Module 8 : Postmarket Information

8.1 Postmarket Surveillance and Studies (PMSS)

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1. PMSS PLAN

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 PMSS 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*." In its MRTPA submitted March 18, 2021, PMP S.A. proposed a Postmarket Assessment Program consisting of a set of diverse approaches covering both surveillance and studies to collect data over time that support the assessment of the Authorized *IQOS* System Holders and Chargers in the postmarket setting. In the MRGO for MR0000192, FDA stated its expectation 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 under this order"[1]. This proposed Postmarket Assessment Program for MR0000192 leverages the protocols and analysis plans submitted for MR0000059 – MR0000061 and MR0000133 originally approved by FDA on December 12, 2019.

Over the past years, and in accordance with the requirements set forth in the MRGO, PMP S.A. and Altria Client Services LLC (ALCS) have further refined the Postmarket Assessment Program originally described in Module 8 of the *IQOS* MRTPA and PMTA. As a result of this additional work, on February 24, 2021, FDA issued its letter of approval for the planned postmarket surveillance studies, which were initiated according to the presented plan. This plan was subsequently updated to incorporate the Authorized *IQOS* 3.0 System[2]. As a result, the PMSS Plan is generally comprising of the following components:

(1) Safety Surveillance

The PMSS Plan will continue to capture, assess, and report adverse experiences associated with the use of the *IQOS* products. The safety surveillance system includes ongoing signal detection and evaluation, as well as mechanisms for safety data communication and reporting.

(2) *IQOS* MRTP Postmarket Studies and Analyses

A combination of 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 studies

[1] PMSS Approval Letter – STN PS0000042, February 24, 2021

[2] Update of the PMSS Plan (PS0000169) to incorporate the Authorized *IQOS* 3.0 System following the issuance of the MRGO – Exposure Modification under section 911 of the FD&C Act (MR0000192). The update submitted on April 7, 2022 with subsequent response to the Request for Information of June 27, 2022 (currently under review).

evaluate exclusive and dual/poly use with *IQOS* and transitions to/away from combustible cigarettes, and they include observations of these behaviors over time. In addition, the program assesses adult consumer perceptions of risk associated with *IQOS* use, including risk perceptions related to the modified risk information.

Assessment of 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 will be conducted through secondary analysis of existing studies.

Reporting *IQOS* sales and distribution data to assist in assessing uptake of *IQOS* products.

(3) PMSS computational toxicology

Generation of data based on computational toxicology assessment of aerosols compounds which are potentially new, or significantly increased in *IQOS* products' aerosol relative to 3R4F 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.

(4) 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.

(5) PMP S.A.'s population health impact model

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

Overall, the available new data gathered in the U.S. until the expiration of both orders is limited, due to the decision of the U.S. International Trade Commission (ITC) which resulted in the mandatory withdrawal of *IQOS* and *HeatSticks* from the U.S. market as of November 28, 2021[3]. The ITC issued its Final Determination (FD), Limited Exclusion Order (LEO), and Cease and Desist Orders (CDO) after concluding that two patents of an affiliate of R.J. Reynolds Tobacco Company (RJR) are violated by PMI and not invalid. The CDO prohibits

[3] Investigation No. 337-TA-1199, *In the Matter of Certain Tobacco Heating Articles and Components Thereof.*

Altria Client Services (ALCS)[4] and PM USA[5] from, among other things, importing, selling, marketing, advertising, distributing, or transferring imported *IQOS* Products (including their components). According to the ITC decision, the PMSS Plan for the authorized *IQOS* products provided and discussed in the context of the original MRTPA, with the subsequent update to incorporate the Authorized *IQOS* 3.0 System (MR0000192) is not advanced per the timelines as initially presented to FDA.

1.1. Postmarket surveillance

Following market authorization of *IQOS* products, PMP S.A. submitted PMTA Annual Reports which incorporated Safety Update Reports (SURs), providing a comprehensive and critical analysis of the safety profile of all *IQOS* device versions, including devices currently authorized in the U.S.

Further information is presented in section m8.2 Adverse Experiences Reports.

1.2. *IQOS* MRTP postmarket studies and analyses

The overarching objective of the PMSS Plan is to determine the impact of the *IQOS* MRGO and the subsequent marketing of the Authorized *IQOS* Systems as modified risk tobacco products on consumer behavior, perception and health in the U.S.

The approved PMSS study protocols and analysis plans relevant to MR0000059 – MR0000061 and MR0000133[6] included the *IQOS* with *Marlboro HeatSticks* Cross-Sectional Postmarket Adult Consumer Study (PACS); *IQOS* with *Marlboro HeatSticks* Cohort Postmarket Adult Consumer Study (PACS); Secondary Analysis: Estimation of Prevalence of *IQOS* Use; Reporting from the U.S. *IQOS* Owners Panel; and Secondary Analysis: Estimation of Awareness and Use of *IQOS* among Underage Individuals.

A summary of each study that was included in the latest version of our approved postmarket studies and analyses and its current status is presented in Table 1. Overall, both *IQOS*

[4] PMP S.A., formerly Philip Morris International Management S.A., has entered into a distribution agreement with Altria Client Services LLC (ALCS) by which ALCS and an ALCS affiliate will be licensed to distribute and sell the candidate product in the United States, upon issuance of the requested marketing order. ALCS is a wholly-owned subsidiary of Altria Group, Inc. ALCS provides certain services to the Altria family of companies.

[5] PM USA is not part of Philip Morris International group of companies.

[6] Refer to *IQOS 2.4* and corresponding *Marlboro HeatSticks*

Cross-Sectional PACS and *IQOS* Cohort PACS study have been paused while reporting from the U.S. *IQOS* Owners Panel has ended.[7]

CTP will be kept informed of updates on the PMSS going forward.

Table 1 Summary and Status of *IQOS* MRTP U.S. Postmarket Surveillance Studies

Study Name	Study Details	Status
IQOS With Marlboro *HeatSticks* Cross-Sectional Postmarket Adult Consumer Study (PACS) ALCS-CMI-17-36-HT	This study is a repeated cross-sectional study of adult (21+) ever established *IQOS* users recruited from the *IQOS* consumer database. The objectives of the online survey are to 1) characterize adult ever established *IQOS* users and their tobacco use patterns; 2) characterize risk perceptions of *IQOS*; and 3) describe initiation, complete switching from cigarette smoking to *IQOS*, transitions to/back to cigarette smoking, and quitting behaviors relevant to *IQOS* use. We plan to field the PACS annually for four years.	(b) (4)
IQOS with Marlboro *HeatSticks* Cohort Postmarket Adult Consumer Study (PACS) ALCS-CMI-17-37-HT	This study will be conducted among ~2,100 adult recent (have used *IQOS* for ≤ 6 months), current, established *IQOS* users and a reference sample of ~1,600 adult combustible cigarette smokers recruited through a mixture of sources. The objectives of this online, longitudinal cohort study are to 1) characterize tobacco product use behaviors; 2) characterize transitions (e.g., initiation, switching, transitioning to/back to cigarettes, and quitting); 3) assess self-reported health-related quality of life, signs and symptoms by product use; and 4) assess risk perceptions of *IQOS* and cigarettes among adult established *IQOS* users and cigarette smokers over time. The *IQOS* Cohort PACS involves a closed 24-month observation period, with follow-ups at 3, 6, 12, 18 and 24 months.	

[7] 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.*

Study Name	Study Details	Status
Secondary Analysis: Estimation of Prevalence of *IQOS* Use	This secondary analysis used *IQOS* relevant data drawn from ALCS' ongoing consumer research study, the Adult Tobacco Consumer Tracking Study (ATCT), among a nationally representative sample of adults in the U.S. The objectives of the secondary analyses are to estimate (1) prevalence of *IQOS* use, (2) prevalence of exclusive, dual and poly tobacco use with *IQOS*, (3) days and amount of product use among *IQOS* users and (4) initiation, quitting and complete switching behaviors relative to *IQOS* use among U.S. adults 21 years of age or older. The extent of the reported analyses depends on the number of current *IQOS* consumers identified in the ATCT dataset.	Data collection relevant to *IQOS* is ongoing.
Reporting from the U.S. *IQOS* Owners Panel	The dynamic longitudinal *IQOS* Owners Panel tracks adult (21 years and older) tobacco consumers' use trajectories with *IQOS* over time. Using results from this study, we describe (1) *IQOS* owners' switching behavior over time, (2) the usage of *IQOS* and other tobacco products among adult *IQOS* owners, and (3) the demographic profile of adult *IQOS* owners. The information we report is consistent with the information reported in support of the *IQOS* PMTA. Outcome measures are reported in three-month intervals.	*IQOS* Owners Panel data collection ceased as of November 29th, 2021, as a result of the ITC decision and *IQOS* becoming unavailable in the U.S. market. We will notify FDA if the *IQOS* Owners Panel resumes.

Study Name	Study Details	Status
Secondary Analysis: Estimation of Awareness and Use of *IQOS* among Underage Individuals	This analysis will use *IQOS* relevant data drawn from ALCS' ongoing Underage Tobacco Use Survey (UTUS), a nationally representative survey of U.S. household-dwelling individuals 13-20 years of age. The objectives of the analyses are to estimate (1) awareness of *IQOS* and (2) ever and past 30-day *IQOS* use among underage individuals, as well as to estimate (3) lifetime use behavior, and (4) past 30-day use behavior among ever and past 30-day underage *IQOS* users, respectively. Use behaviors include exclusive, dual, and poly tobacco use with *IQOS* as well as frequency of use. Some requirements of postmarket reporting necessitated modifications to the UTUS survey specific to *IQOS* and adjustments to the sampling plan.	(b) (4)

1.3. Computational toxicology

The protocol was accepted by FDA on February 24, 2021. PMP SA appointed two Contract Research Organizations (CROs) for the performance of the study. (b) (4)
(b) (4)
he study was divided in 3 phases:

- The project Phase 1 is intended to determine the genotoxicity and/or carcinogenicity potential of the 80 chemicals (parent compounds) 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.

Phase 1 and phase 2 have been completed and the outcome is presented in Module 7.
Phase 3 completion is expected by end of Q2 2023 and will be submitted to FDA by December 2023.

After completion of Phase 3, 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 and the metabolite compounds.

Data are presented in m7 Scientific Studies and Analyses.

1.4. Monitoring of new studies

Information and data are presented in the different sections of Module 6.

1.5. PMP S.A.'s population health impact model

Information and data are presented in m6.5 Population Modelling and Analysis.