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ADDITIONAL INFORMATION RELATING TO THE FDA EXCEL WORKBOOK FOR IQOS SAFETY UPDATE REPORT (SUR)

June 13, 2018

TABLE OF CONTENTS

FDA REQUEST 1 2
PMP S.A. RESPONSE: 2
FDA REQUEST 2 3
PMP S.A. RESPONSE: 3
Appendices 7

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FDA REQUEST 1

Provide any additional information you have related to the 'Death' indicated on page 145 of 186, Appendix 2a of the Safety Update Report and submit the full case report (MedWatch form).

PMP S.A. RESPONSE:

In response to the above request, we are herewith providing the MedWatch form (full case report) related to the 'Death' indicated on page 145 of 186, Appendix 2a of the latest Safety Update Report (SUR) which was submitted to the FDA on May 16, 2018. The full case report is appended to this response (PMI001159_MedWatch_report_final).

Furthermore, we are also providing below additional information regarding this event.

PMI was informed about the event on September 16, 2016 and the initial report (Manufacturer Report # PMI001159) was submitted to the Agency 11 days after the receipt of this information, on September 27, 2016. The submission was received by the Center for Tobacco Products (CTP) and the following receipt number was assigned: STN: XX0000865.

This report concerns an 88-year-old male subject who was enrolled in the ZRHR-ERS-09-EXT-US clinical study. The reported medical history included acid reflux and hypertension. The subject used THS 2.2 during 1 week in the run-in period and then was subsequently randomized to the cigarette arm.

It was reported during the study that the subject had not returned calls and his diary entry had not been completed in over a month. The subject's obituary was found: the subject died due to unknown cause on August 14, 2016 which was 8 months after having been randomized to the cigarette arm. An autopsy was not performed. The investigational site was not able to contact anyone to obtain further information because the subject did not provide an emergency contact.

The Investigator considered the reported event of death to be unrelated to the use of THS 2.2.

During follow-up (September 28, 2016) it was further established that the subject started smoking conventional cigarettes in 1941, at the age of 13 years, on an average of 20 units (1 pack) daily. During the run-in period, the subject used a total of 39 THS (daily amount not specified). On January 4, 2016 the subject was randomized to conventional cigarettes arm. After randomization,

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the subject continued smoking 20 units of conventional cigarettes (1 pack) daily. THS use was stopped after the run-in period. The subject smoked conventional cigarettes throughout the study.

FDA REQUEST 2

Using the attached spreadsheets (Safety Report Excel Workbook for IQOS), add a row in the corresponding spreadsheet for the events in your 2017 safety report and 2018 events that have not yet been reported to FDA. If the event was 'coded' under more than one risk item (e.g., thermal burn and fire/explosion), it should be listed on each spreadsheet.

Note: FDA understands a single AE may include multiple MedDRA codes. List each event only once per spreadsheet; however each individual event should be listed on the corresponding spreadsheet, even if this creates duplicate listing.

PMP S.A. RESPONSE:

As requested by the Agency, we are herewith providing an additional information related to the safety data included in the Safety Report Excel Workbook for IQOS.

Columns A-H of the Excel table have been completed with requested safety information. Two additional columns, 'Case ID' and 'Case report type' (to differentiate between Spontaneous cases and reports from study), have been added, corresponding to the information recorded and stored in our safety database.

Column C of the Excel table, now that the 'Case ID' (column A) was introduced, the corresponding row for additional event(s) in the case can be identified by searching in the relevant tab with the Case number in the 'Case ID'.

Column E of the Excel table corresponds to the date when the case is reported to PMI ('Initial receipt date' field in the database). Please note that for the majority of the cases the consumer does not provide the Event onset date.

Search criteria applied to identify in the Safety database for IQOS cases and all report types (cumulatively up to March 31, 2018):

- Hypersensitivity events: MedDRA SMQ Hypersensitivity (Narrow),

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- Accidental exposure events: Age group: Neonate, Infant, Child, Adolescent, Not specified and Preferred Terms (PTs) Accidental exposure to product by child, Accidental exposure to product,
- Burning sensation events: Customized search including PTs Burning sensation, Burning sensation mucosal, Skin Burning sensation,
- Thermal burn events: PTs Airway burns, Burn esophageal, Burn of internal organs, Burn oral cavity, Burns first degree, Burns fourth degree, Burns second degree, Burns third degree, Eye burns, Thermal burn,
- Battery leakage events: System Organ Class (SOC) Product issues and then PT Device leakage, Events with verbatim mentioning "liquid" or "leak",
- Fire and overheating events: For fire: PTs Device catching fire and Product caught fire, Events with verbatim mentioning "fire", excluding cases where fire is used to describe a sensation (e.g. throat felt like it was on fire). For overheating: PT Device battery explosion and in SOC Product issues, events with verbatim mentioning "overheat".

As explained during the teleconference with the Agency on June 6, 2018, PMI cannot provide information on the specific battery in the device related to a particular adverse event (AE). PMI ensures traceability of components per device including the battery. The unique identification code engraved by the contract manufacturer on each THD enables to retrieve traceability information related to components used in the assembly of the specific device. However, as the AE reports do not contain this unique code, only general information about the device and battery can be provided. The unique device identification code is not collected and recorded due to data privacy constraints in place in a number of jurisdictions. Consumers can choose to register their device at the time of purchase and need to provide the device unique identification code together with their personal information (first/last names and contact details (email/home address, phone number, etc.)). Consequently, collection of the unique device identification code in an AE report would allow PMI to identify the consumer who experienced the adverse event, which is not permitted in a number of jurisdictions. Therefore, **columns I-M** (columns G-K prior to insertion of additional columns 'Case ID' (column A) and 'Case report type' (column F)) of the Excel table (Safety Report Excel Workbook for IQOS) cannot be completed.

PHILIP MORRIS
PRODUCTS S.A.

Due to the production volume and battery stock availability, during production, devices may be assembled using more than one lot of batteries meeting specification requirements from qualified suppliers. During assembly of the device, the contract manufacturer records the supplier of the battery against each unique device identification code. A list of the battery suppliers per PMI device version is listed in the requested Excel file (Safety Report Excel Workbook for IQOS) in the tab "All product versions".

Additional information related to the Accidental exposure events:

The accidental exposure reports received to date include child ingestions of *HeatStick(s)* or any of its constituents and adult ingestions of liquid (e.g. coffee) in which *HeatStick(s)* have been immersed, and these reports are coming mostly from Japan. This can be explained by the fact that we have an agreement with a local poison center in Japan (Japan Poison Information Center (JPIC)).

PMI is setting up an agreement with the American Association of Poison Control Centers to collect the reports of IQOS which have been reported to a US poison center. This will enable PMI to perform appropriate monitoring activities of IQOS once commercialized in the United States.

Additional information related to the Battery Improvements:

In 2017, several consumers reported battery electrolyte leakage, mainly in Korea. A root cause analysis showed that an external short circuit of the THD's battery caused a gas pressure build up that in turn caused the rupture of the safety cap of the battery which led to the leakage of small amounts of electrolytes to the surface of the THD. None of the events reported in Korea led to an Adverse Event.

A risk assessment was performed in parallel to assess the potential safety risks for users who may be exposed to toxic substances found in the battery fluid (lithium iron phosphate, lithium hexafluorophosphate, and ethylene carbonate) and generated by the leakage (hydrogen fluoride). The assessment indicated that the risk of potential harm was low, as the respective levels of those substances were under the threshold above which dermal or inhalation toxicity may occur.

PHILIP MORRIS
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As corrective actions the pressure resistance of the concerned battery type was increased and the THD manufacturing process improved. All design changes for the THD intended for the US market have been reported to FDA either in the original applications or subsequent communications.

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APPENDICES

- The files listed below are provided as appendices to this response:

Filename	Title / Description
PMI001159_MedWatch_report_final	MedWatch form (full case report) related to the individual adverse event specifically discussed during the conference call on June 6, 2018