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2.4 Executive Summary

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1. OVERVIEW

PMP S.A. is submitting this application under section 911(g)(2) of the Federal Food, Drug, and Cosmetic (FD&C) Act to request renewal of the Modified Risk Granted Order (MRGO) – Exposure Modification issued on July 7, 2020, for the *IQOS* 2.4 System Holder and Charger (MR0000133) with three *HeatSticks* variants[1] and on March 11, 2022, for the *IQOS* 3.0 System Holder and Charger[2], which authorized PMP S.A. to market these products with the following authorized reduced exposure information:

"AVAILABLE EVIDENCE TO DATE:

- *The IQOS system heats tobacco but does not burn it.*
- *This significantly reduces the production of harmful and potentially harmful chemicals.*
- *Scientific studies have shown that switching completely from conventional combustible cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."*

When authorizing the products, FDA concluded that "*with respect to the exposure modification order request, the applicant has demonstrated that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order 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*."[3]

FDA should continue to hold this conclusion for the following reasons:

- The MRGO authorized products continue to be appropriate for the protection of public health under the PMTA pathway.
- FDA has not communicated concerns with the information submitted by PMP S.A. under the MRTPAs since FDA's authorization. If FDA believed that new information

[1] MR0000059 - MR0000061: *Marlboro* Amber *HeatSticks*, *Marlboro* Blue Menthol *HeatSticks,* and *Marlboro* Green Menthol *HeatSticks*

[2] MR0000192: *IQOS* 3 line extension

[3] Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911(d) of the FD&C Act – Technical Project Lead, available at: https://www fda.gov/media/139796/download

and data submitted by PMP S.A. changed this conclusion, it would be expected that they would convey concerns to PMP S.A.

- The authorized products have only been marketed in the U.S. in few geographies for 37 months[4] with (b) (4) *HeatSticks* sold in 2021. Based on this limited marketing, there is not any meaningful empirical evidence from the U.S. since FDA's authorization that would change FDA's conclusions at the time of authorization.

- None of the new data included in this application raises any public health concerns. Rather, international data since FDA's authorization supports that many smokers in international markets are completely switching to *IQOS*. And, importantly, none of these non-U.S. markets have seen significant youth uptake of *IQOS*.

Therefore, the new data further support the conclusions drawn by FDA at the time of authorization.

It is important to understand why U.S. marketing of *IQOS* was so limited since authorization. The limited marketing did not stem from any public health concerns with the products. Rather, a patent dispute ruling forced ALCS[5] to cease U.S. marketing of *IQOS*. More specifically, the authorized products are the subject of a mandatory withdrawal from the U.S. market effective on November 29, 2021, as a result of a U.S. International Trade Commission (ITC) decision pertaining to a patent dispute brought by affiliates of British American Tobacco (BAT) plc[6]. As part of that decision, the ITC issued a Final Determination (FD), Limited Exclusion Order (LEO), and Cease and Desist Orders (CDO) based on their conclusion that the *IQOS* System violates two patents of an affiliate of BAT and that the patents are not invalid. The CDO prohibits ALCS from, among other things, importing, selling, marketing, advertising, distributing, or transferring imported *IQOS* products (including their components). As a result, ALCS stopped marketing and selling all *IQOS* devices and *HeatSticks* by November 28, 2021.

[4] October 2019-November 2021

[5] 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 U.S., 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.

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

The limited period during which the *IQOS* products were available with the modified-risk claims to U.S. smokers[7] and limited commercial outreach of the *IQOS* products (commercialized only in a few U.S. markets) have made it difficult to collect and present to FDA a comprehensive U.S.-representative data set and evidence as intended in the agreed PMSS Plan[8]. During the 37 months of sales, approximately 30,000 adult tobacco consumers were registered in the *IQOS* database and of that number, approximately 20,000 adults converted to either partial or full switching of *IQOS* from cigarettes. This number of subjects was sufficient to permit conducting the first wave of a cross-sectional study, and the results from the study were provided with the 2022 Annual Report submitted to FDA on April 29, 2022[9].

At this time, the MRGOs have been effective for a period of four (4) years and will expire on July 7, 2024. Conditions of the orders included monitoring the use of the authorized products with regard to uptake, dual use, and complete switching, including the potential for initiation among youth. As per the FDA request, Postmarket Surveillance and Studies (PMSS) included an assessment of MRTP users' behavior and understanding over time, and the 4-year period was deemed a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate preliminary data on behavior in PMSS to assess whether the standard continues to be met and whether the order should be renewed**Error! Bookmark not defined.**.

In addition, and consistent with the agreed PMSS Plan, PMP S.A. provides results of the computational toxicology assessment that was initiated to assess cancer risk from the exposure to compounds increased in the *IQOS* aerosol compared to cigarette smoke. We also report on safety profile and adverse experiences associated with the use of *IQOS* products worldwide. This information and data are supplemented by international data from Germany, Japan, South Korea, and Italy where *IQOS* products have continued to prove successful in converting millions of adult smokers to this modified-risk tobacco product.

To facilitate review, PMP S.A. utilized cross-referencing to the original MRTPA for the *IQOS* 2.4 System and *HeatSticks*, and where relevant to the sMRTPA for the *IQOS* 3.0 System.

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[7] The MRGO for the *IQOS* 2.4 System Holder and Charger and *HeatSticks* was issued on July 7, 2020. After development of marketing materials and submission of materials to FDA for the required 30-day notification imposed in the PMTA Marketing Order, the first marketing with modified risk (reduced exposure) claims was disseminated in September of 2020.

[8] PMSS Plan (PS0000169) with an update to incorporate the *IQOS* 3.0 System following issuance of the MRGO – Exposure Modification under section 911 of the FD&C Act (MR0000192).

[9] 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

2. PRODUCTS IN THE SCOPE OF RENEWAL

The authorized tobacco products in the scope of this renewal (also referred to as *IQOS* products) are:

- *IQOS* 2.4 System Holder and Charger (MR0000133)
- *IQOS* 3.0 System Holder and Charger (MR0000192)
- *Marlboro* Amber *HeatSticks* (MR0000059)
- *Marlboro* Green Menthol *HeatSticks* (MR0000060)
- *Marlboro* Blue Menthol *HeatSticks* (MR0000061)

The *IQOS* 2.4 System and *IQOS* 3.0 System (Figure 2) consist of two components:

- Holder (electrical heating unit)
- Charger (power supply to the Holder)

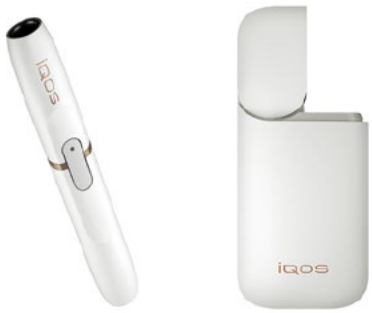
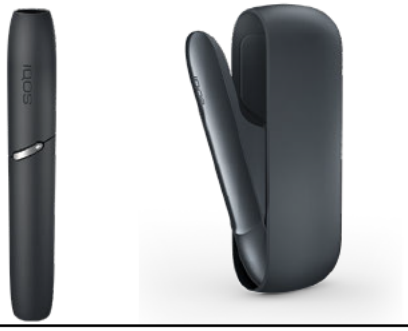
***IQOS* 2.4 System Holder and Charger**	***IQOS* 3.0 System Holder and Charger**
	

Figure 1 *IQOS* 2.4 System and *IQOS* 3.0 System

Both devices have the same operating principles and are to be used with any of the authorized *HeatSticks* (Figure 2 to Figure 4). There have been no changes to the manufacturing or product composition and design relative to the authorized products.

Figure 2 *Marlboro* Amber *HeatSticks*

Figure 3 *Marlboro* Blue Menthol *HeatSticks*

Figure 4 *Marlboro* Green Menthol *HeatSticks*

3. SUMMARY OF SCIENTIFIC EVIDENCE

All studies submitted with the MRTPA for the *IQOS* 2.4 System (and corresponding *HeatSticks*) and sMRTPA for the *IQOS* 3.0 System (and parallel PMTA and sPMTA) remain valid and do not require reanalysis. This section outlines all new data since FDA's authorization. More detailed discussion of the new data is found in the applicable modules of this renewal request.

3.1. Relative Health Risks of the MRTPs to Individual Tobacco Users

Since FDA's authorization, the following four clinical studies have been completed:

- ZRHR-ERS-09-EXT-US: a 6-month extension study of the ZRHR-ERS-09-US previously submitted to FDA shows favorable changes in Biomarkers of Potential Harm (BoPH) when switching to *IQOS* compared to continued cigarette smoking for 12 months.
- SA-SCR-01: a post-hoc analysis to assess the magnitude of changes of all BoPHs assessed in the "Exposure Response Study (both ZRHR-ERS-09-EXT-US and ZRHR-ERS-09-EXT-US) after smokers quit smoking. The results of this analysis were used to perform a cross-study comparison with the results obtained on switching from cigarettes to *IQOS* use for 12 months.
- P1-OHS-01-JP: a 6-month study in Japan with subjects having chronic generalized periodontitis did not show improvements in periodontitis but confirmed reduced HPHC exposure in an ambulatory setting.
- P1-EXC-01-EU: a 12-week exploratory study in Germany did not show improvement in exercise capacity but confirmed reduced HPHC exposure in an ambulatory setting.

The new studies demonstrate that completely switching from cigarettes to *IQOS* significantly reduces HPHC exposure and BoPH levels, consistent with studies that formed the basis of FDA's authorization.

3.2. Consumer Understanding and Perceptions

PMP S.A. has continued to conduct post-market studies in international countries and since FDA's authorization in the United States as part of the PMSS Plan for *IQOS* pursuant to the MRGOs issued by the FDA.

The results of these post-market studies as well as independent studies continue to support previously submitted U.S. pre-market evidence and show that:

- There is a high level of understanding that completely switching to *IQOS* would reduce exposure to HPHCs compared to smoking.
- The perceived health risks associated with using *IQOS* is lower than the perceived health risks associated with smoking cigarettes, *which is in line with the relative health risks of the product that are reasonably likely*. At the same time, post-market data continue to demonstrate that *consumers understand that the product is not without risks*[10] and that there are health risks associated with using *IQOS*.
- Risk communication influences use behavior and that there is a positive effect on complete switching from cigarettes to *IQOS* when *IQOS* is perceived as a modified risk product.

3.3. Tobacco Use Behavior and Impact to the Population as a Whole

Since FDA's authorization, post-market studies in international countries and in the United States as well as independent studies consistently show that:

- There is *IQOS* uptake in many countries with adult cigarette smokers representing the segment of the population that is mostly using *IQOS*, and the majority of *IQOS* users are using *IQOS* exclusively and hence have completely switched away from cigarettes.
- The availability of greater varieties of *HeatSticks* flavors, such as menthol, promotes higher level of complete switching, thereby facilitating the transition of adult smokers from cigarettes to *IQOS*.

[10] Technical Project Lead (TPL) Review for the MRTP exposure modification orders granted on July 7, 2020.

- There is a very low prevalence of *IQOS* use among never smokers, including youth, and low re-initiation and relapse of *IQOS* use among former smokers.

In addition, since FDA's authorization, the following additional data is available:

- Adverse events (AEs) spontaneously reported to PMP S.A. from U.S. market and attributed to *IQOS* products do not signal any unexpected, serious AEs[11].
- Public Health Impact Modeling (PHIM) was done based on feedback from FDA about improvements to the modeling. The revised PHIM shows that, if the population prevalence of *IQOS* grows to 5% and stays steady until 2080, there will be a reduction of 225,000 smoking-attributed deaths and 2.2 million years life saved (YLS) in the United States.

The new studies demonstrate that switching from cigarettes to *IQOS* is occurring without youth uptake, and, as a result, modeling indicates that many U.S. lives can be saved.

There are some data that PMP S.A. originally expected to include in this submission but are not currently available. More specifically, PMP S.A. was unable to complete the PMSS[12].

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*." The available new U.S. data from PMSS is limited due to the decision of the U.S. ITC, which resulted in the mandatory withdrawal of *IQOS* and *HeatSticks* from the U.S. market as of November 28, 2021[13]. Therefore, our timing and plans for PMSS have been adjusted as documented in the letter sent to FDA on January 14, 2022[14].

PMP S.A. agreed to conduct computational toxicology studies when FDA authorized *IQOS*. As part of the initial product characterization of the *IQOS* 2.4 System, non-targeted

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[11] There were (b) non-serious AEs and no serious AEs reported by U.S. consumers.

[12] Some PMSS data was collected and is included in this renewal notice. However, because the limited U.S. marketing of *IQOS*, the data are not as complete as anticipated at the time of authorization.

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

[14] 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.*

differential screening (NTDS) analyses of three *HeatStick* variants[15] were performed to identify compounds that were potentially new or significantly increased in *IQOS* 2.4 aerosol relative to 3R4F cigarette smoke. A hazard identification process 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 includes state of the art *in silico* methods for hazard identification. To identify the hazards, the GIST protocol described by Hasselgen et al. (Hasselgren et al., 2019) is applied, including *in silico* predictions. As toxicity can be mediated not only by the aerosol chemicals but also by their metabolites, potential metabolites are determined from the literature or with *in silico* prediction tools and evaluated like the parent compounds for hazard identification. The study is currently being conducted in three phases:

- Phase 1: 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 cigarette smoke
- Phase 2: determine the potential metabolites of the 80 chemicals relevant to humans
- Phase 3: 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 are 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.

4. CONCLUSIONS

The combined evidence from U.S. pre-market studies and post-market studies, together with evidence from international post-market studies, indicate that *IQOS* products continue to satisfy the requirements of section 911(g)(2) of the FD&C Act, including the requirement that marketing the product is appropriate to promote the public health and is expected to

[15] Regular, menthol, and high menthol

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.

PMP S.A. is requesting a renewal of the MRGO – Exposure Modification for the *IQOS* products issued under section 911(g)(2) of the FD&C Act.