PMI RESEARCH & DEVELOPMENT

Passive Safety Surveillance Reporting System
P1-SUR-01-US

Study Type: Spontaneous AE Reporting

Product: *iQOS* with *HeatSticks*

Country: United States

Sponsor: Philip Morris Products S.A.
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PROTOCOL CONCEPT

Purpose and Background

Philip Morris Products S.A. (PMP S.A.) is developing novel tobacco and nicotine containing products with the potential to reduce harm or the risk of tobacco-related disease associated with smoking conventional cigarettes. In accordance with the United States Food and Drug Administration (FDA), PMP S.A. must demonstrate that "the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- 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." (FDA 2012)

To fully understand the safety of *iQOS* with *HeatSticks* when it is used by consumers, PMP S.A. will implement an adverse event (AE) reporting system to collect spontaneous reports of adverse health effect associated with exposure to *iQOS* with *HeatSticks*.

Definitions

- Adverse Event (AE)[1] = any health-related event associated with the use of a tobacco product in humans that is adverse or unfavorable, whether or not it is considered tobacco product related (FDA 2012)
- Serious Adverse Event (SAE) = an AE that results in any of the following: death; a life-threatening condition or event; persistent or substantial disability or incapacitation; hospitalization or prolonged hospitalization; or a congenital anomaly or birth defect. (FDA 2012)

Adverse Event Call Center

Altria Client Services (ALCS) plans to use one or more call centers, including the ALCS managed third party Consumer Response Center (ALCS Consumer Call Center) to collect all complaints related to *iQOS* with *HeatSticks* in the US market. The ALCS Consumer Call Center has experience in the systematic collection and assessment of unsolicited consumer complaints, including AE.

Population

The *iQOS* Safety database for post-market surveillance will include information on current *iQOS* with *HeatSticks* users and non-users exposed to *iQOS* with *HeatSticks*. The *iQOS* Consumer Call Center telephone number is a hotline available on the product packaging, on company websites (ALCS) and on any *iQOS* branded websites. This hotline is set up to capture the general product or device complaints that can vary in nature from question on how to use the device, product quality issues, and adverse health events associated with the use of or exposure to *iQOS* with *HeatSticks*.

[1] The ALCS Consumer Call Center currently uses the term Alleged Physical Effect (APE) rather than AE. APE is defined by ALCS as any complaint that alleges symptoms, illness or injury. For purposes of this application, PMP S.A. will use the terms Adverse Event and AE.

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Although the population in the database will be primarily composed of *iQOS* consumers, the hotline will collect the report from the consumers directly, as well as, relatives of consumers, and health care professionals that would like to report a health event related to the use of or exposure to *iQOS with HeatSticks*.

Minimum data reporting required to validate a case for inclusion in the database:

- Consumer
- Product
- Event
- Reporter

AE Data Collection (Adverse Event Questionnaire)

The AE data collected by the ALCS Consumer Call Center will be performed by call handlers who are trained on the capturing the AE information. Each consumer call is received by call handlers who are trained to follow a series of pre-defined scripts which ensure that every consumer complaint is collected in a defined and consistent manner that can identify potential AEs. If the complaint is identified as a potential AE, the personnel administers the ALCS Adverse Event Questionnaire.

ALCS has developed the Adverse Event Questionnaire described below based on a combination of the FDA MedWatch form and FDA's Center for Tobacco Products (CTP) Safety Portal Reporting Questionnaire. The questionnaire was designed with a specific data collection flow to capture the relevant case information, and that the cases can be coded and classified consistently by the certified coders.

The ALCS Adverse Event Questionnaire captures detailed information on:

- Identification of the *iQOS with HeatSticks* user;
- The source of the case report (consumer, relative, health care professional);
- AE event-specific details (description of the event, start and duration of event, outcome);
- Exposure to *iQOS with HeatSticks* (dates of use, amount/frequency of use);
- Identification of *iQOS* (model of the device, variant / batch of *HeatSticks*)
- Use of other tobacco products; and
- Other relevant medical information or history (pre-existing medical conditions, medication, allergies)

Although callers may not know all of the answers or may choose not to respond to specific questions, the call handler will continue the interview and collect as much data as the caller can provide.

PMP S.A. has also developed a standard Adverse Event Questionnaire, with some country-specific adaptations to collect spontaneous reports of AEs in the markets outside of the US, where *iQOS with HeatSticks* is commercialized. The adaptations allow the collection of the relevant data in compliance with the country-specific data protection laws.

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Adverse Event Process and Reporting Timelines

Processing Timelines

- Initial processing of each case is performed within 5 calendar days of receiving the report.
- Weekly reconciliation and resolution of any discrepancies identified in the case processing will be performed.

Reporting Timelines

- Adverse Events: consolidated and reported annually
- Serious Adverse Events:
  - Individual cases are reported to the FDA within 15 business days of the first report of the event
  - Consolidated summaries reported annually

Adverse Event Case Processing

All cases are processed by certified coders who are experienced physicians, nurses or pharmacists with training on the AE processing.

All cases included in the safety database will follow a systematic process to ensure that the event is processed and reported within the AE case processing timelines.

1. Validate the case as an AE (verify that it meets the minimum data reporting requirements);
2. Extract the AE verbatim term;
3. Determine if it meets the definition of an SAE;
4. Code the AE verbatim term using Medical Dictionary for Regulatory Activities (MedDRA);
5. Code the severity of the AE;
6. Assign the expectedness of the AE.

The coding standards and conventions for coding are documented in the ALCS coding guidelines which will be in an appendix of the final protocol. For MedDRA coding the certified coders will code each AE case in accordance with the current version of MedDRA® Term Selection: Points to Consider (MSSO 2016) and the ALCS coding guidelines.

The coding and case assessment will be performed by an independent certified coder. All AE coding is reviewed for quality control specialist. The project manager, who is also a physician that provides oversight and training serves as the quality assurance reviewer and makes the final determination.

Data Captured in the AE Questionnaire

The ALCS AE questionnaires capture detailed information on:

- Identification of the *iQOS with HeatSticks* user;
- The source of the case report (consumer, relative, health care professional);
- AE event-specific details (description of the event, start and duration of event, outcome);
- Exposure to *iQOS with HeatSticks* (dates of use, amount/frequency of use);
- Identification of *iQOS with HeatSticks* (model of the device, brand / batch of *HeatSticks*);

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- Use of other tobacco products; and
- Other relevant medical information or history (pre-existing medical conditions, medication, allergies).

AE Safety Analysis

The number of AEs and SAEs will be summarized as total count and annualized counts and presented by System Organ Class (SOC) and Preferred Term (PT). AEs will also be summarized by severity and expectedness.

In order to provide context to the frequency of AE report, market indicators will be used to estimate the number or extent of *iQOS with HeatSticks* use in the population.

Review of aggregated safety data will be performed to assess changes in the number and severity of the AEs reported over time.

In addition to the analysis of the US *iQOS* Safety Database described above, safety summaries will be provided by PMP S.A. for the markets outside the US.

Standards

- Good Pharmacovigilance practices will be followed to the extent defined in the ALCS processes included appropriate medical oversight of the case processing and follow-up.
- Appropriate measures will be implemented to ensure that the data collection, and reporting processes are compliant with data privacy laws.

ABBREVIATIONS	
AE	Adverse Event
ALCS	Altria Client Services
CTP	Center for Tobacco Products
FDA	United States Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
PMP S.A.	Philip Morris Products S.A.
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class

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REFERENCES

[1]	Association IE. Good epidemiological practice: IEA guidelines for proper conduct in epidemiologic research. (IEA 2007).
[2]	FDA (Food and Drug Administration), Guidance for industry - Modified risk tobacco product applications - Draft Guidance. 2012. (FDA 2012)
[3]	Maintenance and Support Services Organization. MedDRA® Term Selection: Points to Consider (MSSO 2016).
[4]	World Medical Association. WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects. (WMA 2013).

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