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7 Scientific Studies and Analyses	Version 1.0

## Module 7 : Scientific Studies and Analyses

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## 1. INTRODUCTION

Scientific studies and analyses provided with the initial MRTPA and PMTA for the Authorized *IQOS* 2.4 System Holder and Changer (PM0000479 and MR0000133), *Marlboro HeatSticks* (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the *IQOS* 3.0 System Holder and Changer (PM0000634 and MR0000192) remain valid and do not require reanalysis.

Thus, the entire Module 7 of the original MRTPAs for the authorized *IQOS* products with related appendices and data, and with subsequent amendments is cross-referenced in the context of this MRTPA renewal.

However, more data from postmarket studies conducted in the U.S. and in international countries have been collected by PMI since the issuance of the MRGOs. Those additional data and analysis have been summarized in the appropriate sections of the Module 6.

### 1.1. Aerosol Chemistry and Physics

PMP S.A. is not providing any new data with this renewal.

The entire Module 7 of the initial MRTPA and PMTA for the Authorized *IQOS* 2.4 System Holder and Changer (PM0000479 and MR0000133), *Marlboro HeatSticks* (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the *IQOS* 3.0 System Holder and Changer (PM0000634 and MR0000192) with related appendices and data, and with subsequent amendments are cross-referenced in the context of this MRTPA renewal.

### 1.2. Non-Clinical

PMP S.A. is not providing any new data with this renewal.

The entire Module 7 of the initial MRTPA and PMTA for the Authorized *IQOS* 2.4 System Holder and Changer (PM0000479 and MR0000133), *Marlboro HeatSticks* (PM0000424 - PM0000426 and MR0000059 - MR0000061) and the *IQOS* 3.0 System Holder and Changer (PM0000634 and MR0000192) with related appendices and data are cross-referenced in the context of this MRTPA renewal.

### 1.3. Clinical Individual Health

#### 1.3.1. Overall Summary of Clinical Evidence

Additional findings are presented in [Appendix 7-a07-clin-ind-health-additional-studies](#) (paragraph 1.1.5 and 1.1.6)

#### 1.3.2. Literature Review on *IQOS* Use and Disease Risk

Results are presented in [Appendix 7-a08-ind-health-lit-review-results](#).

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#### 1.4. Clinical Population Health – Literature Review

Publications (if not previously submitted) are presented as appendices to [section 9 Literature References](#).

Results are presented in [Appendix 7-a09-pop-health-lit-review-results](#).

#### 1.5. Effect on Tobacco Use Behavior Among Current Tobacco Users

New data is presented in [section 6.2 Effect on Tobacco Use Behavior Among Current Tobacco Users](#), in [Appendix 7-a01-description-adult-IQOS-owners-panels](#) and [Appendix 7-a02-all-contries-trend-analysis](#) and Publications (if not already submitted) are presented as appendices to [section 9 Literature References](#).

#### 1.6. Effect on Tobacco Use Initiation Among Non-Users

New data is presented in [section 6.3 Effect on Tobacco Use Initiation Among Non-Users](#), in [Appendix 7-a03-P1-PMX-01-JP-study-report-year-5](#), [Appendix 7-a04-P1-PMX-02-IT-study-report-year-2](#) and Publications (if not already submitted) are presented as appendices to [section 9 Literature References](#).

#### 1.7. Consumer Understanding and Perceptions

New data is presented in [section 6.4 Consumer Understanding and Perceptions](#) and Publications (if not already submitted) are presented as appendices to [section 9 Literature References](#).

#### 1.8. Population Modelling and Analysis

New data is presented in [section 6.5 Population Modelling and Analysis](#), in [Appendix 7-a05-transition-table](#) and Publications (if not already submitted) are presented as appendices to [section 9 Literature References](#).

#### 1.9. Computational toxicology

##### 1.9.1. Phase 1 results

The genetic *in silico* toxicity (GIST) protocol described by Hasselgen et al. (Hasselgren et al., 2019) was applied. For each compound, the final assessment of the genotoxic/carcinogenic potential is mentioned (positive/negative), and the level of confidence linked to the prediction (low, medium, or high). Indications given as to the confidence are based on recent guidance from Johnson et al. (2022), as described in [Appendix 7-a06-comp-tox-tables \(Table 1\)](#). The results are summarized in [Appendix 7-a06-comp-tox-tables \(Table 2\)](#).

##### 1.9.2. Phase 2 results

*In silico* prediction and literature/database search for any mammalian metabolites of the parent compounds were performed. Searches of relevant literature were conducted, and the metabolites identified in published studies and/or Expert group reviews were recorded. Two *in*

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*silico* software packages ((b) (4) ) were used to predict likely mammalian metabolites in a range of models as described in [Appendix 7-a06-comp-tox-tables \(Table 3\)](#). A human expert assessment was included to ensure the biological relevance of the data, their quality, and their robustness. For each compound, the name of the retrieved metabolites, and the related CAS number when available, is mentioned. In addition, the status (known or predicted metabolite) and the ranking are reported. The ranking refers to the biological relevance and the robustness of the data as described in [Appendix 7-a06-comp-tox-tables \(Table 4\)](#). The results are summarized in [Appendix 7-a06-comp-tox-tables \(Table 5\)](#). When the software was not able to retrieve the chemical name of the predicted molecule, the SMILES of the molecule was provided instead. From 80 parent compounds, 1659 (thousand six hundred fifty-nine) metabolites were retrieved.

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