PMSS REPORT
FOR MR0000059-MR0000061 and MR0000133

FDA STN No.	MR0000059 MR0000060 MR0000061 MR0000133[1]
Tobacco Product Name	*Marlboro* Amber *HeatSticks* *Marlboro* Green Menthol *HeatSticks* *Marlboro* Blue Menthol *HeatSticks* *IQOS* System Holder and Charger
Tobacco Product Category	Cigarette
Tobacco Product Sub-category	Non-Combusted
Applicant	Philip Morris Products S.A. (PMP S.A.)
Date of Report	April 29, 2022
Reporting Period	March 1, 2021 to February 28, 2022

[1] On March 11, 2022, FDA has issued Modified Risk Granted Order for Exposure Modification order (MR0000192) for *IQOS 3* System Holder and Charger; no data are reported on this product as the MRGO was issued outside of the reporting period for the 2022 PMSS Report.

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FOREWORD

On September 29, 2021, the United States International Trade Commission (ITC) issued a Cease-and-Desist Order (CDO) that prohibited the importation, marketing, sale and distribution of *IQOS* devices and *Marlboro HeatSticks.*[2] To comply with the CDO, PM USA stopped marketing and selling all *IQOS* devices and *Marlboro HeatSticks* by November 28, 2021, at all third-party retail stores, PM USA owned stores and the getIQOS.com website. Therefore, at the end of November 2021, *IQOS* holders and chargers and *HeatSticks* were not available in any third-party retail outlets in the four-state market area.

As a result of this cessation of marketing and sales, the data in this period report will not show sales beyond November 28, 2021 in this periodic report. This cessation of sales also has a corresponding impact on data on product purchasers, as there have been no product purchasers since November 28, 2021. Lastly, as per our correspondence with CTP on January 14, 2022,[3] this CDO will impact the plans for PostMarket Surveillance and Studies (PMSS).

This cessation of marketing and advertising will impact reporting data related to advertising impressions, dollar amounts and flighting of paid media plans, and other advertising and marketing metrics which are required as part of this annual report. Except where otherwise noted, a lack of data for a given marketing channel or time period is not a reflection of an error in the report, but rather the data accurately reflecting the lack of marketing and advertising activity in that marketing channel and/or during that time period.

CTP will be kept informed of updates on this situation going forward.

1 EXECUTIVE SUMMARY

On July 7, 2020, FDA issued the "Modified Risk Granted Order (MRGO) - Exposure Modification" authorizing the *IQOS* System Holder and Charger with three variants of *Marlboro HeatSticks* to be marketed with reduced exposure claims. The MRGO was issued after the FDA determined that the products satisfy the requirements of section 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including the requirement that marketing of 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.

The Order is conditioned upon agreement to conduct postmarket surveillance and studies (PMSS). Pursuant to the MRGO, PMP S.A. submitted protocols and associated information

[2] Certain Tobacco Heating Articles and Components Thereof, 337-TA-1199 U.S. International Trade Commission (September 29, 2021).

[3] Adjustment to the Postmarket Surveillance and Studies (PMSS) Plan forMR0000059 - MR000061 and MR0000133, January 14, 2022

for the components of the planned PMSS which subsequently were accepted by the FDA on February 24, 2021.[4]

The PMSS has been jointly developed and will be jointly conducted with Altria Client Services LLC (ALCS)[5] and an ALCS affiliate licensed to distribute and sell the product in the United States. The ALCS affiliate that distributes and sells the product in the U.S. is Philip Morris USA Inc. (PM USA).[6]

As the order under 911(g)(2) of the FD&C Act is conditioned on the agreement to conduct PMSS to "*determine the impact of the order on consumer perception, behavior, and health, and to enable the Agency to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the FDA*", the PMSS Plan for the *IQOS* System Holder and Charger with three variants of *Marlboro HeatSticks* comprises the following activities:

(1) Assessment of Behavior and Perceptions

Studies and Analyses of Adults (Age 21+) through 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 using *IQOS*. 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, as well as awareness of the modified risk message and, among those aware, comprehension of the modified risk information.

Analyses of Underage Individuals (ages 13 - 20) to assess awareness and use of *IQOS* among underage individuals, comprised of youth 13 - 17 years of age and young adults 18 - 20 years of age.

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 *IQOS*.

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[4] 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* 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.

[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.

[6] PMP S.A.'s parent, Philip Morris International Management S.A. (PMI), has entered into an agreement with ALCS by which ALCS and its affiliates, including PM USA, are licensed to sell *IQOS* in the United States.

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 the PMP S.A.'s population health impact model as new inputs are obtained from in-market data sources.

(5) Computational toxicology assessment of aerosols to evaluate the cancer risk from exposure to compounds increased in the *IQOS* System aerosol compared to the 3R4F cigarette smoke.

Following FDA approval of the PMSS Plan, PMP S.A. and ALCS will now proceed with execution of proposed studies and analyses in accordance with the PMSS Plan. The studies in progress will be reported on an annual basis, by April 30 of each year in a PMSS Report. The report will include the MRTP specific sections of the joint PMTA/MRTPA annual report that will be submitted by April 30 of each year. Once a study is completed, the PMSS Report will include the final study report.

2 MRTP USE BEHAVIOR AND CONSUMER UNDERSTANDING AND PERCEPTION

2.1 Summary of U.S. Postmarket Studies

During this reporting period, all postmarket surveillance and studies were implemented as planned. We successfully added the *IQOS* module to our ongoing Underage Tobacco Use Survey (UTUS) in the second quarter of 2021, conducted the first wave of the *IQOS* Cross-Sectional Postmarket Adult Consumer Study (PACS) (b) (4) in the third and fourth quarters of 2021, and maintained analyses of ongoing market surveillance. This information is initial evidence related to awareness, consumption, use patterns over time, and adult consumer understanding of the modified risk messaging.

Prevalence of adult *IQOS* use appears to be low, which aligns with its limited time in market and limited distribution in the U.S. In fact, data from the nationally representative Adult Tobacco Consumer Tracking (ATCT) study,[7] revealed three adult (21+) past 30-day *IQOS* users between March 1, 2021, and February 28, 2022. In addition, results of the Underage

[7] PMSS: Secondary Analysis: Estimation of Prevalence of IQOS Use; Ongoing survey that provides a nationally representative sample of ~28,800 U.S. adults (21+) annually

Tobacco Use Survey suggest that underage awareness, ever use, and past 30-day use of *IQOS* is very low. With a sample size of 5,205, only four individuals (one 13-17 year old minor and three 18-20 year old underage young adults) reported that they used *IQOS* in the past 30 days prior to the assessment.[8] Among these four individuals, one correctly identified that *IQOS* "only uses sticks containing actual tobacco," which signals a certain level of confusion about *IQOS* and that self-reported use may be overestimated among underage individuals.

Results of the first wave of *IQOS* Cross-sectional PACS demonstrate that current *IQOS* consumers largely consist of existing tobacco users, especially long-term cigarette smokers. During the limited duration when *IQOS* was marketed in the U.S., almost one in three *IQOS* users had switched from smoking to *IQOS*. And more than 80% of *IQOS* users who were still smoking reported that they reduced their cigarette consumption, potentially signaling a journey toward switching. Initiation of *IQOS* by never users of tobacco is extremely rare. Additionally, initiation and relapse to smoking after first trying *IQOS* is extremely rare. Data from the *IQOS* Owners Panel support a general reduction in combustible tobacco product use over time, as (b) (4) of panelists had completely switched from cigarettes to *IQOS*. Since the last annual report, panelists engaging in dual use with cigarettes (b) (4) Among all panelists, over (b) (4) reported using no other tobacco products.

The *IQOS* Cross-Sectional PACS study evaluated risk perceptions of *IQOS* and cigarettes and adult consumer understanding of the modified risk messaging. Adult established *IQOS* users perceived *IQOS* to be less harmful than cigarettes, but not free of harm. Among current established *IQOS* users, 81% correctly identified that completely switching from cigarettes to *IQOS* would result in less exposure to harmful or potentially harmful chemicals (HPHC). Similarly, 85% of those who had the correct understanding about HPHC exposure identified that to reduce one's exposure to HPHC, individual must completely switch to IQOS.

Overall, data from *IQOS* postmarket surveillance and studies support that *IQOS*, as actually used by consumers, continues to be appropriate to promote the public health and is expected to benefit the health of the population as a whole.

The cessation of sales of *IQOS* due to the aforementioned ITC order limits our study and surveil *IQOS* use. As such, our timing and plans for PMSS moving into 2022 have been adjusted as documented in the letter sent to FDA on January 14, 2022.[9] Changes include pausing *IQOS* Cross-Sectional PACS and *IQOS* Cohort PACS study conduct in 2022 and ending reporting from the current U.S. *IQOS* Owners Panel. Additionally, while UTUS data collection is ongoing into 2022, we halted the oversample in Atlanta, GA, Charlotte, NC and Richmond,

[8] Past 30-day IQOS® use was assessed among individuals who were aware of heated tobacco products, had ever used a heated tobacco product, used a heated tobacco product during the past 30 days.

[9] On January 14, 2022, Philip Morris Products S.A. submitted the *Premarket Tobacco Product Application Amendment and General Correspondence Submission* to LCDR Michael Gu regarding the *Adjustment to the Postmarket Surveillance and Studies (PMSS) Plan for MR0000059 - MR000061 and MR0000133.*

VA starting in the second quarter of 2022. ATCT data collection, including surveillance of *IQOS* use, will be ongoing.

2.2 Summary of Sales and Distribution Data

Over the reporting period, *IQOS* 2.4 devices, *IQOS* 3.0 devices, and three variants of *Marlboro HeatSticks* (*Marlboro Amber HeatSticks, Marlboro Green Menthol HeatSticks, Marlboro Blue Menthol HeatSticks*) have been available for purchase in certain markets where *IQOS* is commercialized.

In April of 2021, PM USA expanded *IQOS* and *Marlboro HeatSticks* (i) into retail stores statewide across Georgia, Virginia, North Carolina, and South Carolina and (ii) to the Northern Virginia metro market. To support the expansion, PM USA opened an *IQOS* boutique in the Tysons Corner Mall in Northern Virginia.

However, on November 29, 2021, the importation ban and cease-and-desist orders imposed by the ITC on the *IQOS* device, *Marlboro HeatSticks,* and infringing components went into effect. As a result of the *IQOS* system being no longer available for sale in the U.S. and devices being returned by retailers due to the ITC orders, sales in the fourth quarter of 2021 were negative.

For the year, compared to 2020, total *IQOS* device sales increased by over (b) (4), largely driven by expanded distribution in retail stores and the launch of the *IQOS* 3.0 device, which features a longer battery life and a faster re-charging time compared to the 2.4 version. On a quarter-by-quarter basis, *IQOS* device sales increased by over (b) (4) from Q1 to Q2 before declining by approximately (b) (4) from Q2 to Q3.

Year over year, *Marlboro HeatSticks* retail sales volumes also increased by over (b) (4). *Marlboro HeatSticks* sales increased by over (b) (4) from Q1 to Q2, followed by a decline of approximately (b) (4) from Q2 to Q3.

See Table 1 below for a summary of volume and percent change by quarter and full year 2021.

Annex P01-5 provides full-year 2021 U.S. sales and distribution by calendar quarter. PM USA uses this full calendar year and quarter timeframe approach to report PMSS Sales and Distribution data as first-quarter data is not available to report by April 30, 2022.

Table 1. Summary of Quarterly and Annual Volume Change (*HeatStick* Volume in

(b) (4)

3 MRTP USE AND HEALTH RISK – TOXICOLOGY

As part of the initial product characterization of the *IQOS* System, non-targeted differential screening (NTDS) analyses of the aerosol generated from *Marlboro* Amber *HeatSticks* (MR0000059), Marlboro Green Menthol *HeatSticks* (MR000060), and Marlboro Blue Menthol *HeatSticks* (MR000061) with the *IQOS* System Holder and Charger (MR0000133) were performed to identify compounds which were potentially new, or significantly increased in *IQOS* aerosol relative to 3R4F cigarette smoke. A hazard identification protocol was developed to determine the genotoxic and carcinogenic potential of both these inhaled tobacco product constituents and their potentially reactive and toxic metabolites.

The study is divided in three phases:

- The project Phase 1 is intended to determine the genotoxicity and/or carcinogenicity potential of the 80 chemicals identified as potentially new, or significantly increased in IQOS aerosol relative to 3R4F smoke.
- The project Phase 2 is intended to determine the potential metabolites of the 80 chemicals relevant to humans.
- The project Phase 3 is intended to determine the genotoxicity and/or carcinogenicity potential of the relevant metabolites.

The phase 1 has been completed and the outcome is presented in Annex P02 of this report. Phase 2 completion is expected by Q3 2022 and Phase 3 completion by end of Q2 2023.

After completion of Phase 2 and Phase 3 of the project, identified hazards will be reported for each group of compounds (parents and metabolites) and segmented according to the quality and the reliability of data. Any collected data will be integrated into a narrative by human experts to evaluate and discuss all relevant factors associated with the data to help understand the formation of metabolites from parent compounds as well as the potential genotoxicity/carcinogenicity risk of the parent compounds.

4 MRTP USE AND HEALTH RISK – SERIOUS AND UNEXPECTED ADVERSE EXPERIENCES

The global safety database was searched for serious and unexpected adverse events reported with the use of *IQOS* System that originated from unsolicited sources in the U.S. The search covered the period from January 1, 2021, to December 31, 2021, which stands for both reporting and cumulative period of this report.

There were no serious and unexpected adverse experiences with the use of the *IQOS* System retrieved in the search. Considering that no safety related information was identified, the knowledge on the product remains unchanged.

5 SURVEILLANCE OF NEW RESEARCH STUDY FINDINGS ON THE MRTPS AND CONSUMER PERCEPTION, BEHAVIOR, OR HEALTH

As explained in section 2, *IQOS* cross-sectional study (b) (4) and *IQOS* cohort study (b) (4) have been paused. To date, the data from the *IQOS* Owners Panel is limited, however results are promising as they point to a general reduction in combustible tobacco product use over time and they show that the majority of active panel participants have (b) (4) in the past year (for additional information please refer to Annex 1 of the 2022 PMSS Report).

In addition to conducting the above-mentioned studies, we will continue reporting ongoing and completed behavioral studies performed outside of the U.S. as well as provide a summary of significant findings in publications not previously reported as part of the Pre-Market Tobacco Application (PMTA) Marketing Order requirements. Please refer to the summary of the behavioral studies performed outside of the U.S. and significant findings in previously not reported publications in 2022 PMTA Annual Report and corresponding Annexes 2-1 and 2-2.

6 MODELING THE IMPACT OF THE MRTP ON POPULATION HEALTH

The Population Health Impact Model (PHIM) is used to assess the population health effects of introducing a new Reduced-Risk Product (RRP) as a function of the risk of the product to the individual user, and the prevalence and patterns of product use. The model allows the exploration of a wide range of scenarios assessing the possible effect of RRP introduction on the prevalence of CC and RRP use, individually and in combination. By comparing mortality attributable in a scenario where RRP is introduced (Business Case scenario) on the U.S. market

in 1990 with one (Null scenario) where it is not, the model estimated the mortality attributable to CCs and RRP, as well as the reduction in deaths over a twenty-year period following the introduction of a new product. The simulations are built on a number of assumptions. The robustness of the results is investigated in terms of sensitivity analyses.

PMP S.A. and ALCS intended to start the PMSS Plan with latest version of the PHIM (PHIM v 8.) during the reporting period (March 1, 2021, to February 28, 2022). However, as a result of the cessation of marketing and sales due to the aforementioned ITC order, PHIM v.8 could not be deployed, and no data are provided in this year's report.