Module 6: Summary

6.4 Conclusions

TABLE OF CONTENTS

1. SUMMARY OF FINDINGS AND CONCLUSIONS THAT SUPPORT A NEW TOBACCO PRODUCT MARKETING AUTHORIZATION ORDER 2

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

1. SUMMARY OF FINDINGS AND CONCLUSIONS THAT SUPPORT A NEW TOBACCO PRODUCT MARKETING AUTHORIZATION ORDER

The *IQOS* 3 System is a modified version of the Authorized *IQOS* System developed by Philip Morris Products S.A. (PMP S.A.), which is intended to be exclusively used with specially-designed non-combustible cigarettes refered as *HeatSticks*. (b) (4)

(b) (4)

The *IQOS* 3 System has the same basic operating principles as the Authorized *IQOS* System. Therefore, the product performance has not changed and the principles of aerosol generation remain the same as in the Authorized *IQOS* System. This results in an aerosol that is comparable in terms of its physico-chemical properties to the aerosol generated with the Authorized *IQOS* System.

More specifically, the data presented in Module 3, Section 3.2.1.5 *Constituents* and discussed in Module 6, Section 6.3 *Health Risk Investigations* show that:

- The levels of Harmful and Potentially Harmful Constituents (HPHCs) from the PMI-58 list[1] of HPHCs in the aerosols generated with the *IQOS* 3 System, in combination with standard monitor *HeatSticks* under the two operating conditions[2] (C28-6 Heating Profile "On", and C28 Heating Profile "Off") are comparable to the levels present in the aerosol generated with the Authorized *IQOS* System with the same standard monitor *HeatSticks*, with all nominal differences within the range of normal method variability;
- The substantial reductionsof the levels of HPHCs from the FDA-18[3] abbreviated list in the aerosols generated with the *IQOS* 3 System using the commercial firmware setting and each of the *HeatSticks* variants commercially available in the U.S. (PM0000424 – PM0000426) compared to those of combustible cigarette (CC) smoke, are essentially the

[1] Section 6.1.1.1 *Aerosol Chemistry* of the PMTA for the Authorized *IQOS* System.

Redacted

[3] FDA Draft Guidance for Industry. Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

same as those reported in the PMTA for the Authorized *IQOS* System, with all nominal differences attributable to normal method variability;

- The four additional compounds, which are neither part of the PMI-58 nor of the FDA-18 list of HPHCs, and were reported at higher levels in the aerosol generated with the Authorized *IQOS* System in comparison to the 3R4F reference cigarette smoke[4], remain at comparable levels whether aerosols are generated with the *IQOS* 3 System or with the Authorized *IQOS* System;
- The Droplet Size Distribution (DSD) of aerosols generated with the *IQOS* 3 System is essentially the same as DSD of aerosols generated with the Authorized *IQOS* System;
- Similarly to the aerosol of the Authorized *IQOS* System, the aerosol generated by the *IQOS* 3 System contains certain genotoxic or cytotoxic chemicals. They are present in very low levels and their potential negative effects are outweighed by the substantial decrease in the number and levels of HPHCs present in the *IQOS* 3 System aerosol compared to those found in CC smoke..

The *IQOS* 3 System generates an aerosol with nicotine levels comparable to those measured in the aerosol from the Authorized *IQOS* System. The nicotine levels of both aerosols do pose an addiction risk for non-tobacco users who initiate use of the *IQOS* Systems. However, this risk is the same with any version of the *IQOS* System and is not higher than for other, currently available, tobacco products. In addition, initiation with the *IQOS* 3 System is expected to be low generally.

In addition, PMI has maintained the same process controls and quality assurance procedures that were demonstrated for the Authorized *IQOS* System, subject to the current Marketing Order. There are adequate process controls and quality assurance procedures to help ensure the *IQOS* 3 System is manufactured in a compliant manner to meet the applicable specifications. The *IQOS* 3 System will be manufactured by the same, already qualified, manufacturer that is producing the Authorized *IQOS* System (Module 3, Section 3.3.1 *Manufacturers*).

The *IQOS* 3 System has similar overall patterns of use to the Authorized *IQOS* System (*e.g.* daily *HeatSticks* use, total tobacco consumption) as evidenced by data from countries where the *IQOS* 3 System has been commercialized for many years (Module 6, Section 6.3 *Health Risk Investigations*).

Comparable reductions in levels of HPHCs in the aerosol of the *IQOS* 3 System lead to a conclusion that effects observed in preclinical and clinical studies with the Authorized *IQOS* System will be comparable to the *IQOS* 3 System. Consequently, bridging to the nonclinical and clinical evidence and data, provided with the PMTA for the Authorized *IQOS* System,

---

[4] The December 8, 2017, Amendment to PMTA for the Authorized *IQOS* System providing Non-Targeted Differential Screening (NTDS) reports identifying chemical constituents present in the THS aerosol that are either unique, or present at higher concentration compared with 3R4F cigarette smoke.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.

instead of conducting new studies, is appropriate. Therefore the nonclinical and clinical assessment submitted as part of the PMTA for the Authorized *IQOS* System remain valid and applicable to the *IQOS* 3 System (Module 6, Section 6.3 *Health Risk Investigations*).

Furthermore, based on PMP S.A.'s experience with the *IQOS* 3 System from the countries where it has been commercialized since 2018, there are no meaningful differences in the safety profile of the *IQOS* 3 System and the Authorized *IQOS* System (Module 6, Section 6.3 *Health Risk Investigations* and Module 8, Section 8.2 *Adverse Experience Reports*).

Finally, the design of the *IQOS* 3 System does not contain any features that are expected to alter the low level of interest in trial and use among adult never smokers and former smokers that was found with the Authorized *IQOS* System. These observations, along with the nonclinical and clinical data, confirm that the *IQOS* 3 System is comparable to the Authorized *IQOS* System.

Based on the presented evidence, PMP S.A. believes that authorization of the marketing of the *IQOS* 3 System, is equally appropriate for the protection of the public health as authorization of the Authorized *IQOS* System.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris International.