PHILIP MORRIS PRODUCTS SA

May 30, 2024

CDR Collins Mason
Director, Division of Enforcement and Manufacturing
Office of Compliance and Enforcement

Elizabeth Do
Regulatory Health Project Management, *Division of Regulatory Project Management, Branch IV*
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Center for Tobacco Products
U.S. Food and Drug Administration
Document Control Center (DCC)
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Submitted via CTP Portal

Subject: Update of the Postmarket Surveillance and Studies (PMSS) Plan for *IQOS* Products (MR0000059 - MR0000061, MR0000133 and MR0000192)

Dear Mr. Collins and Ms. Do,

We, Philip Morris Products S.A. (PMP S.A.), the holder of the Modified Risk Granted Orders (MRGOs) for *IQOS* products[1], are submitting an update to the existing PMSS Plan[2] for these products.

As outlined in the MRGOs, the issuance of an exposure modification orders is conditioned on the agreement "*to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of the determinations on which the order is based.*" The MRGOs further state that "*If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly.* […] *For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology,*

[1] MR0000059 - MR0000061, MR0000133 and MR0000192

[2] PMSS Plan accepted by FDA on February 24, 2021, for MR0000059-MR0000061 and MR0000133 with subsequent amendment to include MR0000192 accepted by FDA on January 10, 2023.

etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval."

We agreed with Altria Group, Inc. to end our commercial relationship covering *IQOS* products in the United States as of April 30, 2024[3]. As of May 1, 2024, we are solely responsible for fulfilling post-market requirements pursuant to the MRGOs. Consequently, an update of the existing PMSS Plan for *IQOS* products is required.

An overview of the updates is provided in Annex A. The individual study-specific documents submitted with this update further explain how we will continue fulfilling all requirements to ensure that the products subject to the MRGOs remain appropriate to promote the public health and continue to benefit the health of the population as a whole.

In this update, we also reference our March 28, 2024, application[4] in which we notified FDA that the *IQOS* consumables will be renamed such that the "*Marlboro*" branding will be removed and "*HeatSticks*" will be renamed "*HEETS*". The name of *IQOS* 3.0 System Holder and Charger was also changed. Being relevant for the PMSS Plan, these updates are referenced in the current submission. The new names of *IQOS* products are listed in the Table below.

STN	Name	New Name
PM0000634 / MR0000192	*IQOS* 3.0 System Holder and Charger	*IQOS* Originals
PM0000424 / MR0000059	*Marlboro* Amber *HeatSticks*	*HEETS* Amber
PM0000425 / MR0000060	*Marlboro* Green Menthol *HeatSticks*	*HEETS* Green
PM0000426 / MR0000061	*Marlboro* Blue Menthol *HeatSticks*	*HEETS* Blue

Upon agreement regarding the updated PMSS Plan, the studies in progress will be reported on an annual basis, by April 30 of each year in a PMSS Report[5]. This PMSS 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.

[3] See Philip Morris International Reaches Agreement with Altria Group, Inc. to End the Companies' Commercial Relationship Covering *IQOS* in the U.S. as of April 30, 2024, available at https://www.pmi.com/investor-relations/press-releases-and-events/press-releases-overview/press-release-details/?newsId=25656 (October 20, 2022).

[4] On March 28, 2024, we notified FDA of changes in product names for the authorized *IQOS* products: *Marlboro* Amber *HeatSticks* to *HEETS* Amber for MR000059, *Marlboro* Green Menthol *HeatSticks* to *HEETS* Green for MR0000060, *Marlboro* Blue Menthol *HeatSticks* to *HEETS* Blue for MR0000061, and *IQOS* 3.0 System Holder and Charger to *IQOS* Originals for MR0000192.

[5] Similar to the Annual Report associated with the April 30, 2019, MGO for *IQOS* products, the cut-off date for data and report generation will be the end of February.

We appreciate FDA's consideration of the proposed update of the PMSS Plan and look forward to working with the Agency to review it further.

Sincerely,

(b) (6)

Mark Bowden
VP Scientific Regulatory Affairs
& Standards Management

Philip Morris Products S.A.

(b) (6)

Laura Leigh Oyler
Global Head of U.S. Regulatory Affairs
U.S. Agent
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Enclosures:

Annex A Updated PMSS Plan for *IQOS* Products

Annex B Overview of U.S. Adult PMX Revisions Relative to *IQOS* Cross-Sectional PACS

Annex C Index of documents provided for the update of the PMSS Plan for *IQOS* products

Please note that this submission contains confidential commercial information, and/or trade secret information, and the legal protections provided to such information are hereby claimed under the applicable provisions of United States law, including relevant provisions of the Federal Freedom of Information Act, 5 U.S.C. 552 et seq. (specifically, 5 U.S.C. 552(b)(4)), the Trade Secrets Act (18 U.S.C. 1905), the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq. (specifically FD&C Act §§ 301(j) and 906(c), 21 U.S.C. 331(j) and 387f(c)) and FDA's implementing regulations, 21 CFR Part 20 (specifically 21 CFR 20.47 and 20.61). PMP S.A. understands that FDA will hold this documentation confidential and will refrain from the public disclosure of the information contained in this submission in conformity with such provisions of the law. Accordingly, if FDA tentatively determines that any portion of this submission is disclosable to the public, FDA is required to provide PMP S.A. with notice and an opportunity to object in accordance with 21 CFR 20.47 and 20.61. PMP S.A. reserves all legal rights to protect against public disclosure of its trade secrets and confidential commercial information and to seek legal recourse against anyone who discloses such information without legal authorization.

Annex A: Updated PMSS Plan for *IQOS* Products

PMSS Plan	Current	Update	Rationale
Appendix A	Principal Investigators from Altria Client Services LLC (ALCS): - Hui Cheng, Principal Scientist I - Richard Brendan Noggle, Principal Scientist II - Lai Wei, Principal Scientist Principal Investigators from PMI: - Gregory Rodrigo, Manager Scientific Regulatory Strategy and Compliance - Nicolas Blanc, Principal Medical Safety Officer	Principal Investigators from ALCS: None Principal Investigators from PMI: - Jessica R. Seifert, Head of Regulatory Post-Market Research - Nicolas Blanc, Principal Medical Safety Officer	Update required since principal investigators from ALCS will no longer be involved in conduct of the PMSS Plan for *IQOS* products. PMI staffing changes result in updates being needed to PMI principal investigators.
Appendix B	*IQOS* with *Marlboro HeatSticks* Cross-Sectional Postmarket Adult Consumer Study (PACS) ALCS-CMI-17-36-HT	Adult *IQOS User* Postmarket Cross-sectional Study in the United States (U.S. Adult PMX) PMSS-PMX-01-US	As PMI is solely responsible for monitoring the impact of *IQOS* product commercialization on adult consumers, the U.S. Adult PMX will be launched. This study was adapted from the most recent version of the *IQOS* Cross-Sectional PACS materials provided by ALCS. No substantive changes were made to the study design or objectives. See Annex B for an overview of revisions.

PMSS Plan	Current	Update	Rationale
Appendix C	*IQOS* Cohort Postmarket Adult Consumer Study (PACS) ALCS-CMI-17-37-HT	Postmarket Adult *IQOS* Consumer Cohort Study in the United States (U.S. Adult COH) PMSS-COH-01-US	As PMI is solely responsible for monitoring the impact of *IQOS* product commercialization on adult consumers, the U.S. Adult COH will be launched. This study was adapted from the most recent version of the *IQOS* Cohort PACS materials provided by ALCS. No substantive changes were made to the study design or objectives. Other non-substantive updates include harmonizing protocol, informed consent statements, and questionnaires with revisions made for the U.S. Adult PMX (see Annex B) and two adjustments to improve statistical robustness: 1) Updated sample size calculation to account for study design 2) Updated covariate balance method (*i.e.*, propensity score matching replaced with propensity score weighting)
Appendix D	Secondary Analysis: Estimation of Prevalence of *IQOS* Use	Analysis will be discontinued	This analysis is being discontinued due to: - Substantial overlap in reporting outcomes with U.S. Adult PMX and U.S. Adult COH - Limited and targeted product rollout, which means the prevalence of *IQOS* product use is expected to extremely low and, therefore, reliable estimates cannot be generated

PMSS Plan	Current	Update	Rationale
Appendix E	Reporting from the U.S. *IQOS* Owners Panel	Reporting will be discontinued	This reporting is being discontinued due to: - Substantial overlap in reporting outcomes with U.S. Adult PMX and U.S. Adult COH - Planned U.S. adult studies are more robust in design - Complete overlap in recruitment source with U.S. Adult PMX and U.S. Adult COH - Limited and targeted product rollout, which means the prevalence of *IQOS* product use is expected to extremely low and, therefore, reliable estimates cannot be generated

PMSS Plan	Current	Update	Rationale
Appendix F	Secondary Analysis: Estimation of Awareness and Use of *IQOS* among Underage Individuals	American Underage Tobacco Use (AUTM) Study PMSS-AUTM-01-US	As PMI is solely responsible for monitoring the impact of *IQOS* products commercialization on youth and young adults, the AUTM Study will be launched in the United States. AUTM study materials were adapted from the most recent versions of the UTUS postmarket secondary research analysis plan provided by ALCS. No substantive changes were made to study objectives or design. On April 3, 2024, we submitted to FDA the study protocol and accompanying documents for review and acceptance.
Appendix G	*IQOS* U.S. sales and distribution Reporting Plan	Reporting Plan revised to describe approach and processes followed by PMI	As of May 1, 2024, PMI is solely responsible for fulfilling postmarket requirements pursuant to the MRGOs for *IQOS* products.
Appendix H	PMP S.A.'s Post Market Safety Surveillance System for *IQOS* System in the United States Document v2.0	PMP S.A.'s Post Market Safety Surveillance System for *IQOS* System in the United States Document v3.0	Information related to ALCS removed.
Appendix I	Literature Review Process Document v2.0	Literature Review Process Document v3.0	Updated search strings and literature databases.

PMSS Plan	Current	Update	Rationale
Appendix J	Population Health Impact Model (PHIM) Document v2.0	Population Health Impact Model (PHIM) Document v3.0	Updated model (v8.2) to include prediction based on probabilistic models rather than simulations, f-factor varying by disease and the expansion of the number of products that can be considered from 4 to 10.
Computational Toxicology	Cancer Risk and Exposure to Chemicals Increased in THS 2.2 Aerosol Compared to 3R4F Smoke: Hazard Identification Protocol for PMSS. Document v3.0	Assessment has been finalized	The study was executed in three phases: • Phase 1: to determine genotoxicity and/or carcinogenicity potential of 80 chemicals identified as potentially new, or significantly increased in *IQOS* aerosol relative to 3R4F smoke. • Phase 2: to determine potential metabolites of 80 chemicals relevant to humans. • Phase 3: to determine genotoxicity and/or carcinogenicity potential of relevant metabolites. Phase 1 was completed and reported in the 2022 Annual Report[6]. Phase 2 was completed and reported in the 2023 Annual Report[7]. At the time of this submission, the assessment (Phase 3) is still ongoing, and the study report is expected by June. We will submit the report immediately upon

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

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

PMSS Plan	Current	Update	Rationale
			its completion. Submission of the report will complete the requirements of the PMSS Plan, and no further investigations are proposed (*i.e.*, this commitment will be fully met).

Annex B: Overview of U.S. Adult PMX Revisions Relative to *IQOS* Cross-Sectional PACS

Revision Type	Revisions
Administrative	Ownership adjustments: ▪ Study name change: "*IQOS with Marlboro HeatStick Cross-Sectional Postmarket Adult Consumer Study*" to "*Adult IQOS User Postmarket Cross-Sectional Study in the United States*". ▪ Signatories, approvals, and Sponsor reference changed. ▪ PMP S.A.'s Principal Investigator will be responsible for executing study procedures and reporting. Substantive copy-editing for clarity, conciseness, and completeness: ▪ Missing protocol sections / sub-sections added (*i.e.*, "Study Strengths & Limitations"; "Ethical, Regulatory, and Legal Considerations"). ▪ Missing operational definitions for study terms added. ▪ Protocol sections reordered. ▪ Text/language revised across study materials.
Procedural	Limited market rollout accommodations: ▪ Study execution will be restricted to states where *IQOS* Products are commercialized. Study Duration: ▪ Expected annual study duration (*i.e.*, from first participant in to last participant out) reduced from 12 weeks to 6-8 weeks. Ethical, Regulatory, and Legal adjustments: ▪ Participant debrief added to questionnaire end. Adverse Health Event Reporting: ▪ Updated adverse health event reporting language to reflect PMP S.A.'s procedures. Statistical robustness adjustments: ▪ Guidelines for reporting small ns added to analytic procedures. ▪ Nicotine dependence measure (Heaviness of Smoking Index) replaced with measure validated for use across product categories (Fagerström Tobacco Nicotine Dependence). ▪ Risk perception assessment (Perceived Risk Instrument for General Risk) replaced with validated instrument aligned with PMP S.A.'s best practice (ABOUT™ – Perceived Risk).

Annex C: Index of documents provided for the update of the PMSS Plan for *IQOS* products

Attachment [Filename]
Appendix A – Principal Investigator Credentials [A-principal_investigator_credentials]
Appendix B – PMSS-PMX-01-US - Study Protocol [B-PMSS_PMX_01_US-Protocol]
Appendix B – Appendix 1 – Participant Screener, Informed Consent Statement, Main Survey [B-PMSS_PMX_01_US-A01-Screen_quest]
Appendix B – Appendix 2 – Statistical Analysis Plan (SAP) [B-PMSS_PMX_01_US-A02-SAP]
Appendix C – PMSS-COH-01-US - Study Protocol [C-PMSS_COH_01_US-Protocol]
Appendix C – Appendix 1 – Participant Screener, Informed Consent Statement, Baseline Survey [C-PMSS_COH_01_US_A01_Baseline]
Appendix C – Appendix 2 – Follow-Up Surveys: Months 3, 6, 12, 18, & 24 [C-PMSS_COH_01_US-A02-Follow_up]
Appendix C – Appendix 3 – Statistical Analysis Plan (SAP) [C-PMSS_COH_01_US-A03-SAP]
Appendix G – Reporting Plan - U.S. IQOS products Sales & Distribution Data [G-Reporting_plan_US_IQOS_sales_distribution]
Appendix H – PMP S.A.'s Post Market Safety Surveillance System for IQOS System, as applicable for the United States [H-US_specific_safety_surveillance_system]
Appendix I – Literature Review Process [I-Description_of_literature_monitoring]
Appendix J – Population Health Impact Model (PHIM) [J-Population_Health_Impact_Model-PHIM]