 24, 2021 (STN: PS0000042) confirming that the FDA completed its review of the PMP S.A.'s amendments and revised protocols for the proposed Postmarket Surveillance and Studies (PMSS) submission for the *IQOS* 2.4 System with 3 variants of *Marlboro HeatSticks* (MR0000059 - MR0000061 and MR0000133) without any concerns and that PMP S.A. may proceed with initiation of the studies.

Assessment of awareness and use of *IQOS* among underage individuals, comprised of youth 13-17 years of age and young adults 18-20 years of age will be conducted.

Reporting *IQOS* Sales and Distribution Data to assist in assessing uptake of *IQOS*.

(2) Safety Surveillance

Consistent with the program in place to support PMTA reporting, the PMSS program will continue to capture, assess and report adverse experiences associated with the use of the *IQOS* System. The safety surveillance system includes ongoing signal detection and evaluation, as well as mechanisms for safety data communication and reporting.

(3) Monitoring of New Studies.

Consistent with the program in place to support PMTA reporting, we will continue to monitor and report significant findings from published studies and results from our own research studies relevant to *IQOS* and consumer perceptions, behavior, health and safety.

(4) Update of PMP S.A.'s population health impact model as new inputs are obtained from in-market U.S. data sources.

(5) When this data becomes available, computational toxicology assessment of aerosols to predict potential adverse effects in users before toxicity may be evident.

5. SUMMARY OF FINDINGS AND CONCLUSIONS THAT SUPPORT ISSUANCE OF THE MODIFIED RISK GRANTED ORDER – EXPOSURE MODIFICATION FOR THE *IQOS* 3 SYSTEM

Available data and analyses demonstrate that, like the *IQOS* 2.4 System, if the *IQOS* 3 System is sold or distributed with the proposed modified risk information, it meets 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 in subsequent studies, and issuance of a modified exposure order is appropriate to promote the 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.

This sMRTPA is for the *IQOS* 3 System Holder and Charger, which will be used with the same *Marlboro HeatSticks* as were authorized for use with the *IQOS* 2.4 System. The product design and characteristics are similar, the tobacco source (*Marlboro HeatSticks*) is unchanged, and the aerosol produced from using the *HeatSticks* in the two devices is comparable. Substantial reduction across the constituents on FDA's HPHCs list demonstrates that, on the whole, as compared to combusted cigarette smoke, the process used to heat tobacco in the *IQOS* 3 System

significantly reduces the production of HPHCs compared to cigarette smoke, similarly to the *IQOS* 2.4 System. Therefore, there is no reason to believe the impact on population health will be different for the *IQOS* 3 System as compared to the *IQOS* 2.4 System.

It has been demonstrated with the *IQOS* 2.4 System that the magnitude of differences in biomarkers of exposure (BoEs) to 15 HPHCs when smokers switch completely to *IQOS* is substantial. The reduced BoEs represent a range of chemical classes (*e.g.*, carbonyls, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines) and toxicity classes (*e.g.*, carcinogenic, cardiovascular, respiratory, reproductive). Although BoEs are not available for every constituent on the FDA's HPHCs list (Established list of 93 HPHCs), the comparative aerosol data provided demonstrate that many other HPHCs are significantly reduced compared to combusted cigarette smoke. Given the similarity between the *IQOS* 3 System and the *IQOS* 2.4 System, it is scientifically reasonable to expect that a similar effect will be achieved when the *IQOS* 3 System is used.

The data about use patterns from international markets support the conclusion that adult smokers who switch completely to the *IQOS* 3 System should achieve reduced exposure to harmful and potentially harmful chemicals similar to when switching completely to the *IQOS* 2.4 System.

Given the product similarities, there is no evidence of increased risk for youth initiation and use for the *IQOS* 3 System as compared to the *IQOS* 2.4 System. It can reasonably be expected that irrespective of the *IQOS* System version, current adult cigarette smokers will represent the segment of the population that is most likely to use *IQOS*. The likelihood of starting using *IQOS* among non-smokers, including former and never smokers, regardless of the *IQOS* System version is low. Therefore, an increased risk of unintended consequences, *e.g.*, high tobacco use initiation and re-initiation with the *IQOS* 3 System, is not to be expected in the U.S. if the *IQOS* 3 System will be authorized with the MRGO by the FDA.

Overall, the scientific evidence presented for the *IQOS* 3 System, demonstrates that "*the IQOS system heats tobacco but does not burn it*," "*this significantly reduces the production of harmful and potentially harmful chemicals*," and "*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*."

Based on the demonstrated comparability of the *IQOS* 3 System to the *IQOS* 2.4 System in performance, use patterns, product consumption, and user profiles, successful switching of adult smokers to this modified-risk tobacco product as well as minimal use among non-users of tobacco products (including youth), issuing an exposure modification order for the *IQOS* 3 System is equally appropriate to promote the public health and is expected to benefit

the health of the population as a whole. Therefore, an order under 911(g)(2) of the FD&C Act for the *IQOS* 3 System is warranted.