PHILIP MORRIS
PRODUCTS S.A.

April 07, 2022

LCDR Michael Gu
Director, Division of Enforcement and Manufacturing
Office of Compliance and Enforcement
Center for Tobacco Products
Food and Drug Administration
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Submitted via CTP Portal

Subject: Postmarket Surveillance and Studies (PMSS) Program for *IQOS* 3 System Holder and Charger (MR0000192)

Dear Lieutenant Commander Gu,

In accordance with Section 911(g)(2)(C)(ii) of the Food, Drug and Cosmetic (FD&C) Act, Philip Morris Products S.A. (PMP S.A.), the holder of the MRTP Order authorizing the marketing of the *IQOS* 3 System Holder and Charger as modified risk tobacco product[1], hereby confirms its agreement to conduct the required PMSS Program as described in the "Modified Risk Granted Order - Exposure Modification" (MR0000192) issued on March 11, 2022.

As outlined in the MRTP Order, the issuance of an exposure modification order is conditioned on the applicant's 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 Order further states that "*FDA expects 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 required under this order*."

[1] The *IQOS* 3 System Holder and Charger was granted the exposure modification order under 911(g)(2) of the FD&C Act on March 11, 2022.

As stipulated in the Marketing Order, we hereby confirm that only minor updates and revisions to the PMSS Program previously submitted by PMP S.A. and approved by FDA for the *IQOS* 2.4 System Holder and Charger (MR0000133)[2], with subsequent updates[3,4], are required in the context of the MR0000192.

An overview of updates and revisions, to make the approved PMSS Program responsive to all requirements of the Order for MR0000192, is provided in the table below.

Table 1 Overview of the PMSS Program for MR0000192

PMSS Appendix	Description	Current Status
Appendix A Principal Investigators Credentials	Credentials of all Principal Investigators involved in the PMSS Program	**Update not required** All previously declared Principal Investigators will also be involved in execution of the PMSS Program for MR0000192
Appendix B *IQOS* Cross-sectional Postmarket Adult Consumer Study (PACS) (protocol ID: ALCS-CMI-17-36-HT)	An on-line survey study to (i) characterize *IQOS* established users, their tobacco use patterns and reasons for *IQOS* use; (ii) characterize risk perceptions of *IQOS* and awareness and comprehension of the *IQOS* MRTP message; and (iii) describe initiation, complete switching from cigarette smoking to *IQOS*, transitions to/back to cigarette smoking, and quitting behaviors relevant to *IQOS* use among adult ever established *IQOS* users.	**Update to the Study Protocol and Documents not required** Documents submitted to FDA on June 14, 2021: - Study Protocol: v3.1, - Study Instrument: v3.1, - SAP: v3.1, together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines, equally apply to MR0000192.

[2] 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* 2.4 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.

[3] Amendment of June 14, 2021, to PMSS Plan for MR0000059 - MR000061 and MR0000133

[4] Amendment of January 14, 2022, introducing adjustments to timelines and study plans due to current *IQOS* market unavailability (also referred to as the 2022 Adjustment).

PMSS Appendix	Description	Current Status
Appendix C *IQOS* Cohort Postmarket Adult Consumer Study (PACS) (protocol ID: ALCS-CMI-17-37-HT)	An on-line longitudinal cohort survey study to (i) characterize tobacco product use behaviors (*e.g.*, current use, dual use, number of days and amount used), (ii) characterize transitions (initiation, switching from tobacco/cigarettes to *IQOS*, transitioning to/back to cigarettes and quitting), (iii) assess self-reported health-related quality of life, signs and symptoms by product use, and (iv) assess risk perceptions and (at baseline) MRTP message awareness and comprehension among adult established *IQOS* users and cigarette smokers over time.	**Updated to accommodate the MR000192**[5] Updated documents: - Study Protocol: v4.0 of March 28, 2022 - Baseline Questionnaire: v4.0 of March 28, 2022 - Follow-up Questionnaire: v4.0 of March 28, 2022 - SAP: v4.0 of March 28, 2022 together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines.
Appendix D Secondary Analysis: Estimation of Prevalence of *IQOS* Use	A secondary analysis using *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 these analyses are to estimate (i) prevalence of *IQOS* use, (ii) prevalence of exclusive, dual and poly tobacco use with *IQOS*, (iii) days and amount of product use among *IQOS* users and (iv) initiation, quitting and complete switching behaviors relative to *IQOS* use among U.S. adults 21 years of age or older.	**Update to the Research Analysis Plan not required** Research Analysis Plan v3.0 submitted to FDA on December 22, 2020, together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines, equally apply to MR0000192.

[5] Detailed overview of updates to Appendix C is provided in Appendix 1

PMSS Appendix	Description	Current Status
Appendix E Reporting from the U.S. *IQOS* Owners Panel	Reporting data from ALCS' dynamic longitudinal *IQOS* Owners Panel. The *IQOS* Owners Panel tracks adult (21 years and older) tobacco consumers' use trajectories with *IQOS* over time. Using results from this study, we will describe (i) *IQOS* owners' switching behavior over time, (ii) the usage of *IQOS* and other tobacco products among adult *IQOS* owners, and (iii) the demographic profile of adult *IQOS* owners. The information we report is consistent with the information reported in support of the *IQOS* PMTA.	**Update to the Reporting Plan not required** Reporting Plan v2.0 submitted to FDA on November 4, 2020, together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines, equally apply to MR0000192.
Appendix F Secondary Analysis: Estimation of Awareness and Use of *IQOS* among Underage Individuals	Analysis plan using *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 (i) awareness of *IQOS* and (ii) ever and past 30-day *IQOS* use among underage individuals, as well as to estimate (iii) lifetime use behavior, and (iv) past 30-day use behavior among ever and past 30-day underage *IQOS* users, respectively.	**Updated to reflect changes to research analysis plan communicated to FDA on January 14, 2022**[6] Research Analysis Plan v4.0 of April 5th, 2022, together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines, equally apply to MR0000192.
Appendix G Reporting of U.S. *IQOS* Sales and Distribution Data	To further evaluate uptake in the marketplace, we intend to report sales and distribution data consistent with the program in place to support *IQOS* PMTA reporting. Reporting of the *IQOS* sales and distribution data for the MRTP will occur in April of each year.	**Update to the Reporting Plan not required** Reporting Plan v2.0 submitted to FDA on November 4, 2020, together with PMP S.A.'s correspondence of January 14, 2022, regarding adjustments to the study timelines, equally apply to MR0000192.

[6] Detailed overview of updates to Appendix F is provided in Appendix 1

PMSS Appendix	Description	Current Status
Appendix H U.S.-specific Safety Surveillance System	PMP S.A. and ALCS have coordinated efforts to establish a comprehensive safety surveillance program for *IQOS* use in the U.S. The safety surveillance system is organized around six main components: safety data collection, safety case processing, expedited reporting, signal detection, risk communication, and regulatory submissions.	**Updated** Updated document: - Study Protocol: v2.0 of March 24, 2022
Appendix I Literature Monitoring	PMP S.A. will continue to monitor and report on published studies from the peer reviewed literature as well as findings from PMP S.A. studies relevant to *IQOS* and consumer perceptions, behavior or health.	**Updated** Updated document: - Study Protocol: v2.0 of March 24, 2022
Appendix J Population Health Impact Model (PHIM)	Population health modelling that incorporates long-term health impacts, additional functionality, and in-market data sources for the estimation of transition probabilities (*i.e.*, the rate at which people transition between different product use behaviors). In addition, predicted health impact will be based on probabilistic models rather than simulation, disease-specific risk reduction estimates and will be implemented in the open source statistical programming language R.	**Update to the PHIM not required** PHIM v2.0 submitted to FDA on November 4, 2020, equally applies to MR0000192.
Computational Toxicology	Methodology for computational toxicology assessment of *HeatStick* aerosols that will be applied to assess the cancer risk from exposure to compounds increased in *IQOS* System aerosol compared to the 3R4F cigarette smoke.	**Update to the Study Protocol not required** Study Protocol v3.0 submitted to FDA on February 17, 2021, equally applies to MR0000192.

In addition to the above listed modifications and revisions, a detailed summary of the proposed updates to the PMSS protocols and analysis plans, originally approved on February 24, 2021 "*IQOS* 3.0 US Postmarket Program Overview", is attached to this letter.

The PMSS Program for the *IQOS* System, including the recently authorized *IQOS* 3 System, has been jointly developed by PMP S.A. and Altria Client Services LLC (ALCS)[7]. The PMSS Program will be jointly conducted with ALCS and an ALCS affiliate licensed to distribute and sell the product in the United States, on behalf of PMP S.A. The ALCS affiliate that distributes and sells the product in the U.S. is Philip Morris USA Inc. (PM USA)[8].

Upon agreement of the updated PMSS Program with FDA, the studies in progress will be reported on an annual basis, by April 30 of each year in a PMSS Report[9]. The 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.

We appreciate FDA's consideration of our proposed updated PMSS Program for the *IQOS* System and look forward to working with the Agency to review it further.

Sincerely,

(b) (6)

Mark Bowden
VP Scientific Reg. Affairs & Standards Management
Philip Morris Products S.A.

(b) (6)

Jeff Walker
Head of U.S. Regulatory Affairs
U.S. Agent for PMP S.A.

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 Unites States law, including relevant provisions of the Federal Freedom of Information Act ("FOIA"), 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 FDCA §§ 301(j) and 906(c), 21 U.S.C. §§ 331(j) and 387f(c)) and FDA's implementing regulations, 21 C.F.R. Part 20 (specifically 21 C.F.R. §§ 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 C.F.R. §§ 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.

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

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

[9] Similar to the annual report associated with the April 30, 2019 PMTA Order, the cut-off date for data and report generation will be the end of February.

Enclosures: Annex A

Annex A:

Index of documents provided for the update of the PMSS Program for the *IQOS* System with *Marlboro HeatSticks* to make the approved PMSS Program responsive to all requirements of the Order for MR0000192:

Attachment [Filename]
Overview of updates to the PMSS protocols and analysis plans, originally approved on February 24, 2021 [iqos3-US-postmarket-program-overview]
Appendix 1 - Overview of updates to Appendix C and Appendix F of the PMSS Program [A01-overview-of-updates-to-appendix-C-and-F]
Appendix C - Study Protocol: v2.0 of November 4, 2021 [C1-iqos-cohort-PACS-protocol]
Appendix C - Baseline Questionnaire: v2.0 of November 4, 2021 [C2-iqos-cohort-PACS-baseline-questionnaire]
Appendix C - Follow-up Questionnaire: v2.0 of November 4, 2021 [C3-iqos-cohort-PACS-follow-up-questionnaire]
Appendix C- SAP: v2.0 of November 4, 2021 [C4-iqos-cohort-PACS-sap]
Appendix F - Secondary Analysis: Estimation of Awareness and Use of *IQOS* among Underage Individuals [F-research-ana-plan-awareness-use-underage]
Appendix H - U.S.-specific Safety Surveillance System _Study Protocol: v2.0 of March 24, 2022 [H-postmarket-safety-surveillance-iqos-US]
Appendix I - Literature Monitoring_ Study Protocol: v2.0 of March 24, 2022 [I-literature-review-process]