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# 8. POST-MARKET ASSESSMENT PROGRAM

## 8.1. Background and Objectives

The Family Smoking Prevention and Tobacco Control Act ("**Tobacco Control Act**") directs the Food and Drug Administration (FDA) to require post-market surveillance and studies from applicants that receive a risk reduction order or an exposure reduction order (§ 911(g)(2)(C)(ii)). The FDA has provided recommendations for post-market surveillance and studies in the Draft Guidance for Industry on Modified Risk Tobacco Product Applications (MRTPa), (FDA 2012). This FDA MRTP Draft Guidance describes the need for the FDA to understand the short- and long-term impacts of the authorization of MRTPs on consumer perception, behaviors, and health through post-market surveillance and studies. As stated in the FDA MRTP Draft Guidance, "… postmarket surveillance is a very important tool for monitoring the effects of the MRTP on individual and population health" [lines 1199-1200] (FDA 2012) that can allow for identification and collection of "unanticipated and undesired events related to the tobacco product once it is introduced to the market" [lines 1143-1144] (FDA 2012). For this reason, Philip Morris Products S.A. (PMP S.A.) proposes a "**Post-Market Assessment Program"** consisting of a set of multiple and diverse approaches covering both surveillance and studies to collect both quantitative and qualitative data over time that support the assessment of "*iQOS* with *HeatSticks"* (referred to herein as *iQOS*) once it is introduced on the United States of America (US) market.

This program is designed to capture and evaluate the effect of the issuance of the risk modification order and the subsequent marketing of *iQOS,* as a reduced risk of harm product, on consumer perception, behavior, and health over time. This program will enable the identification and collection of unanticipated and undesired health-related events associated with the use of *iQOS*, monitoring of the use of *iQOS* and other selected tobacco products at the population-level, as well as determine the related tobacco use behaviors.

### 8.1.1. Explanation of the Parties

Although PMP S.A. is submitting this application, PMP S.A. has entered into an agreement with Altria Client Services LLC ("ALCS")[1] by which ALCS or an affiliate has a license to distribute and sell *iQOS* in the US. The ALCS affiliate that will distribute and sell *iQOS* in the US is Philip Morris USA (PM USA), however ALCS will be responsible for certain aspects of the Post-Market Assessment Program. For the purposes of this module, references to activities undertaken to support the post-market surveillance and studies in the US by PMP S.A. may ultimately be carried out by PMP S.A., ALCS, PM USA or as a collaboration between these parties.

PMP S.A. has already introduced *iQOS* in markets outside the US beginning in late 2014 and will continue to expand the number of markets in which *iQOS* is marketed outside the US. The Post-Market Assessment Program presented in this document is focused on the assessment to support the MRTP application, and only includes relevant information on

[1] Altria Client Services LLC is a wholly-owned subsidiary of Altria Group, Inc. ALCS provides certain services to the Altria group of companies.

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*iQOS* commercialization in the US as indicated in details in the Module and appendices. PM USA will commercialize *iQOS* in the US under the license from PMP S.A. and pursuant to the issuance of the marketing authorization.

#### 8.1.2. *iQOS* Commercialization Plan

PM USA is responsible for developing and implementing the *iQOS* commercialization plan and is currently working to select the markets within the US for initial retail distribution and fully define the commercialization plan. PM USA intends to take a disciplined approach for the introduction of *iQOS* in the US market after PMP S.A. receives marketing authorization from the FDA. PM USA will initially introduce *iQOS* into limited retail distribution within a few selected markets. Because *iQOS* will be a novel product with which US consumers are unfamiliar, PM USA will engage with adult smokers through a variety of channels to provide information about *iQOS*. PM USA will use the selected markets to assess marketplace results by evaluating post-launch metrics and based on these learnings, PM USA will determine how to best expand distribution to other markets in the US.

## 8.2. General Scope of the *iQOS* Post-Market Assessment Program

This document provides an overview of the *iQOS* Post-Market Assessment Program, including the types of studies PMP S.A. plans to conduct, the data it plans to collect, and the overall scientific approach.[2]

PMP S.A. and ALCS are working to develop and test new approaches to post-market assessment specifically tailored for *iQOS*. Based on the learnings from this testing and the ongoing post-market studies and surveillance for *iQOS* in other markets, PMP S.A. plans to refine the study concepts and tools presented in this Module and submit fully developed study protocols and study documentation to the FDA. PMP S.A. will provide *inter alia* the following information and documents to the FDA; the final survey instrument(s) and questionnaires, the sampling approach, the recruitment and retention strategy, the detailed data handling methods and the analysis and reporting plan. The timing of the proposed studies, as well as the sampling strategies are dependent on the commercialization plan (Section 8.1.2) and the subsequent uptake of *iQOS* in the US market.

Following market authorization of *iQOS*, PMP S.A. will submit to the FDA, on an annual basis, the *iQOS* Annual Safety Summary Report that will summarize the outcomes to date of all US post-market surveillance and studies. In addition to the summary of data to date generated from the US Post-Market Assessment Program, PMP S.A. will review the status and approaches implemented in the Post-Market Assessment Program and provide an overview of any changes that were or will be implemented into the assessment. PMP S.A.

[2]Under the Tobacco Control Act, FDA may require applicants for modified risk tobacco product orders to conduct postmarket surveillance and studies. Tobacco Control Act § 911(g)(2)(C)(ii) and 911(i). Each applicant required to conduct postmarket surveillance must, within 30 days after receiving notice, submit a protocol to FDA. Although these protocols will not be submitted until after receipt of notice from FDA, FDA encourages MRTP applicants in the MRTP Draft Guidance to submit draft protocols or detailed outlines of the postmarket surveillance and studies they plan to conduct as part of their MRTPa.

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will also provide a summary of *iQOS* safety events for the markets outside the US where *iQOS* is commercialized (Section 8.2.1).

### 8.2.1. Overview of Post-Market Safety Surveillance

The surveillance approach is a mixture of passive and active surveillance that includes the collection of consumer reported adverse events (AEs)[3], and a review of the scientific literature, and other available sources of information.

PMP S.A. and ALCS have both implemented passive surveillance programs to capture spontaneous reports of AEs. For the US market consumers and healthcare professionals will be able to contact and report any health related event using ALCS's established AE collection system (Appendix A8.1).

Outside the US, PMP S.A. has implemented a similar, but independent AE collection system for countries where *iQOS* has been launched. The system is adapted to the country specific regulations and language(s). Reporting patterns vary from one market to another, therefore, the *iQOS* Annual Safety Summary Report will include a detailed reporting for the US as well as a summary of the AEs reported in markets were *iQOS* is commercialized.

In addition to the passive surveillance through the AE collection systems, PMP S.A. will collect and analyze AEs identified and reported through other data sources, as defined in this Post-Market Assessment Program including literature reviews (Appendix A8.4), and may develop a system to allow Internet forum monitoring (Appendix A8.5), the FDA AE Reporting System, the Health and Human Services Safety Portal and the World Health Organization Vigibase Database System. Other sources of data that have been identified are being explored, such as the National Poison Data System from the American Association of Poison Control Centers (AAPC). PMP is exploring the possibility of registering *iQOS* with the AAPC to allow the identification and tracking of AE reports.

There will be two independent safety databases; (1) for all AEs from the US market, regardless of their source and (2) for all AEs from outside the US market. In the safety databases, AEs from the different sources (e.g., spontaneous AE reports, literature searches) will be consolidated, coded and summarized. This information will be includedin the *iQOS* Annual Safety Report (Section 8.2.4).

In addition to the AE reporting and the summary of AEs in the *iQOS* Annual Safety Summary Report, serious AEs (SAEs)[4] reported in the US market will be submitted to the FDA as individual cases within 15 business days of receiving the reported events.

In addition to the passive surveillance program, PMP S.A. is working to develop and test a systematic data collection tool and analysis infrastructure for the *iQOS* Post-Market

[3] Defined in MRTP Draft Guidance as "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)

[4] Defined in the MRTP Draft Guidance as "…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)

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Assessment Program using Internet forum data (Appendix A8.4). This infrastructure could be utilized to monitor discussions related to the use patterns, consumer perceptions (including risk perception), abuse, misuse, and product tampering as well as health-related information pertaining to *iQOS,* its brand family, and product category. This infrastructure would serve as a signal detection tool to identify potential "unanticipated and undesired events related to the tobacco product once it is introduced to the market" [lines 1143-1145] (FDA 2012), and to help contextualize observations from other sources of data.

### 8.2.2. Overview of the Post-Marketing Studies

The FDA MRTP Draft Guidance states that the study designs used for post-marketing studies "could include observational epidemiological studies, interventional studies, such as randomized clinical trials, or studies of other design" [lines 1284-1285] (FDA 2012). In the near-term, including periods before and after the launch of *iQOS* in the US market, the Post-Market Assessment Program will include repeated observational cross-sectional surveys (Appendix A8.2) to evaluate the effect of *iQOS* among US adults of legal age to purchase tobacco products. This will allow PMP S.A. to assess the tobacco use point prevalence and potential behavioral influences, and to monitor and assess trends over time in tobacco use prevalence.

The first observational, cross-sectional surveys will be initiated before the launch of *iQOS* in the US market to establish reference consumer perceptions and behaviors. After the launch of *iQOS*, the cross-sectional surveys will be repeated annually (Appendix A8.2).

Collectively these surveys will collect information on:

- Current and previous tobacco product use to determine the prevalence and patterns of product use. *iQOS* will be incorporated and assessed once it is marketed, however in the initial waves it is recognized that there will be challenges in estimating prevalence for *iQOS* because of the known issues for any product with low marketplace penetration;
- Initiation and cessation-related behaviors; and
- Perceptions of *iQOS* (including intention to try or use *iQOS* and perceptions of risk).

The Post-Market Assessment Program will also include an observational Post-Market Behavioral Cohort studies (Appendix A8.3). These studies would recruit *iQOS* consumers from the market and follow them over period of time to assess:

- Tobacco and/or nicotine containing tobacco product use;
- Switching behaviors between tobacco and/or nicotine containing tobacco products (including transition to more or less harmful products);
- Dual product use including product use patterns and rates;
- Quitting of tobacco and/or nicotine containing tobacco products individually and complete cessation;
- Perceptions of risk;
- Impact on the individual health through changes in self- reported smoking related signs and symptoms over time;

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The US studies conducted within the Post-Market Assessment Program will be designed in accordance and compliance with the following standards for study conduct and electronic data capture (where applicable):

- Council of American Survey Research Organization's (CASRO) Code of Standards and Ethics
- Guidance for Industry: Computerized Systems Used in Clinical Investigations
- Guidance for Industry: Electronic Source Documentation in Clinical Investigations
- Guidance for Industry: Patient Reported Outcome Measures – Use in Medical Product Development to Support Labeling Claims
- The International Chamber of Commerce/European Society for Opinion and Marketing Research's (ESOMAR) International Code on Market and Social Research
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP)
- The International Epidemiological Association (IEA) ethical principles of Good Epidemiological Practices (GEP)
- 21 CFR Parts 50 and 56

### 8.2.3. Use of the Population Health Impact Model (PHIM)

The summary of the development, testing and validation of the Population Health Impact Model (PHIM) are presented in Section 6.5 Effect on the population as a whole, with the detailed reports in Module 7. Within this section, we will focus on how the PHIM will be used within *iQOS* Post-Market Assessment Program.

The PHIM will be used as a tool to quantify the impact that the introduction and subsequent use of an MRTP within a market, may have on the health of the population as a whole. The PHIM is made up of two components: the "Prevalence Component" and "Epidemiological Risk Component". The Prevalence Component uses the tobacco transition probabilities to evaluate the prevalence of the different tobacco use patterns (never smokers, current cigarette smokers, current iQOS users, dual users, and former tobacco users). The Epidemiological Risk Component applies an estimate of the relative exposure for the different tobacco use patterns and a negative exponential decay in excess relative risk once an individual switches to a tobacco use pattern with a lower relative exposure to determine the cumulative smoking attributable mortality over a period of up to 20 years (Weitkunat 2015).

The PHIM allows PMP S.A., regulators and the public health community to examine scenarios and predict the overall and smoking-attributable mortality over-time by comparing smoking-attributable deaths under two scenarios (1) with the introduction of *iQOS* in the market and (2) without the introduction of *iQOS* in the market. The difference between the two scenarios is the impact of the introduction of *iQOS*. The PHIM examine four major smoking-related diseases (i.e., lung cancer, ischemic heart disease, stroke and chronic obstructive pulmonary disease), and looks at the accumulation of death.

Initially this model will use initial assumptions to predict what may happen following the launch of the product. However, data from the Post-Market Assessment Program can serve as

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input into the model (replacing the initial assumptions, with actual market-derived data) and can also be used to refine the assumptions moving forward. This will allow the PHIM to be used as a tool not only to obtain the marketing authorization but also to monitor and estimate the impact of *iQOS* on the health of the population as a whole using the real-life scenarios observed in the market.

#### 8.2.4. *iQOS* Annual Safety Report

PMP S.A. plans to perform an extensive annual review of the *iQOS* Post-Market Assessment Program (as defined in this plan), this may include:

- Review and summary of the AEs and SAEs data
- Review of the AE coding consistency and conventions
- Summary of the literature review findings
- Review of the literature review process and coding manual
- Summary of the internet forum surveillance findings
- Review of the internet forum process and coding manual
- Summary of the cross-sectional survey recent wave and population-level trends to date
- Summary of the cohort enrollment and findings to date.

The summaries will be consolidated and reported in the *iQOS* Annual Safety Report, as well as a description of any changes to the process implemented as part of this review.

The details of the reporting processes and requirements will be discussed and agreed to with the FDA.

## 8.3. The Surveillance Program

#### 8.3.1. Adverse Events Reporting

PMP S.A. plans to use one or more call centers, including the ALCS managed third party Consumer Response Center (ALCS Consumer Call Center) to collect *iQOS* related complaints in the US market. The ALCS Consumer Call Center has processes and experience to implement the systematic collection and assessment of unsolicited consumer complaints and potential AEs associated with the use of or exposure to tobacco products.

The calls to the ALCS Consumer Call Center can include cases with various issues such as general questions about product or device-use, complaints about product quality, and reports of health events associated with the use of *iQOS*. Each consumer call is received by personnel 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.[5] If the complaint is identified as a potential AE, the personnel administers the Adverse Event Questionnaire (Appendix A8.1) which consists of a series of questions to

[5] 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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obtain detailed information about the nature of the reported AE, their medical history and their exposure to *iQOS*. PMP S.A. is also developing country-specific Adverse Event Questionnaires to collect spontaneous reports of AEs in the countries where *iQOS* is commercialized, and there may be country-specific differences, depending on the data protection laws.

AEs captured by the ALCS Consumer Call Center are reviewed, processed and coded by or assessed for:

- Identify medical concept from the verbatim text
- AE Term – Section 8.3.1.1.
- AE Seriousness – Section 8.3.1.2
- AE Severity – Section 8.3.1.3.
- AE Expectedness – Section 8.3.1.4.

The initial coding will be performed within 5 calendar days of the case report, to allow time to address any discrepancies while ensuring the timeliness of a SAE report.

In addition to the standard individual AE and SAE case reporting, aggregated safety data will be reviewed regularly for the detection of new safety signals. Such safety signals will be included in the *iQOS* Annual Safety Summary.

#### 8.3.1.1. MedDRA Coding

All AEs reported through the ALCS Consumer Call Center are captured in the product-complaint database and processed. The processing of each case involves extracting the verbatim term from the case description provided by the reporter. The verbatim term is then used to identify the appropriate medical concept and mapped to the most appropriate lower level term available in MedDRA in accordance with the current version of MedDRA® Term Selection: Points to Consider (MedDRA 2015) and the ALCS coding guidelines.

Determining appropriateness requires that the trained professional coders choose the term that:

(1) best reflects the clinical concept conveyed in the verbatim;
(2) is least presumptive;
(3) would always hold true; and
(4) is in accordance with established 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.

Over time the version of MedDRA will change In order to ensure consistency and full transparency on the impact of the MedDRA version. The up versioning of the dictionary will be performed annually. The summary of the impact of the change on the previous report will be assessed at the time of the up versioning. Any AE cases that require upcoming will be flagged and the new MedDRA LLT will be identified following the same process as the original coding.

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#### 8.3.1.2. Assessing the **Seriousness** of the Event

The FDA MRTP Draft Guidance provides a clear set of criteria to assess whether or not an AE is a SAE. A 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.

#### 8.3.1.3. Coding the **Severity** of an Adverse Event

Each AE case is reviewed to assess the severity of the AE based on the clinical judgment of the certified coder following the coding guidelines. The coding guidelines for severity were developed based on commonly accepted industry best practices for the Common Terminology Criteria for Adverse Events, Version 4.0 (NCI 2010). However, given the nature of the adverse events, the severity is limited to the following three categories:

(1) **mild**: annoying but does not interfere with daily activities;

(2) **moderate**: interferes with some daily activities;

(3) **severe**: interferes with most of the daily activities.

#### 8.3.1.4. Assessing the **Expectedness** of the Event

The process of determining the "expectedness" of a reported AE, is an assessment of reported event term against the cumulative safety reports and the foreseeable risks listed in the current *iQOS* Reference Safety Information (*iQOS* RSI).

An unexpected AE is an AE in which the nature, severity or frequency is not consistent with the known or foreseeable risks associated with exposure to *iQOS* as described in the *iQOS* RSI. Other considerations for assessing the expectedness of an AE is the consistency of the event with the natural progression of any underlying diseases, disorders or conditions that the person(s) may have.

Currently the *iQOS* Investigator's Brochure (IB) serves as the *iQOS* RSI, however as the marketing and uptake of *iQOS* expands, the *iQOS* RSI will be developed as separate document from the IB and will be reviewed and updated annually in a similar manner than the IB.

### 8.3.2. Data Monitoring from Internet Forum

ALCS is exploring the development of a process and infrastructure to monitor and evaluate a defined set of Internet forums as part of *iQOS* Post-Market Assessment Program (Appendix A8.4). ALCS has already conducted a similar proof-of-concept study exploring the feasibility of Internet forums monitoring and assessment as a component of post-market surveillance activities for its e-Vapor products. This proof-of-concept study confirmed that Internet forum data can be systematically collected, organized, and evaluated for various tobacco and nicotine containing tobacco products and has the potential to be expanded to include *iQOS* with *HeatSticks*.

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The Internet forum content can be evaluated quantitatively and qualitatively on a regular basis using a qualitative codebook developed for this surveillance activity to ensure consistency in the reported observations. The content of the qualitative codebook would include the following areas:

- product use patterns;
- consumer perceptions (including risk perception);
- health-related information;
- information related to the product characteristics (e.g., brands and flavors); and
- concepts related to abuse, misuse, and tampering.

The data extracted from the Internet forums would be assessed as counts and proportions of product-specific mentions and could be used to track possible changes over time which may indicate how and whether discussion related to *iQOS* changes in relation to selected comparators.

In addition, qualitative review of the data could be used to provide context to the findings and to better understand the observations over time. Implementation of a large-scale, systematic data-collection and monitoring program could provide a real-time window into the opinions and experiences of those who discuss product use, and allow for a consistent approach to enable identification of new information and changes over time. Furthermore, it could provide an opportunity to use Internet forum data to contextualize observations from other data sources. It could also serve as a hypothesis generating tool and may provide product-specific information about *iQOS* in a Post-Market setting.

### 8.3.3. Comprehensive Literature Review

PMP S.A. is developing a comprehensive literature review framework specific to *iQOS* (Appendix A8.5). The literature search will be defined in a protocol and associated coding manual that includes the searched sources, inclusion and exclusion criteria, search topics and define search queries. The focus will be to identify articles with content in at least one of the following categories:

- Product: *iQOS*, *HeatStick*(s), Tobacco Heating System, heated tobacco, tobacco stick, Reduced Risk Product, Modified Risk Tobacco Product, electronic heated tobacco, Philip Morris, Marlboro, nicotine, dual use, heat not burn
- Health Events: adverse events, allergy, hypersensitivity, injury, overdose, carcinogen, mutagen, teratogen, toxic, cytotoxic, reaction, pregnancy, safety, monitoring, surveillance, tolerance, risk;

Once the potential articles are identified, the abstracts will be reviewed to assess it against the inclusion and exclusion criteria. The abstracts will be selected and the full articles will be reviewed based on the quality of the publication. The quality of the article's data will be assessed and the article's reference list will be used to identify other relevant publications for review. The findings from the literature review will be summarized in *iQOS* Annual Safety Summary Report.

Adverse events identified by the literature review will be submitted to the safety database and follow the process of coding and assessment defined for the passive safety surveillance

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process (e.g., MedDRA coding). The individual case reports will not be reported within the context of the literature review because the denominator from this data are not appropriate for presenting or interpreting safety, however cases will be summarized.

#### 8.3.4. Poison Control Center Surveillance

PMP S.A. plans to register *iQOS* with the AAPC to monitor the types and frequency of spontaneous AEs reported into National Poison Data System (NPDS) database.

### 8.4. Post-Market Studies

#### 8.4.1. Cross-Sectional Survey Studies

In accordance with the FDA MRTP Draft Guidance, PMP S.A. proposes to conduct a series of observational cross-sectional post-marketing studies with adult tobacco consumers of legal age to purchase tobacco products (Appendix A8.2). The purpose of these studies will be to collect data on the real-world use of and attitudes towards *iQOS* and other tobacco and nicotine containing tobacco products. The studies will be designed to provide data on:

- Patterns of use of tobacco and nicotine containing tobacco products;
- How consumers use *iQOS*, and how *iQOS* use changes over time;
- Initiation, re-initiation, and cessation of tobacco and nicotine containing tobacco products in context with *iQOS;*
- Risk perceptions of *iQOS* and other tobacco- and nicotine containing tobacco products and changes in the risk perceptions over time; and
- Reasons and rationale for *iQOS* use.

These studies will obtain information on whether current smokers, former smokers, or never smokers initiated with or switched to *iQOS* from their usual tobacco product. These studies will also capture use of other tobacco and nicotine containing tobacco products (i.e., nicotine replacement therapy) among *iQOS* consumers.

These studies will assess if smokers continue using their tobacco product concurrently with *iQOS*, smokers who would otherwise quit all tobacco use switch to *iQOS* instead of quitting all tobacco use, and non-consumers or former tobacco consumers start using *iQOS*.

PMP S.A. will also assess use of *iQOS* among different segments of the population. The observational, cross-sectional survey will include a broad selection of demographic items: age, sex, race, ethnicity, education, employment status, information on socio-economic status, military service, sexual orientation, and whether the respondent is currently pregnant or nursing, suffers from mental health conditions or self-reported medical conditions such as lung disease (e.g., chronic obstructive pulmonary disease), or cardiovascular disease.

We anticipate that the observational, cross-sectional studies will initially be limited in their ability to use probability-based sampling to recruit sufficient numbers of participants due to *iQOS* low market penetration. Therefore, these studies will rely on panel-based sampling strategies to obtain data sufficient to examine the outcomes of interest.

This approach will be complemented by an ongoing, cross-sectional study designed to provide a national probability-based sample to estimate tobacco use prevalence, including use of *iQOS* as feasible.

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These studies will be conducted so that the natural environment is not disturbed and snapshots of the current adult behaviors can be reflected.

### 8.4.2. Observational Cohort Studies

In addition to conducting the observational cross-sectional surveys, PMP S.A. plans to conduct an observational behavioral cohort study. The study would prospectively follow *iQOS* users. PMP S.A. is also considering to include consumers of conventional cigarettes. The prospective cohort study will focus on tobacco use patterns and behaviors over time (Appendix A8.3).

To fully understand the effect of *iQOS* on the use of tobacco product(s), specific segments of the population (*e.g.*, recent adopters – within 1 year of initiating *iQOS*, long term consumers – greater than 1 year of *iQOS* use) may be targeted to monitor and assess how changes in the market awareness, product trial and regular use of *iQOS* affect the population over time. Health-related objectives will be limited to characterizing potential changes in self-reported, smoking-related signs and symptoms over time and assessing changes in these prevalence.

Currently, PMP S.A. is not planning to conduct additional post-marketing studies (*e.g.*, health outcome studies, case-control studies, or studies in disease-specific populations) as a part of the Post-Market Assessment Program conducted in the US. However, these types of studies will be considered if there is a further need to evaluate signs or signals observed in other parts of the Post-Market Assessment Program.

### 8.4.3. Tools and Instruments for Post-Market Studies

#### 8.4.3.1. Informed Consent

Considering that all studies conducted under the Post-Market Assessment Program involve the enrollment of participants and the active collection of data, PMP S.A. will comply with Good Clinical Practice, Good Epidemiological Practice, or other appropriate standards based on the type of study. The difference in the approach will be determined by the objectives of the study and nature of subject recruitment and retention. Clinical studies will be conducted in compliance with ICH Good Clinical Practice. Under both approaches, all participants will be fully informed about the nature and objectives of the study and possible risks associated with their participation in the study and will be required to provide their written consent prior to the collection of study related information.

The study protocol and informed consent form, as well as all participant-related materials, will be submitted for review to an Institutional Review Board for approval before the study is initiated.

#### 8.4.3.2. Age Verification

For studies that recruit participants via online registration, an independent, third party organization (*e.g.*, (b) (4) ) will be used to verify the age of potential respondents based on the information they provide during the respondent screening process (i.e., name, address, telephone number, e-mail address, and date of birth). The process is included in the participant screening questionnaire, and requires that the respondent information is sent to (b) (4) , who evaluates it in real time against data from multiple databases. Once the information is confirmed, the participant continues in the study,

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completing the remainder of the questionnaire. Otherwise, if the identity of the participant cannot be confirmed, their participation in the study is automatically terminated. Additional information about (b) (4) is available at: (b) (4)

Depending on the nature and objectives of the study, participants may need to be recruited using other methods, such as Central Location Testing. In each instance, the process for performing age verification will be defined and documented in the study protocol (*e.g.*, requiring a valid government issued identification).

8.4.3.3. Demographics

Studies will collect a range of items to fully describe the demographic characteristics of the study population. The demographic characteristics are defined based on common characteristic collected in national surveys (*e.g.*, National Health Interview Survey). Demographic characteristics include age, gender, race and ethnicity.

Additionally, to gather insights about other populations of interest, certain studies (*e.g.*, observational, cross-sectional studies) may also include items to identify military service, sexual orientation, pregnancy, and pre-existing medical or mental conditions.

8.4.3.4. Socioeconomic Status

The socioeconomic questionnaire has been developed to identify socioeconomic status within the US population and is comprised of multiple questions. The questions are related to household size, annual household income, education and employment status.

8.4.3.5. Tobacco Product Use History

We have developed a product use questionnaire to evaluate self-reported awareness, trial and use of a variety of tobacco products, including but not limited to:

- *iQOS;*
- conventional cigarettes;
- e-cigarettes;
- cigars;
- smokeless tobacco; and
- pipes

This product use questionnaire is administered in a hierarchical manner, meaning that only participants that are aware of the different tobacco products will be asked if they have tried the product, and then only the participants who have tried the product will be asked about their current and past use of the product.

For current users of *iQOS* or cigarettes, participants are also asked about the quantity and frequency of use and the initiation of that product. Participants who are past consumers of a given tobacco product are asked questions related to the quitting of that product.

8.4.3.6. Intention to Quit

Recently in the literature there has been an indication that intention may be predictive of quit attempt. A systematic review of the scientific literature, "[I]ntention to stop smoking was

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found to predict a quit attempt in all six studies to examine it" (Vangeli 2011). To further examine this and understand the relationship between intention to quit and quit attempt we plan to include it in our Post-Market Assessment program. For this reason we are planning to assess intention to quit and are developing a questionnaire for use in the Post-Market Assessment Program. This questionnaire will ask respondents currently using one or more tobacco products about their intention to quit tobacco products. Conventional cigarette smokers will also be asked their intention to quit smoking (Etter 2002).

#### 8.4.3.7. Quit Attempts

As mentioned above, recent quit attempts may predict a future attempt (Zhou et al., 2009). In accordance with the National Health Interview Survey, our questionnaire will ask participants who report current use of one or more tobacco products (including *iQOS* and conventional cigarettes) if they have stopped use of these products for more than 1 day because they were trying to quit.

In addition to past quit attempts, the questionnaire will ask participants who report that they are currently trying to quit smoking about the methods they are using. The intent is to understand what methods participants are using to quit smoking, especially to determine if participants are using *iQOS* as a method to quit smoking.

#### 8.4.3.8. Perception of Risk Instrument

PMP S.A. has developed and validated a scale to quantify and assess the perception of "personal" risk associated with using cigarettes, *iQOS* (or other MRTPs), Electronic Nicotine Devices (ENDs, or e-cigarettes), Nicotine Replacement Therapies (NRTs), or other related tobacco / nicotine containing tobacco products.

The "Perception of Risk Instrument – Personal" (PRI-P) and "Perception of Risk Instrument – General" (PRI-G) are self-report instruments that assess the perceived risks associated with the use of tobacco and nicotine containing tobacco products. More specifically, they assess the perceived risks within the following three domains:

1. **Perceived Health risk,**
2. **Perceived Addiction risk,** and
3. **Perceived Harm** to others.

The instrument can be administered in its entirety (all three risk domains) or as individual risk domains depending on the objectives of the study. As well, the scale can be used for a single specific product or any set of tobacco and/or nicotine-containing products to meet the objectives of the study. This scale is implemented and can also be used within the cross-sectional surveys to understand the overall perception of risk across the population (smokers, non-smokers, *iQOS* users and other categories of tobacco product users), as well to understand how this change over time following the launch of *iQOS*. The scale can also be used within cohort studies to look at how individual perceptions may change over time in relation to the population and in relation to their product use.

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#### 8.4.3.9. Reasons for Use

The survey items will assess *iQOS* consumers' reported reasons for first trying and now using the product, drawing upon items from the Population Assessment of Tobacco and Health Study (2012) as well as upon information presented in several recent studies among adult e-cigarette and other noncombustible tobacco product consumers (Biener 2015; Pepper 2014; Hall 2016, Richardson 2014).

#### 8.4.3.10. Health Signs and Symptoms Questionnaire

ALCS and PMP S.A. are currently developing health survey instruments to capture changes in self-reported symptoms associated with tobacco use after starting to use *iQOS*. The development and validation of these tools are underway and where applicable will follow the FDA guidance on patient reported outcomes (FDA 2009).

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