PMI RESEARCH & DEVELOPMENT

Safety Summary Report

Passive Safety Surveillance for Perception & Behavior Assessment Study n° THS-PBA-07-US

Appendix 2 Safety Management Plan

Report Number:	PMI_SURV_2016_SSR02
Study Title:	Actual Use Study of THS 2.2 – THS-PBA-07-US
Study ID:	THS-PBA-07-US
Safety ID	THS-PBA-07-US_PSS
Products Name:	Tobacco Heating System 2.2 / Regular and Menthol
Passive Safety Surveillance by:	Philip Morris Products S.A. PMI Research & Development Quai Jeanrenaud 5 2000 Neuchâtel, Switzerland
Version:	Final v 2.0
Date:	30-Aug-2016
Author:	Nicoleta Ciuria Senior Medical Safety Associate Philip Morris Products S.A.
Reviewed and approved by:	Alexandr Mészáros Senior Medical Scientist - Surveillance Philip Morris Products S.A.

PMI RESEARCH & DEVELOPMENT

Safety Management Plan THS-PBA-07-US_PSS

Premarket Passive Safety Surveillance

Study Title:	Actual Use Study of THS 2.2 – THS-PBA-07-US
Study Identifier:	THS-PBA-07-US, study protocol version 3.0 of July 22nd, 2015 including Study Protocol Amendment No3 (1.0) dated October 26, 2015
Passive Safety ID:	THS-PBA-07-US_PSS (passive safety surveillance for THS-PBA-07-US)
Product name:	Tobacco Heating System THS 2.2 Regular Tobacco Heating System THS 2.2 Menthol
Passive Safety Surveillance by:	Philip Morris Products S.A. PMI R&D, PASS Product Surveillance Quai Jeanrenaud 5 2000 Neuchâtel Switzerland
Version number:	Version 2.0
Issued date:	November 30, 2015
Author:	Alexandr Mészáros, MD Senior Medical Scientist – Surveillance

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
(b) (4)	(b) (4)
CATI	Computer assisted telephone interview
CAWI	Computer assisted web interview
CC	Conventional / combustible cigarettes
D0	Day 0 is defined as the day of first awareness of an AE or pregnancy report by PMI employee or designee (e.g. call center operators, interviewers or site staff)
FDA	Food and Drug Administration
FDA-CTP	Food and Drug Administration Center For Tobacco Products
GP	General practitioner
HCP	Healthcare professional
ICF	Informed consent form
ICSR	Individual case safety report
iQOS system	Represents the investigational tobacco product
IRB	Institutional Review Board
ISDCF	Individual safety data collection form
ITP	Investigational tobacco product
KH	Kantar Health
MedDRA	Medical dictionary for regulatory activities
Participant	Subjects who have signed informed consent form and were enrolled to take part in the concept stage as a part of the representative sample
PBA	Perception and behavior assessment
PMI	Philip Morris International
PMI-MR	PMI-Market Research
PMI-PASS	PMI-Product Assessment and Scientific Substantiation Department
PMI-PSSD	PMI Product Safety Surveillance Department
PMI RO	PMI Regulatory Operations

QC	Quality control
SAE	Serious adverse event
Safety Population	Subjects exposed to at least a single *HeatStick* use
SMP	Safety management plan
THS	Tobacco heating system
UBC	United BioSource Corporation

1 OVERVIEW

This safety management plan (SMP) is set for handling of unsolicited adverse events spontaneously reported by study participants in the THS-PBA-07-US study testing the investigational tobacco product (ITP), called Tobacco Heating System generation 2.2 (THS 2.2) according to the product definition in the study protocol and corresponding Amendment(s).

Table 1. Study Identification

Description	Identification	Sponsor / Accountable
Study Title	THS-PBA-07-US	Philip Morris International Management SA Marketing & Sales PMI Avenue de Rhodanie 50 1001 Lausanne Switzerland
Passive safety surveillance for THS-PBA-07-US study	THS-PBA-07-US_PSS	Philip Morris Products SA PMI R&D PASS – Product Safety Surveillance Department (PSSD) Quai Jeanrenaud 5 2000 Neuchâtel Switzerland

1.1 Study Information

Philip Morris International (PMI) is currently developing and conducting a comprehensive program to study consumer perception and behavior in relation to THS 2.2, known as the *Perception and Behavior Assessment* (PBA) program.

THS 2.2 is comprised of a device commercialized (in some countries outside the USA) under the brand name "*iQOS*" and THS Tobacco Sticks branded as "*HeatStick*s" designed to be exclusively used with the *iQOS* device. Therefore, in the context of this study, the terminology of "the *iQOS* system" will be used to describe "THS 2.2" and "*HeatSticks*" will be used to describe "THS Tobacco Sticks".

The THS-PBA-07-US Actual Use Study will focus on how US adult current daily smokers of conventional / combustible cigarettes (CC) use the *iQOS* system under near to real world conditions. In particular, the study will assess the quantities of CC and of *Heatsticks* consumed by individual participants over time.

With the proposed study design, there will be a baseline assessment period, an observational period, a close out period, and a 30-day follow-up interview which will take place 30 days-60 days after the start of the close out period to document tobacco and nicotine-containing products (electronic e-cigarettes, Nicotine Replacement Therapies products) use after six-week exposure/use of *HeatSticks* (i.e. observational period).

Each participant will participate in this study for a total of eight weeks after the recruitment period: one-week baseline period of CC + six-week observational period with THS 2.2 exposure + one-week of CC close out period. Additionally, a 30-day follow-up interview will be conducted 30 days-60 days after the start of the close out period. All enrolled participants will be eligible for the 30-day follow-up interview.

At rescreening, socio-demographic information will be collected for participants via an electronic data collection tool, a Computer Assisted Web Interview (CAWI) survey. Information concerning delivery of product to the participant (e.g. home address) will be collected, however this will not be part of the study database.

During the one-week baseline period, all enrolled participants will be requested to enter information into an e-diary every time they consume a CC. In addition, participants will also record in their e-diary use of any other products containing nicotine on a daily basis.

During the six-week observational period, they will report each CC and *HeatStick* consumption using the e-diary, and will continue to report other products containing nicotine using the e-diary on a daily basis. All spontaneously reported adverse events starting from subjects first use of THS 2.2 will be collected as described below using Individual Safety Data Collection Form (ISDCF).

Participants will have follow-up CAWI conducted at the site after the baseline period and at the end of the observational period, when the participant is at the study site to obtain/return the *iQOS* system. In addition, interim follow-up interviews will be planned every other week during the observational period (Weeks 2, 4). The interim follow-up interview will be performed using Computer Assisted Web Interview (CAWI) surveys. Trained interviewers will administer all follow-up interviews (i.e. both CAWI and CATI surveys). All ITP-emergent (i.e., with temporal relationship to the product use) adverse events will continue to be collected until end of close-out period for each subject.

The 30-day follow-up interview will be conducted using CATI surveys. Trained interviewers will administer the 30-day follow-up telephone interview. The main topic covered in these interviews is the documentation of tobacco and nicotine-containing products use after participation in the main study.

The data resulting from the 30-day follow-up interview will be reported as an Addendum to the Study Report. Data on adverse experiences provided up to the 30-day follow-up interview for the last study participant will be reported as part of a separate study-specific safety surveillance report.

Table 2. THS-PBA-07-US Study Information

Study protocol	THS-PBA-07-US
	Version 3.0 issued on July 22nd, 2015 including Study Protocol Amendment No3 (1.0) dated October 26, 2015
Study participants	1300 participants are expected to enter the study; each of them will have access to the investigational product for the duration of their participation in the study
General inclusion / exclusion criteria	• 18 years of age or above or the minimum local or State legal smoking age and above, whichever is higher • Current daily smokers of regular and/or menthol CC with no intention of quitting within the next 30 days (current daily smoker is defined as an individual who has smoked at least 100 cigarettes in his/her lifetime and is currently smoking at least one regular or menthol CC (no brand restrictions) per day, disregarding religious fasting) • Individuals who sign Informed Consent Form (ICF) and are able to understand the information provided in the ICF • Individuals available and interested in participating in an eight-week study about tobacco • Individuals with positive intention to use the *iQOS* system • Individuals currently living in the United States Participants meeting the following criteria will <u>not</u> be eligible for recruitment: • Women of childbearing potential who are not using adequate means of contraception • Pregnant or breastfeeding women (based on self-reported status) • Individuals with no proof of age (photo ID, such as passport, driver's license) • Individuals who have started smoking within the last 30 days • Individuals who cannot read and speak English • Individuals who are employed in the fields of market research, marketing, advertising, media or journalism, law, manufacturers or distributors of tobacco products, or who are health care providers. • Individuals who have taken part in a consumer or clinical study in the past three months.

Investigational tobacco product(s) (ITP) description and labelling	2 product variants: • THS 2.2 regular (Dorado II / Ron) (i.e. *HeatStick* regular) • THS 2.2 menthol (Dorado I / Vinny Low menthol) (i.e. *HeatStick* menthol)
Blinding	Not applicable
Product use	*Ad libitum* use any of the two products at home for 6 weeks
Study Location(s)	The study sites are planned to be located in the following mall research facilities in USA: 1. Las Vegas, NV - Galleria Mall 2. Denver, CO - Aurora Mall 3. Detroit, MI - Laurel Park Place 4. Oklahoma City, OK - Quail Springs Mall 5. Asheville, NC - Asheville Mall 6. Charlotte, NC - Eastridge Shopping Centre 7. Tampa, FL - Westfield Countryside Mall 8. Miami/Fort Lauderdale, FL - Westfield Broward Mall
Expected Duration of the Entire Study	This study conduct is expected to be held • from September 2015 • to February 2016
Hotline (call center)	The hotline will be available • Monday – Sunday, 8am – 8pm eastern standard time, from September 2015 to February 2016, with exception of Seasonal Holidays

1.1.1 Study Research Objectives

The primary, secondary and exploratory study objectives are described in the study protocol.

1.1.2 PBA Study Standards

This study will be conducted in compliance with Good Epidemiology Practices (GEP).

1.2 Passive Safety Surveillance

The scope of this passive safety surveillance is the collection and assessment of adverse events (AEs) and pregnancies spontaneously reported by study participants in the THS-PBA-07-US study conducted with investigational tobacco products, including those captured in open-ended questionnaires.

Table 3. Passive Safety Surveillance Information

Safety surveillance number	THS-PBA-07-US_PSS
Safety surveillance population	1300 product users (all study participants who used at least one *HeatStick)*
Data collection methods	• ISDCF of spontaneously reported health problems collected by hotline operators and interviewers • Pregnancy forms of spontaneously reported pregnancies collected by hotline operators and interviewers • Health problems captured in open-ended questionnaires
Expedited reporting requirements to regulatory authorities	All adverse events (AEs) assessed by UBC as serious (i.e. serious adverse events (SAEs) are subject to expedited reporting by the sponsor to the Food and Drug Administration, Center for Tobacco Products(FDA-CTP), Office of Science, within 15 business days of first awareness. Reporting of reportable AE and SAE cases to Institutional Review Board (IRB) will be ensured by the study designee (Kantar Health) within required timelines (within 10 business days of first awareness of reportable AE cases, except death and life threatening AE cases, to be reported immediately)

Table 4. Safety Surveillance - Provisional Timelines

Training on safety surveillance	August/September 2015
Product use period	September 2015-December 2015
Safety surveillance period (hotline is open)	September 2015-February 2016
Last day for receiving ISDCF initial reports	February 2016
End-of-Study health problems listing provided to UBC (if any, see provision in section 4.2.2)	March 2016
Safety Line Listing and Summary Tables to be generated by UBC	April 2016
Safety Surveillance Report (SSR)	April 2016

Provision for long-term follow up (e.g., in case of pregnancies or ongoing SAEs at end of study, if any)	December 2016

1.2.1 Passive Safety Surveillance Objective

The objective is to gather and analyse safety information for the ITP, received from study participants who spontaneously reported that they experienced a health problem (adverse event) that they judge to be associated with and/or caused by the use of the *iQOS* system or who spontaneously reported that they are pregnant or became pregnant during the use of the Investigational Tobacco Product.

1.2.2 Passive Safety Surveillance Standards

This passive safety surveillance is executed under the following standards:

- The safety information is collected in the context of THS-PBA-07-US study. The obtained information will subsequently be part of a product-specific annual safety analysis which may be reported to regulatory authorities if required.
- The safety information handling (collection and processing) is derived from Good Epidemiology Practice.
- The processing of ICSR will be executed according to the PMI pre-market safety assessment subcontractor United BioSource Corporation (UBC) procedural documents.
- Individual health data will be treated as confidential information. A written statement will be given to study participants and their consent to disclose such information will be obtained by signing an informed consent form prior to any study procedure for the THS-PBA-07-US study.

1.3 Investigational Tobacco Products

Two product variants will be tested in the THS-PBA-07-US study. The reference Investigator's Brochure to be used for the assessment of expectedness of product-emergent adverse events is presented in the table below:

Table 5. Investigational Tobacco Products and Reference Safety Information

Products	**Reference Document, version, date**
THS 2.2 Menthol (Dorado I / Vinny Low Menthol) (i.e. *HeatStick* menthol)	Investigator's Brochure THS 2.2 Menthol Edition 3.0, dated 27 April 2015

THS 2.2 Regular (Dorado II / Ron) (i.e. *HeatStick* regular)	Investigator's Brochure THS 2.2 Edition 5.0, dated 27 April 2015

1.4 Overall Organization

There are different parties (contact details in Section 7) involved in the study and surveillance:

- PMI Product Safety Surveillance Department (PMI-PSSD), accountable for the passive safety surveillance
- PMI Market Research (PMI-MR), sponsor of the THS-PBA-07-US study
- Kantar Health (KH) the contract research agency, executing the THS-PBA-07-US study
- ((b) (4)), operating the study hotline (call center), supervised by Kantar Health
- United BioSource Corporation (UBC), executing the safety case processing
- (b) (4) site staff who will conduct the 1st and final follow up interviews, supervised by Kantar Health
- (b) (4) who will conduct the 2nd and 3rd follow up interviews, supervised by KH
- The study participants, and
- Dr. James Davis, Rose Research Center, the Local Physician, will be available to respond to product related questions asked by local healthcare professionals if any.

Figure 1, in Section 6 provides also a diagramatic view of the study organization.

2 ROLES AND RESPONSIBILITIES

2.1 PMI – Product Safety Surveillance Department

Within the Product Assessment and Scientific Substantiation (PASS), PSSD is accountable for the pre-market passive safety surveillance of the ITPs and is responsible for the actions listed below:

- Prepares the THS-PBA-07-US study-specific safety surveillance management plan and its subsequent updates as necessary, based on approved THS-PBA-07-US study protocol and information provided by the PMI-MR team
- Provides UBC with ITP description and study details in due time to allow safety database configuration
- Ensures adequate training of the study personnel (supervisors, interviewers, hotline operators, site staff and local physician) on safety processes prior to study start
- Ensures due diligence assessment of any serious adverse event (SAE) transmitted by UBC, with special attention to death and life-threatening cases and to other SAEs to be reported to IRB , if any

- Reviews/approves by calendar Day 11 draft MedWatch forms for serious adverse events received from UBC by calendar Day 9
- Provides the final/approved MedWatch reports of IRB-reportable AE / SAE cases to KH (on PBAstudysafety@kantarhealth.com) for further distribution to the IRB
- Ensures expedited and/or periodic submission of safety information (SAE cases) to FDA-CTP in collaboration with PMI Regulatory Operations Department (PMI RO)
- Requests acknowledgement of receipt from KH who ensures submission of reportable safety information to Sterling IRB.

2.2 PMI – Market Research

PMI – MR acts as the study sponsor, and contributes to the safety surveillance by:

- Providing PMI PSSD with all necessary information on the THS-PBA-07-US study, such as study protocol, timelines, ITPs, sample size, study organization, contact details
- Organizing the venue of training sessions and contribute to the safety training of interviewers and/or of hotline operators
- Ensures provisions for follow up safety information collection (U.S. hotline number) up to 1 year after study completion (last subject last visit).

2.3 Kantar Health, the Contract Research Agency

Kantar Health executes the conduct of the THS-PBA-07-US study and organizes the study-specific hotline. Kantar Health contributes to the safety surveillance in:

- Ensuring, in collaboration with PMI, the safety training of interviewers, site staff and of hotline operators (e.g., train to ensure that data privacy requirements are respected - participants' contact details not provided to PMI, train to ensure that interviewers do not proactively ask health-related questions during interviews according to training material, train to ensure that interviewers are asking participants, who have spontaneously indicated that they have experienced an unexpected health or safety problem they believe has been caused by or associated with the use of the investigational product, to call the hotline, if they wish to report the problem)
- Inform PMI-MR of the occurrence of any adverse event (see definition in Section 4.1) and pregnancy within 1 working day of first awareness
- Ensure submission of reportable safety information to Sterling IRB[1] as required: All SAEs that are unexpected and related or possibly related to participation in the research should be reported to Sterling IRB within 10 business days of when the site becomes aware of the event. All fatal or life threatening events should be reported immediately to Sterling IRB

[1] See Sterling IRB reporting requirements by principal investigator (they are not limited to safety) http://www.sterlingirb.com/investigator-smo/investigator-handbook html

- Provides to PMI PSSD (pmssafety.pmi@pmi.com) acknowledgement of receipt of reportable safety events to IRB
- Ensure that health problems cases and pregnancy cases spontaneously reported outside the hotline (i.e., reported to study staff or to CATI/CAWI interviewers) are transferred to the hotline or collected by interviewers or study staff and forwarded to UBC within 1 business day of awareness.
- Provides to PMI PSSD (pmssafety.pmi@pmi.com) listing of health related events collected from open-ended questionnaires within 6 weeks after end of the study, in March 2016
- Provides exposuree per product (see tabulation below) at the end of the study (sample size meaning participants who have used the Investigational Tobacco Product at least once) within 6 weeks after end of the study:

Product variant	**Sample size**
THS 2.2 Menthol (Dorado I / Vinny Low Menthol) (i.e. *HeatStick* menthol)	
THS 2.2 Regular (Dorado II / Ron) (i.e. *HeatStick* regular)	
Overall	

2.4 (b) (4) , the Hotline (Call Center) Provider

Subcontracted (b) (4) Hotline employees are operating according to effective (b) (4) procedural documents. (b) (4) provides call center services with respect to PMI passive safety surveillance as follows:

- Call center operators will not proactively ask health-related questions during phone calls, unless callers spontaneously report health problems
- Call center operators will recognize and identify the participants' phone calls, differentiating health related problems vs. other complaints / inquiries
- Call center operators will complete the Individual Safety Data Collection Form (ISDCF - paper or electronic form) in English, as much as the participant accepts to provide information
- In case a study participant reports she is pregnant or became pregnant during the course of the study, the same process is followed by completing a pregnancy form
- Call center operators will send each completed ISDCF or pregnancy form to UBC within 1 business day to: Fax number: 011 41 22 596 44 46 or E-mail: EUsafety@ubc.com
- Call center operators, interviewers or site staff receiving information on a study participant's AE, will advise the caller to seek medical or professional help and advise the participant to stop using any tobacco product, including *HeatSticks*

- Call center operators will approach study participant reporting pregnancy and AEs/SAEs with follow up questions requested by PMI-PSSD/UBC
- (b) (4) will send, within one week after the end of the study or upon PMI-PSSD request, all completed ISDCF paper forms and pregnancy forms to PMI PSSD and will not retain any paper copy
- Call center operators will ensure that if a participant's health care professional (for example, the treating physician of the participant) requests or asks for additional details, this healthcare professional is invited to call the local physician on the following number in the USA: (b) (4)
- Call center operator's supervisors will maintain the log of ISDCFs (containing the participant's study number, date of ISDCF/call, date of transmission to UBC and number of contact attempts as recorded on the Data Collection Forms), which will be used on a weekly basis to allow a weekly ISDCF and pregnancy reconciliation with the UBC provided reconciliation listing. A separate log for pregnancies should be maintained to allow pregnancy follow-up.

2.5 Local Physician

The local physician has the following duties:

- To be available (during business days and business hours (9am to 5pm Eastern standard time) during the safety surveillance period as specified in *Table 4*) by phone for answering questions from healthcare professionals about the study, the investigational tobacco products or health issues.
- To issue a summary note for each interaction, to be provided to PMI PSSD
- To issue a final summary report (summary of interactions with healthcare professionals) at the end of the project, to be provided to PMI PSSD.

3 PHARMACOVIGILANCE: UNITED BIOSOURCE CORPORATION (UBC)

UBC has set up and currently maintains the Safety Database for PMI. UBC is responsible for processing individual safety data collection forms and pregnancy forms. In particular, UBC:

- Receives and checks the ISDCFs and the pregnancy forms for consistency, completeness and potential duplicate
- Allocates a unique reference number for each safety case by logging minimum information into the Safety Database
- Acknowledges receipt to the sender (e.g., hotline operators or common mailbox: (b) (4)) and PMI-PSSD (pmssafety.pmi@pmi.com) within 1 business day

- Ensures due diligence to identify immediately death and life-threatening cases and inform immediately PMI-PSSD (pmssafety.pmi@pmi.com)
- Provides AE/SAE and pregnancy case assessment
- Provides assessment of the case reportability - seriousness, expectedness and causality according to UBC effective procedural documents
- Performs entry of the safety information into the Safety Database and codes the reported term(s) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, current version
- Writes the case narrative (and a company comment for SAE reports only) and performs Quality Control (QC) of the data entry
- Performs medical review of the safety case report
- Generates draft individual safety case report (MedWatch form) for all serious cases and forwards them by calendar Day 9 to PMI-PSSD for final review/approval
- Implements comments received from PMI-PSSD, if any and updates the case as appropriate
- Generates final individual safety case report for all SAEs reported in this study and forwards them to PMI-PSSD (pmssafety.pmi@pmi.com) by calendar Day 12
- Ensures, in collaboration with PMI PSSD, case follow up as necessary
- Reconciles the list of ISDCFs and pregnancies with the hotline on a weekly basis
- Provides PMI-PSSD with adverse events Line Listings and Summary Tabulations (details in Table 4)
- Provide PMI-PSSD with a study-specific safety surveillance summary report

4 SAFETY DATA MANAGEMENT

4.1 Definitions

Adverse event	"An adverse event (AE) is any health-related event associated with the use of a tobacco product in humans that is adverse or unfavourable, whether or not it is considered tobacco product related" *[FDA 2012, draft guidance Modified Risk Tobacco Product Applications*]
Seriousness	A serious AE (SAE) is 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, Draft Guidance Modified Risk Tobacco Product Applications*]

Causality	All spontaneously reported AEs are suspected to be tobacco product related ("implied causality") unless impossible from a temporal point of view, as people who spontaneously report an AE judge that this AE has been caused by use of the investigational product.
Expectedness	AEs not listed in the current product-specific investigator's brochure are assessed as unexpected.

4.2 Adverse Events and Pregnancy Data Collection

In this observational study AE reporting will follow a mechanism established by the Sponsor for post-market Safety Surveillance of spontaneously reported events. Participants in this study will be informed that a dedicated hotline has been set up for use during the study so that participants can report product quality complaints, including adverse events associated with the use of the *iQOS* system. Proactive data collection is set up for the follow-up of SAE and pregnancy cases.

4.2.1 Individual Adverse Events Passively Collected Through ISDCF

Individual Adverse Event (AE) reports are passively collected by the hotline operators and by interviewers during the study period and until the 30-day follow up interview is completed for the last study participant.

The hotline operators and interviewers must notify all AEs reports to UBC Pharmacovigilance using the ISDCF by faxing or e-mailing in attachment within one business day of first awareness:

UBC Pharmacovigilance

Fax number: 011 41 22 596 44 46

E-mail: EUsafety@ubc.com

The minimum information to be provided on the ISDCF is as follows:

- Description of the health problem
- Participant study number *["identification number"],* age and gender
- ITP identification (e.g., product batch number) and use dates
- Information about the person who called the hotline (limited to his/her qualification, without any contact details, except if the caller is a healthcare professional)
- Information about the person who filled out the form
- Date of the current form completion

4.2.2 End-of-Study Health Problems Listing

At the end of the study, in case other health problems have been inadvertently collected in CAWI or CATI questionnaires, UBC will receive from KH a listing of the unsolicited health problems information in tabulated format.

4.2.3 Self-reported Pregnancy Cases

After enrolment, until the end of the close out period, any pregnancy spontaneously reported to the call center operators, interviewers or site staff must be reported to UBC and the Sponsor.

Pregnancy potentially associated with the exposure to the *HeatStick*s will be followed-up by PSSD/UBC until the pregnancy outcome is reached.

The hotline operators / interviewers or study staff must notify all pregnancy reports to UBC Pharmacovigilance using the pregnancy form by faxing or e-mailing in attachment within one business day of first awareness to UBC (see Section 4.2.1)

The minimum information to be provided by the hotline operators on the pregnancy form is as follows:

- Participant study number *["identification number"]* and age
- ITP identification (e.g., batch number) and product use dates
- Information about the pregnancy: date of first day of last menstrual period, date of pregnancy awareness by the study participant and expected date of delivery, if known
- Information about the person who called the hotline (limited to his/her qualification, without any contact details, except if the caller is a healthcare professional)
- Information about the person who filled out the form
- Date of the current form completion

4.3 Safety Case Processing

4.3.1 Reception

Upon receipt of an ISDCF or a pregnancy form, UBC ensures that the information received is legible/consistent and sends an acknowledgment of receipt by e-mail within 1 business day to the sender (i.e., (b) (4) hotline operator email: (b) (4) or sender from other affiliation – see list in Section 1.4) and to PMI-PSSD pmssafety.pmi@pmi.com.

A unique reference number is allocated to each safety case by logging minimum information into the Safety Database.

4.3.2 Case Prioritization

UBC Safety Scientist / Safety Physician assesses the seriousness of the safety case based on the information provided on the ISDCF according to effective UBC procedural documents. Safety cases assessed as "serious" by UBC are notified to PMI-PSSD by e-mail within 1 business day to pmssafety.pmi@pmi.com, as described in the above section**.** Death or life threatening cases will be also notified within 1 business day to PMI-PSSD (pmssafety.pmi@pmi.com). PMI-PSSD will forward the information to Kantar Health, which can make a preliminary notification to IRB, which will be followed by a follow-up notification including the final MedWatch when it is available (see timelines below).

5 DATA ENTRY

Qualified personnel at UBC enters the safety information presented in ISDCFs into the Safety Database. The current version of the MedDRA dictionary is used to code the reported adverse event term(s). A case narrative (and a company comment for an SAE report only) is/are prepared and QC of the data entry is performed.

Each adverse event from the end-of-study health problems listing will be processed in the same way as for ISDCFs.

Each case is reviewed by UBC Safety Physician according to effective procedural documents.

For SAE reports only, once the safety information has been processed into the Safety Database, UBC generates a draft individual case safety report (e.g. MedWatch report) and forwards it by calendar Day 9 to PMI-PSSD (pmssafety.pmi@pmi.com) for final review/approval.

5.1 Final Review/Approval by PMI-PSSD

PMI-PSSD reviews / approves by calendar Day 11 the draft MedWatch forms for SAEs reports received from UBC.

Once the SAE report has been reviewed/approved by PMI-PSSD, UBC generates a final individual case safety report (MedWatch form) and forwards it to PMI-PSSD on pmssafety.pmi@pmi.com, no later than calendar Day 12. PMI-PSSD completes the Sterling IRB Reportable Events form and forwards it together with final MedWatch form to KH for submission to Sterling IRB by business Day 10 as to required Sterling IRB safety reporting timelines (which is equivalent to calendar Day 12 driven by case processing).

5.2 Follow-up Request for AEs and SAEs

Upon request from UBC/PSSD, AEs/SAEs will be followed up until resolved, stabilized (i.e., no worsening of the event), or a plausible explanation for the event has been found until the end of the close out period.

UBC in collaboration with PMI-PSSD will organize follow up of AEs and SAEs when necessary to complete the case documentation, by sending queries / data clarification forms (DCFs) from PMI: pmssafety.pmi@pmi.com to the reporter of the initial ISDCF copying UBC (EUsafety@ubc.com). Joined email address (b) (4) will be used by PMI-PSSD for sending to (b) (4) Data Clarification Form (DCF), or any other reason PMI-PSSD needs to communicate with (b) (4)

The call center operators, interviewers or site staff will facilitate case documentation/follow-up requested by UBC for all subjects who reported any adverse health events until 30-day follow up interview is completed for the last study participant.

Call center operator calls the number provided by participant and asks follow up questions generated by PMI-PSSD and UBC on the DCF. Verbatim answers, excluding participant's personal or contact information is collected from participant, his/her relative or treating physician will be returned by a call center operator to UBC as soon as relevant information is obtained (1 business day) or contact attempt failed and was documented.

If a participant reports a health problem mentioning medical care or overnight stay in hospital, the participant will be asked by a call center operator for her/his consent to follow up on medical aspects of the current hospitalisation. If the participant's consent is obtained, participant or participant's relation provides a contact number on which participant or her/his treating physician can be reached. Contact details will remain only with the hotline and KH.

At the end of the 30-day follow up period, all ongoing AEs/SAEs will be documented as "ongoing" and follow-up information will no longer be recorded by the call center operators, interviewers or site staff using the DCF. At that point, the call center operators, interviewers or site staff will refer the participant to his or her healthcare professional for proper care of the participants ongoing AEs/SAEs.

In case the safety information received is not meeting the minimum criteria, the UBC/PSSD starts to follow-up for missing information immediately, with two (for AE cases) or three (for SAE cases) attempts. All contact attempts should be documented.

New information received on a case supersedes previous information and is processed within the same timelines as initial report.

5.3 Follow-up of Pregnancy Cases

Pregnancy potentially associated with the exposure to the *HeatSticks* will be followed-up by PSSD/UBC until the pregnancy outcome is reached. UBC/PSSD will address follow up questions to the call center provider (b) (4) during the course of the pregnancy and at the date of expected delivery until an outcome reached. Further follow up request will be sent to ask for infant`s and mother`s condition 8 weeks after delivery of the baby. Two further attempts will be performed if no response is received. Follow up attempts for pregnancy cases may be amended by the UBC/PSSD upon individual case assessment.

5.4 Safety Reporting

5.4.1 Individual Case Safety Report for AE and Pregnancy

For each case UBC will issue an individual case safety report (ICSR) (e.g., using the MedWatch form).

5.4.2 Adverse Events Line Listings and Summary Tabulations

Within 6 weeks after end of the study listings are (if any) received at UBC and confirmation by PMI-PSSD that no more ISDCF will be forwarded to UBC, UBC will generate product-specific and overall AEs Line Listings and Summary Tabulations which will be used for a product-specific safety analysis at the study level and which may be reported to regulatory authority, if required. These AEs Line Listings and Summary Tabulations will be saved on UBC safety portal.

The format of such listings and tables will be agreed between PMI-PSSD and UBC in due time.

5.4.3 End of study listing

KH provides PMI PSSD with listing of health related event collected from open-ended questionnaires within 6 weeks after end of study, in March 2016. This information will be provided in a tabular format and include the following items: Date of record, Gender, Age, Verbatim event term, ITP use dates and ITP variant (Regular vs Menthol).

5.4.4 Study-specific Safety Surveillance Summary Report

The results of the safety surveillance for the THS-PBA-07-US will be subject to a study-specific safety surveillance summary report.

5.4.5 Reporting to Competent Authorities

PMI-PSSD ensures that expedited and/or periodic safety reports are provided in due time to PMI Regulatory Operations (RO) for submission to FDA-CTP if required.

MedWatch Form together with completed by PMI-PSSD APP022 Reportable Events Form required by Sterling IRB will be sent from PMI: pmssafety.pmi@pmi.com to PBAstudysafety@kantarhealth.com for submission in required timelines.

After the case is assessed by UBC on reportability (including seriousness, causality, expectedness and medical evaluation), all cases classified as serious adverse events will be submitted by the PMI RO to the FDA-CTP within 15 business days of first awareness by the sponsor or designee. Only initial SAE reports will be expedited to the FDA-CTP (and not the follow-up reports).

Safety reporting to IRBs will be ensured by the study designee (Kantar Health) by submitting safety information to Sterling IRB as per IRB requirements: all SAEs that are unexpected and related or possibly related to participation in the research should be reported to Sterling IRB within 10 business days of when the site becomes aware of the event. All fatal or life threatening events should be reported to Sterling IRB immediately.

5.5 Document Filing

All safety-related documentation is saved electronically on the UBC server and on the portal.

At the end of the study, UBC will transfer a copy on an electronic medium (e.g., an USB key) of the study-specific safety documentation to PMI for archiving. UBC is not responsible for long-term archiving of safety documentation pertaining to the present study.

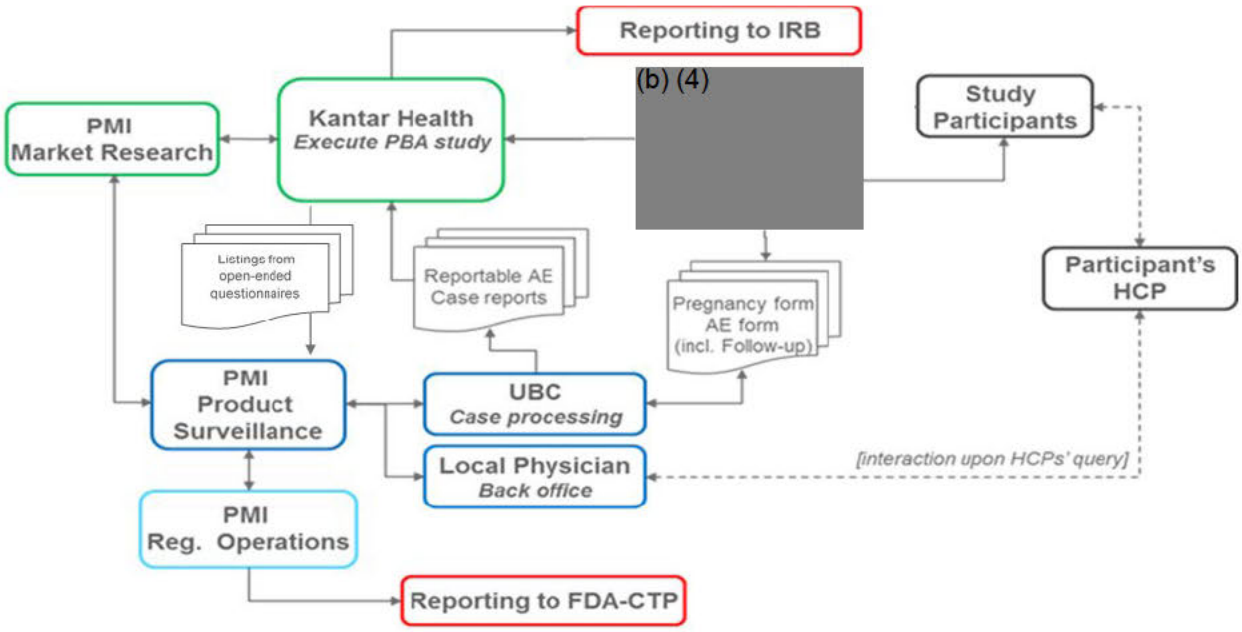
5.6 Reconciliation

On a weekly basis, UBC provides the study hotline (and other senders) with a listing of safety case reports received from them during the previous week. The study hotline and other senders have to check all required fields and confirm the safety case reports mentioned in this listing match those they have received from the product users. Any discrepancies identified during reconciliation are promptly addressed.

6 FLOWCHART – SAFETY COMMUNICATION

The safety communication channels in THS-PBA-07-US study is summarized in Figure 1.

Figure 1 Study Safety Communication Flowchart



7 CONTACT DETAILS

7.1 Reporting Health Problems and Pregnancies to UBC

UBC Pharmacovigilance
Fax number: 011 41 22 596 44 46
E-mail: **EUsafety@ubc.com**

7.2 Contact Details for Medical Safety

7.2.1 Contact Details for PMI Product Safety Surveillance Department

Philip Morris Products S.A.
PMI Research & Development
Product Assessment & Scientific Substantiation, Product Safety Surveillance Department
Quai Jeanrenaud 5
2000 Neuchâtel
Switzerland

Name	Function	Phone / Mobile	E-mail address
Alexandr MÉSZÁROS	Senior Medical Scientist – Surveillance	Phone: 011 41 58 242 2775 Mobile: 011 41 79 226 3101	pmssafety.pmi@pmi.com
John L. MAGNETTE	Manager Product Safety Surveillance	Phone: 011 41 58 242 2200 Mobile: 011 41 79 623 0965	johnL.magnette@pmi.com

7.2.2 Contact Details for UBC

United BioSource Corporation
16, Chemin des Coquelicots
1214 Vernier/Geneva
Switzerland

Name	Function	Phone	E-mail address
Alexandra BANDERIER	Senior Safety Scientist Pharmacovigilance	011 41 22 596 44 15	alexandra.banderier@ubc.com
Mallorie CLEMENT	Associate Director Pharmacovigilance	011 41 22 596 44 22	mallorie.clement@ubc.com
Fabienne PLATTNER	Senior Safety Scientist, Pharmacovigilance	011 41 22 596 4439	fabienne.plattner@ubc.com
Stephanie CARPENTIER	Safety Scientist, Pharmacovigilance	011 41 22 939 41 74	stephanie.carpentier@ubc.com

7.3 Contact Details for Market Research

7.3.1 Contact Details for PMI Market Research

Philip Morris International Management SA
Avenue de Rhodanie 50
1001 Lausanne
Switzerland

Name	Function	Phone	E-mail address
Pierpaolo MAGNANI	Director RRP Smokeless & Smokeless Market Research	011 41 58 242 4072	Pierpaolo.Magnani@pmi.com
Steve ROULET	Manager Market Research RRP	011 41 58 242 5338	Steve.Roulet@pmi.com

7.3.2 Contact Details for Kantar Health

Kantar Health LLC
11 Madison Avenue, 12th Floor
New York, New York 10010
United States of America

Name	Function	Phone	E-mail address
Ariella DUGAN	Senior Director Health Outcomes	+1 212-706-4267	ariella.dugan@kantarhealth.com
Chris GAGE	Vice President Strategic Consulting	+1 484-442-1446	chris.gage@kantarhealth.com
Joined KH email address for reporting from PSSD to KH of reportable AE/SAE case for submission by KH to Sterling IRB. This email is monitored by KH on daily basis.			PBAstudysafety@kantarhealth.com

7.3.3 *Contact Details for* (b) (4) *Hotline*

(b) (4)

Name	Function	Phone	E-mail address
(b)(4)			
Joined email address of (b) (4) used by UBC for sending to (b) (4) 1) confirmation of ISDCF or Pregnancy form receipt and Joined email address of (b) (4) used by PMI-PSSD for sending: 2) Data Clarification Form to (b) (4) This email is monitored by (b) (4) on a daily basis			(b)(4)

7.3.4 *Contact Details for Mall Research Facilities*

(b) (4)

Name	Function	Phone / Fax	E-mail address
(b) (4)			

7.3.5 *Contact Details for Local Physician*

Dr. James Davis
Rose Research Center, LLC
7920 ACC Bld, Suite 110
Raleigh, NC 27617
United States of America

Name	Function	Phone	E-mail address
Dr James DAVIS, MD	Local Physician	+1 919-328-2345	james.davis@roseresearchcenter.com

8 HISTORY OF CHANGES

Document version and date	Description of changes	Type of changes (a)
Version 1.0 17-Aug-2015	Initial document	-
Version 1.1 25-Aug-2015	Addition of shared email address for Kantar Health (section 5.2.4 and section 7.3.2) Addition of shared email address for (b) (4) (section 4.3.1, section 5.1.2 and section 7.3.3). Precision regarding end-of-study health problems not reported during study (deleted from section 1.1, section 2.3 section 3 and section 5.2.2; kept as provisional in section 4.2.2) Precision regarding reporters (not only (b) (4), but also interviewers and study staff) and for follow-up queries (section 4.2.3, section 4.3.1 and section 5.4) Precision regarding correspondence between calendar days (used for individual case processing) and business days (used for reporting to competent authorities) provided in section 5.1.1	1
Version 2.0 30-Nov-2015	According to Study Protocol Amendment No3 (1.0) dated October 26, 2015 which describes the inclusion of 30-day follow-up interview Only initial SAE reports will be expedited to the FDA-CTP (and not the follow-up reports) Specifies distribution and collection of Data Clarification Form for follow up procedure Describes collection and reporting format of health related events from open-ended questionnaires at the end of the study	2

(a) 1: minor changes; 2: major changes

9 SIGNATURES

9.1 Sponsor Signatures

SPONSOR SIGNATURES

Document:	Safety Management Plan THS-PBA-07-US_PSS
Version Number:	2.0
Version Date:	30-Nov-2015

This Safety Management Plan was subject to critical review and has been approved by the Sponsor.

Approval: _____ Date: 1 Dec. 2015

John L. Magnette, MD, DipPharmMed, FFPM
Manager Product Safety Surveillance
Philip Morris International R&D, Neuchâtel, Switzerland

Approval: _____ Date: 01-DEC-2015

Steve Roulet, Manager Market Research
Philip Morris International, Lausanne, Switzerland

9.2 Third Parties Personnel Signatures

THIRD PARTIES PERSONNEL SIGNATURES

Document:	Safety Management Plan THS-PBA-07-US_PSS
Version Number:	2.0
Version Date:	30-Nov-2015

The following third-party personnel contributed to writing and approving this safety management plan:

Approval: A. Banderier Date: 01-DEC-2015
Alexandra Banderier, Senior Safety Scientist
United Biosource Corporation, Vernier, Switzerland

Approval: _____ Date: _____
Ariella Dugan, Senior Director Health Outcomes
Kantar Health LLC, New York, NY, USA

(b)(4)

9.2 Third Parties Personnel Signatures

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Document:	Safety Management Plan THS-PBA-07-US_PSS
Version Number:	2.0
Version Date:	30-Nov-2015

The following third-party personnel contributed to writing and approving this safety management plan:

Approval: _____ Date:_____
Alexandra Banderier, Senior Safety Scientist
United Biosource Corporation, Vernier, Switzerland

(b)(4)

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Document:	Safety Management Plan THS-PBA-07-US_PSS
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The following third-party personnel contributed to writing and approving this safety management plan:

Approval: _____ Date: _____
Alexandra Banderier, Senior Safety Scientist
United Biosource Corporation, Vernier, Switzerland

(b)(4)