PMSS REPORT
FOR MR0000059 - MR0000061 and MR0000133

FDA STN No.	MR0000059 MR0000060 MR0000061 MR0000133
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 30, 2021
Reporting Period	July 7, 2020 to February 28, 2021

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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 for the components of the planned PMSS which subsequently were accepted by the FDA on February 24, 2021[1].

The PMSS has been jointly developed and will be jointly conducted with Altria Client Services LLC (ALCS)[2] 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)[3].

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

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[1] 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.

[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] 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.

over time. In addition, the program will assess adult consumer perceptions of risk associated with *IQOS* use, as well as 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*. 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.

This first Annual Report provides only limited information and data related to the PMSS Plan because the plan was agreed only on February 24, 2021[4] and as requested by the FDA the PMSS Plan could only start upon the FDA's approval.

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.

[4] Similar to the Annual Report associated with the April 30, 2019 PMTA Order, the cut-off date for data and report generation is the end of February each year.

2 MRTP USE BEHAVIOR AND CONSUMER UNDERSTANDING AND PERCEPTION

2.1 Summary of U.S. Post Market Studies

On February 24, 2021, FDA issued its letter of approval for the planned post market surveillance and studies. As directed, PMP S.A did not start any planned post market surveillance studies prior to FDA's approval and thus, this report is limited to the data and information gained from our ongoing market surveillance and does not include information from any new studies or amendments to ongoing studies. This means that to date we have a limited amount of evidence related to awareness, consumption, use patterns over time, and adult consumer understanding of the modified risk messaging. We plan to implement the Underage Tobacco Use Survey (UTUS) *IQOS* module and launch the first *IQOS* cross-sectional study (ALCS-CMI-17-36-HT) in the 2nd and 3rd quarters of 2021, respectively. We do not plan to launch the first *IQOS* cohort study (ALCS-CMI-17-37-HT) until 2022.

Early evidence from the US suggests low uptake at a national level which is likely due to *IQOS* only being available in select markets. Data from Adult Tobacco Consumer Tracking[5], our ongoing survey that provides a nationally representative sample of **(b) (4)** **(b) (4)** past 30-day use between July 1st, 2020 to February 28th, 2021. In addition, there are no indications of youth and underage young adult use of *IQOS* at the time of this report. The low uptake of *IQOS* use combined with the planned start dates for our cross-sectional (ALCS-CMI-17-36-HT) and cohort (ALCS-CMI-17-37-HT) studies and for implementation of the UTUS *IQOS* module led to a relatively small amount of evidence related to awareness, use patterns over time, and adult consumer understanding of the modified risk messaging at this time. As the *IQOS* market expands and more adult cigarette smokers become aware of the *IQOS* system as a reduced exposure tobacco option, we expect that adult *IQOS* uptake will increase.

Limited data from the *IQOS* Owners Panel points to a general reduction in combustible tobacco product use over time. Over time, panel members who switched completely have made up the largest percentage of the active sample (54% **(b) (4)** as of February 28, 2021), while dual users made up the second highest percentage (27% as of February 28, 2021). In addition, over time, reported use of fancy, hand-rolled and everyday cigars declined while e-cigarettes/e-vapor remained the most commonly reported other tobacco product used. The early data from the *IQOS* Owners Panel is promising given that over 50% have switched completely to *IQOS* from cigarettes in the past year, over 75% of whom report exclusive use of *IQOS* (*i.e.*, no other tobacco use).

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[5] PMSS: Secondary Analysis: Estimation of Prevalence of *IQOS*® Use

To date, the limited data that we have are positive indications that Adult *IQOS* users who switch completely from cigarettes are likely to become exclusive *IQOS* users and underage use of *IQOS* is, thus far, undetectable.

2.2 Summary of Sales and Distribution Data

Over the reporting period, *IQOS* devices and three variants of *Marlboro HeatSticks* have continued to be available for purchase in the markets where *IQOS* is commercialized. While the MRGO was issued on July 7, 2020, PM USA began using the claim in its Marketing materials in September 2020. This short timeframe makes it difficult to isolate the impact of the claim on sales. However, *IQOS* sales grew across all markets in 2020. Safety measures driven by the pandemic were taken at the *IQOS* stores in both Atlanta and Richmond, including temporary store closures in March through June 2020. Sales growth trends resumed mid-year as boutiques re-opened and *IQOS* was launched in the Charlotte market. The *IQOS* store opened in the Charlotte market in July 2020. Third party retail outlets in Charlotte began receiving shipments of *HeatSticks* shortly after in August 2020. Annex P01-1 provides full year 2020 US sales and distribution by calendar quarter. PM USA plans to use this full calendar year and quarter timeframe approach to report PMSS Sales and Distribution data as first quarter 2021 data would not be available to report by April 30, 2021.

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 approach combines state of the art *in silico* methods and literature/database search for hazard identification. Briefly, literature/database search and *in silico* prediction based on read-across, Quantitative Structure-Activity Relationship (QSAR), and Expert knowledge-based prediction will be performed for the identified compounds and for any mammalian metabolites of these compounds. A human expert assessment will be included to ensure the biological relevance of the data, their quality, and their robustness. 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 April 30, 2019 to December 31, 2020, 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 the chapter 2, *IQOS* cross-sectional study (ALCS-CMI-17-36-HT) and *IQOS* cohort study (ALCS-CMI-17-37-HT) are planned to start in second quarter of this year and in 2022, respectively. 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 over half of active panel participants have switched completely to *IQOS* from cigarettes in the past year (for additional information please refer to Annex 1 of the 2021 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 2021 PMTA Annual Report and corresponding Annexes 1 and 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.

Following acceptance of the PMSS Plan, PMP S.A. will prepare an updated version of the PHIM (PHIM v.8) to incorporate the following additional features recommended by the FDA:

- Prediction based on probabilistic models rather than simulations (in the current version the Markov chain stochastic process is simulated based on the hypothetical population),
- f-factor varying by disease (the current version uses the same f-factor applied to all diseases),
- Implementation in R (current version is in SAS).

Only limited information and data were gathered from the ongoing market surveillance studies and analyses because PMP S.A and ALCS was not able to start the PMSS Plan prior to the FDA's approval. Due to these limitations a new assessment with the latest version of the PHIM was not conducted for the purpose of this Annual Report. It is anticipated that the next report, the 2022 Annual Report, will include assessment with the latest version of the PHIM. As requested in the MRGO the future PHIM for the *IQOS* System will include data from the PMSS studies and analyses, in particular:

- % of former smokers initiating *IQOS,*
- % of current smokers initiating *IQOS* and becoming dual users,
- % of current smokers initiating *IQOS* and becoming exclusive users,
- % of youth and young adults below legal age of purchase who initiate *IQOS,*
- % of initiating *IQOS* who then initiate or re-initiate cigarette smoking,
- The latest information on acute and long-term health effects of using *IQOS* relative to combusted cigarette smoking.

As recommended by the FDA, the next annual PMSS report will 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,
- 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.