PMSS REPORT

FDA STNs	Tobacco Product Names
MR0000059	*Marlboro* Amber *HeatSticks*
MR0000060	*Marlboro* Green Menthol *HeatSticks*
MR0000061	*Marlboro* Blue Menthol *HeatSticks*
MR0000133	*IQOS* System Holder and Charger
MR0000192	*IQOS* 3 System Holder and Charger
Tobacco Product Category	HTP
Tobacco Product Sub-category	open HTP and HTP consumable
Applicant	Philip Morris Products S.A. (PMP S.A.)
Date of Report	April 28, 2024
Reporting Period	March 1, 2023, to February 29, 2024

TABLE OF CONTENTS

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*[1]. To comply with the CDO, Altria Client Services LLC (ALCS)[2] stopped marketing and selling all *IQOS* devices and *HeatSticks* by November 28, 2021, at all third-party retail stores, PM USA owned stores and the get*IQOS*.com website. Therefore, at the end of November 2021, *IQOS* devices 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, no data is shown in this period 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 impacted the plans for PostMarket Surveillance and Studies (PMSS).

1 EXECUTIVE SUMMARY

On July 7, 2020, FDA issued the "Modified Risk Granted Order (MRGO) – Exposure Modification" authorizing the *IQOS* device (MR0000133) with three variants of *Marlboro HeatSticks* (MR0000059 – MR0000061) 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. Subsequently, on March 11, 2022, the FDA issued a MRGO – Exposure Modification authorizing the *IQOS* 3.0 device (MR0000192), which is an upgraded version of the previously authorized *IQOS* device.

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

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

[3] Adjustment to the PMSS Plan for MR0000059 - MR000061 and MR0000133, January 14, 2022.

The MRGOs were conditioned upon agreement to conduct PMSS. Pursuant to the MRGO, we submitted protocols and associated information for the components of the planned PMSS, which subsequently were accepted by the FDA[4, 5].

The PMSS has been jointly developed and is jointly conducted with ALCS and an ALCS affiliate (Philip Morris USA Inc.) licensed to distribute and sell the product in the United States.

As the order under section 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 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* products. Further, the research evaluates exclusive and dual/poly use with *IQOS* products and transitions to/away from combustible cigarettes, and it includes observations of these behaviors over time. In addition, the program assesses 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* products 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* products.

(2) Safety Surveillance

Consistent with the program in place to support PMTA reporting, the PMSS program aimed to capture, assess and report adverse experiences associated with the use of *IQOS* products. The

[4] February 24, 2021, letter (STN: PS0000042) confirming that the FDA completed its review of our amendments and revised protocols for the proposed PMSS submission for the *IQOS* device (MR0000133) with three variants of *Marlboro HeatSticks* (MR0000059 - MR0000061) without any concerns and that we may proceed with initiation of the studies.

[5] January 10, 2023, letter (STN: PS0000169, PS0000194, PS0000231, PS0000268) confirming that the FDA completed its review of our amendments and revised protocols for the PMSS update to incorporate the *IQOS* 3.0 device (MR0000192) without any concerns and that we may proceed with initiation of the studies.

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 our 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* product aerosol compared to 3R4F cigarette smoke.

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

2 MRTP USE BEHAVIOR AND CONSUMER UNDERSTANDING AND PERCEPTION

2.1 Summary of U.S. Post Market Studies

The cessation of sales of *IQOS* products due to the ITC CDO has limited our ability to study and surveil *IQOS* use. As such, timing and plans for PMSS moving into 2022 were adjusted as documented in the letter sent to FDA on January 14, 2022. Changes included pausing the *IQOS* cross-sectional study (ALCS-CMI-17-36-HT), postponing the *IQOS* cohort study (ALCS-CMI-17-37-HT) and halting reporting from the U.S. *IQOS* Owners Panel[6]. Additionally, while the Underage Tobacco Use Survey (UTUS) data collection has continued, the oversample in Atlanta, GA, Charlotte, NC and Richmond, VA was halted starting in the second quarter of 2022. The Adult Tobacco Consumer Tracking (ATCT) study data collection, including surveillance of *IQOS* use is ongoing. However, only a small sample of *IQOS* users was collected through ATCT, which precluded analysis regarding dual/poly use, amount and frequency of use, initiation, complete switching, and tobacco quitting behaviors relative to *IQOS* products. No recent post market studies were undertaken to capture adult consumer

[6] 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 Post market Surveillance and Studies (PMSS) Plan for MR0000059 - MR000061 and MR0000133.*

understanding and perception of *IQOS* products, and the latest data was presented in 2022 Annual Report[7].

Prevalence of adult *IQOS* use continued to be low, with just four adult 21+ past 30-day users reported amongst a sample of 28,835, which aligns with the absence of marketing and distribution in the United States. In addition, results of UTUS suggest that underage awareness, ever use, and past 30-day use of *IQOS* products is very low. With a sample size of 5,676 individuals aged 13 - 20 years, about one in five participants (n = 1,103) replied they were "not sure" whether they had ever seen or heard of *IQOS* products and another eight participants did not reply to the question. In the remaining sample of 4,565 participants, an estimated 3.5% of youth (13 - 17 years) and 9.4% of young adults (18 – 20 years) reported having ever seen or heard of *IQOS*. An estimated 0.4% of youth and 1.3% of young adults reported ever use of *IQOS*. Less than 0.5% of youth and young adults reported past 30-day use of *IQOS*. Among the 27 individuals who had indicated use of *IQOS*, but not within the past 30 days (*i.e.*, *IQOS* ever-users), three correctly identified that *IQOS* "only uses sticks containing actual tobacco," while another three did not know. Of the eight individuals who reported use of *IQOS* in the 30 days prior to taking the survey, three correctly identified *IQOS*.

The *IQOS* Cross-Sectional (ALCS-CMI-17-36-HT), *IQOS* Owners Panel, and the *IQOS* Cohort (ALCS-CMI-17-37-HT) were not conducted during the reporting period. Results of the first wave of *IQOS* Cross-sectional Post market Adult Consumer Study (PACS), previously submitted as part of the 2022 Annual Report[8], demonstrate that current *IQOS* consumers largely consist of existing tobacco users, especially long-term cigarette smokers. During the limited duration when *IQOS* products were marketed in the United States, almost one in three *IQOS* users had switched completely from smoking to *IQOS* products. 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* products by never users of tobacco is extremely rare. Additionally, initiation and relapse to smoking after first trying *IQOS* products is also extremely rare. Data from the *IQOS* Owners Panel support a general reduction in combustible tobacco product use over time, as 43% of panelists had completely switched from cigarettes to *IQOS* products. Since the last annual report, panelists engaging in dual use with cigarettes decreased from ~ 40% to 27%. Among all panelists, over 72% reported using no other tobacco products.

[7] 2022 Annual Report for PM0000424 - PM0000426, PM0000479 and PM0000634 and MR0000059 - MR0000061 and MR0000133 and PMSS Report for MR0000059 - MR0000061 and MR0000133, covering the reporting period from March 1, 2021, to February 28, 2022, submitted to FDA on April 29, 2022.

[8] Appendix P01-1_-_*IQOS*_Cross-Sectional_PACS_-_Wave_1_Final_Study_Report submitted to FDA on April 29, 2022, as part of the 2022 Annual Report

Overall, data from *IQOS* post market surveillance and studies support that *IQOS* products, as actually used by consumers, continue to be appropriate to promote the public health and are expected to benefit the health of the population as a whole.

2.2 Summary of Sales and Distribution Data

IQOS products have not been marketed or distributed in the United States since the removal of *IQOS* products from the market on November 28, 2021[9]. As a result, no new sales data is provided, and previous sales data submitted as part of the 2022 Annual Report[10] is cross-referenced.

3 MRTP USE AND HEALTH RISK – TOXICOLOGY

As part of the initial product characterization of the *IQOS* products, 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* device (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.

[9] In September 2021, the International Trade Commission (ITC) issued an order imposing an importation ban on the *IQOS* device and Marlboro *HeatSticks* into the United States, and a cease and desist order on the marketing and sale of product already imported into the United States.

[10] 2022 Annual Report for or PM0000424 - PM0000426, PM0000479 and PM0000634 and MR0000059 - MR0000061 and MR0000133 and PMSS Report for MR0000059 - MR0000061 and MR0000133, covering the reporting period from March 1, 2021, to February 28, 2022, submitted to FDA on April 29, 2022.

Phase 1 was completed and reported in the 2022 Annual Report[11]. Phase 2 was completed and reported in the 2023 Annual Report[12]. Phase 3 of the project is on-going, assessment is completed. We are currently reviewing the data, and the study report is being under preparation. We will submit the report immediately upon its completion.

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* products that originated from unsolicited sources in the United States. The search covered the period from January 1, 2023, to December 31, 2023.

There were no serious and unexpected adverse experiences with the use of the *IQOS* products 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 (ALCS-CMI-17-36-HT) was paused, *IQOS* cohort study (ALCS-CMI-17-37-HT) has been postponed and the data collection for the *IQOS* Owners Panel was halted. Previously submitted data for the *IQOS* Owners Panel has shown a general reduction in combustible tobacco product use over time and that the majority of active panel participants switched completely to *IQOS* products from cigarettes in the past year (for additional information please refer to Annex 1 of the 2022 PMSS Report[13]). ALCS also conducted a study to characterize tobacco use patterns and behaviors among U.S. adults 21 years of age or older who smoke when provided with the *IQOS* 3.0 device under near "real-world" conditions for six weeks (Phase II Tobacco Product Portfolio Study / Pilot Actual Use Study of *IQOS* 3.0, see Annex 14 to the 2023 Annual Report). The Phase II Tobacco Product Portfolio Study / Pilot Actual Use Study of *IQOS* 3.0 revealed ~40% switching from smoking to *IQOS*. In addition, among participants who continued smoking, ~60% reduced their cigarette consumption by half or more.

We will continue reporting summaries of significant findings in publications not previously reported as part of the PMTA Marketing Order requirements. Please refer to the summary of

[11] Appendix P02 - MRTP Use and Health Risk - Toxicology submitted to FDA on April 29, 2022, as part of the 2022 Annual Report

[12] Appendix A02 - MRTP Use and Health Risk - Toxicology submitted to FDA on April 28, 2023, as part of the 2023 Annual Report

[13] Annex P01-3_-_*IQOS*_Owners_Panel_Report_for_*IQOS*_PMSS_2022 submitted to FDA on April 29, 2022, as part of the 2022 Annual Report

the behavioral studies performed outside of the United States and significant findings in previously not reported publications in 2023 PMTA Annual Report and corresponding Annexes 2-1 and 2-2[14].

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 where it is not (Null scenario), 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 the latest version of the PHIM (PHIM v 8.) during the reporting period (March 1, 2022, to February 28, 2023). 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.

[14] 2022 Annual Report for PM0000424 - PM0000426, PM0000479 and PM0000634 and MR0000059 - MR0000061 and MR0000133 and PMSS Report for MR0000059 - MR0000061 and MR0000133, covering the reporting period from March 1, 2021, to February 28, 2022, submitted to FDA on April 29, 2022.