RESPONSE TO OCTOBER 05, 2020 INFORMATION REQUEST LETTER for PS0000042.

November 4, 2020

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A. IQOS® CROSS-SECTIONAL POSTMARKET ADULT CONSUMER STUDY (PACS) (PROTOCOL ID: (b) (4) [redacted])

FDA REQUEST A-1

In the "IQOS Cross-Sectional PACS" and "IQOS Cohort PACS," you plan to present the IQOS MRTP message to participants, ask participants about whether they have previously seen the message and assess participants' comprehension of the message. Specifically, on items 161-167 in the IQOS Consumer Cross-Sectional Study Instrument (pp. 51-52) and items 210-216 in the IQOS Longitudinal Cohort Postmarket Adult Consumer Study Baseline Questionnaire (pp. 75-76), you will show participants the "Available Evidence to Date" statement (which describes reductions in the production of and exposure to HPHCs from IQOS) and ask participants questions about it. These items ask participants what they believe the MRTP message states, rather than asking participants what they believe about the risks of using IQOS. Instead of showing participants the MRTP message and asking people what it says, ask people about their own understanding of the risks of using IQOS. To accomplish this, revise the following items:

a. Eliminate item 161 in the Cross-Sectional PACS Instrument and item 210 in the Cohort PACS Baseline Questionnaire, such that you will not show the IQOS MRTP message to participants in the study.

b. Eliminate items 162-164 and 166 in the Cross-Sectional PACS Instrument and items 211-213 and 215 in the Cohort PACS Baseline Questionnaire

c. Delete the phrase "Based only on this product message for IQOS that you recall having seen" from items 165 and 167 in the Cross-Sectional PACS Instrument and from items 214 and 216 in the Cohort PACS Baseline Questionnaire.

d. Only ask item 167 (in the Cross-Sectional PACS Instrument) and item 216 (in the Cohort PACS Baseline Questionnaire) among people who respond "Have less exposure…" on items 165 and 214 in the corresponding study instrument

e. On items 165 and 167 (in the Cross-Sectional PACS Instrument) and items 214 and 216 (in the Cohort PACS Baseline Questionnaire), counterbalance the order of response options across respondents (*i.e.*, present the items to half of participants with the response options as shown in the instrument and with the response options in reverse order for the other half of participants [keep "Don't know/ don't recall" as the final option in both versions]).

f. In the Cohort PACS, add items 214 and 216 to each of the other waves of the study (Surveys 2-6).

g. Add tables to the Cohort PACS SAP to show the results of items 214 and 216 at each wave of the Cohort PACS. Include cells for percentages and CIs for each response option separately, rather than aggregating responses into "correct" and "incorrect" categories.

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h. Add tables to the Cohort PACS SAP to report inferential statistical testing of changes in responses to items 214 and 216 at each wave compared to baseline (Survey 1, Time 0; IQOS Cohort PACS SAP).

FDA determined that these changes are necessary to monitor participants' understanding of the risks of using IQOS at baseline and over time.

RESPONSE A-1

To support assessments of participants' perceptions of the risks of using *IQOS*, we revised the Cross-sectional and Cohort Study instruments and made corresponding adjustments in the protocols and statistical analyses plans as directed by FDA. We document the changes made with respect to the Cross-sectional Study here and respond with respect to the Cohort Study in Section B.

With respect to the Cross-sectional Study, we made the following changes to the questionnaire (Appendix B2):

- We eliminated original item 161 (MRTP message)
- We eliminated original items 162-164 (questions related to having seen the MRTP message) and original item 166 (knowledge that exposure reduction is relative to cigarettes)
- We revised original items 165 and 167 (now items 160 and 161) to delete the phrase "Based only on this product message for IQOS…" and replaced it with "Based on what you know or believe…"
- We conditioned original item 167 (now item 161, "Based on what you know or believe, what do smokers need to do in order to reduce their body's exposure…") to be asked only of those who respond "Have less exposure…" to original item 165 (now item 160, "Based on what you know or believe, please complete the following: Smokers who switch completely from cigarettes to IQOS…")
- For original items 165 and 167 (now items 160 and 161) we counterbalanced the response options such that half of respondents will be presented the response order as shown in the questionnaire and half will see the options in reverse order (excluding "Don't know" which will always be presented last).

We adjusted study Objective #2 to focus only on risk perceptions (which includes the two revised items discussed above), reflecting the removal of the message awareness and comprehension elements. This and corresponding changes were made in the protocol (Appendix B1) and statistical analyses plan (SAP) (Appendix B3).

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FDA REQUEST A-2

In the "IQOS Cross-Sectional PACS," you plan to assess current smokers' intentions to quit smoking cigarettes (Item 52, IQOS Consumer Cross-Sectional Study Instrument: "Are you currently trying to completely quit smoking?" [yes/ no]). The proposed item is coarse, and most smokers will likely respond affirmatively to this item even though they are unlikely to successfully quit smoking cigarettes within the next year. Replace this item with a more granular item such as the Motivation to Stop Scale (MTSS; Kotz, Brown, & West, 2013, Drug Alcohol Depend 128(102): 15-19), which is necessary for monitoring smokers' levels of intention to quit smoking.

RESPONSE A-2

We replaced item 52 of the Cross-sectional Study questionnaire (Appendix B2) with the Motivation to Stop Scale (Kotz et al., 2013)[1]. All study participants who are current cigarette smokers will be asked the following:

Which of the following best describes you? (SELECT ONE RESPONSE)

I don't want to stop smoking ..... ❍ 1
I think I should stop smoking but don't really want to..... ❍ 2
I want to stop smoking but haven't thought about when..... ❍ 3
I REALLY want to stop smoking but I don't know when I will..... ❍ 4
I want to stop smoking and hope to soon ..... ❍ 5
I REALLY want to stop smoking and intend to in the next 3 months . ❍ 6
I REALLY want to stop smoking and intend to in the next month..... ❍ 7

We made corresponding changes in the study protocol (*e.g.*, see outcome measure within Objective #3, Section 6, Appendix B1) and SAP (*e.g.*, see Tables 15-1 and 15-2, Section 11, Appendix B3) to reflect this change.

[1] Kotz D, Brown J, West R. Predictive validity of the Motivation To Stop Scale (MTSS): a single-item measure of motivation to stop smoking. Drug Alcohol Depend. 2013;128(1-2):15-9.

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FDA REQUEST A-3

In the "IQOS Cross-Sectional PACS," you plan to assess IQOS users' self-reported reasons for using IQOS (Item 26, IQOS Consumer Cross-Sectional Study Instrument: Why are you NOW using IQOS?). This item is unnecessary. To reduce participant burden, delete this item.

RESPONSE A-3

We removed the original item 26 ("Why are you NOW using IQOS?") from the Cross-sectional Study questionnaire (Appendix B2). We made corresponding changes to the protocol (Appendix B1) and SAP (Appendix B3) to remove assessment of reasons for use.

In addition, because we plan to recruit qualified participants from the Cross-sectional Study to enter the Cohort Study and utilize their data for the baseline assessment, we removed the reasons for use question from the Cohort Study baseline questionnaire (original item 34, Appendix C2) and follow-up survey (original item 8, Appendix C3). We revised the protocol (Appendix C1) and SAP (Appendix C4) to remove assessment of reasons for use.

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FDA REQUEST A-4

In the "IQOS Cross-Sectional PACS," you described data quality checks and treatment of outliers (Statistical Analysis Plan, p. 35). You stated that you will conduct a qualitative review of the data to identify outliers on single items and across items, and that your method of identifying outliers will not use any a priori specifications. This method appears vague and subjective.

a. Include in the protocol a well-defined a priori criteria for identifying outliers (*e.g.*, greater than 3 standard deviations from the mean on an open-ended item) or, if you seek to identify people who are not paying attention to the survey, propose to exclude "speeders" (*i.e.*, people who complete the survey faster than a predetermined time), or include an *attention check* at the end of the survey such as an *instructed-response item* from Kung, Kwok, and Brown (2018; Applied Psychology, 67(2):264-283; *i.e.*, "For this question, please select number two to demonstrate your attention.").

b. Conduct all descriptive and inferential analyses first with the complete dataset (*i.e.*, all respondents), and follow up with sensitivity analyses in which you exclude respondents based on the pre-specified criteria. Reporting both of these analyses will enable the agency to understand whether excluding potentially invalid data influenced results substantively.

In the cross-sectional study protocol, you plan to report the use of HeatStick flavors as only basic demographics (Table 24, Appendix B3). However, use behaviors are not stratified by flavored HeatStick use. Given the role flavors play in use behaviors, certain analyses should be further stratified by users' flavor preferences, particularly menthol flavors compared to regular. These should include the endpoints of initiation, complete switching from cigarettes to IQOS, dual use of IQOS and cigarettes, and quit attempts/complete quitting. Revise the statistical analyses plan to include these analyses by use of menthol vs. regular HeatStick flavor. This information can help identify, for example, if certain HeatStick flavors would increase the likelihood of complete switching among adult smokers, compared to their tobacco varieties. This information can also identify if certain flavors are preferred by IQOS users who are not established tobacco users.

According to your protocol, you did not mention any plan to collect information on the use of menthol cigarettes by study participants. This information is necessary to evaluate the role of menthol HeatSticks in increasing IQOS adoption and complete switching in menthol cigarette smokers. Add additional items concerning menthol cigarette use to all protocols and, as sample size allows, report use behavior patterns by menthol and regular HeatStick flavor use, stratified by current or former menthol cigarette status. This information can help determine, for example, if menthol HeatSticks would increase the likelihood of complete switching among menthol cigarette smokers, compared to regular tobacco varieties.

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Your cross-sectional study protocol (Appendix C) does not capture the use of tobacco cessation treatments (including, but not limited to, Nicotine Replacement Therapy (NRT), varenicline, or bupropion) in quitting attempts. This information can capture participants' attempts to quit smoking cigarettes with such therapies, which is needed to control for their effects and to understand IQOS's independent impact on use behaviors. Assess and report current, past 12-month and lifetime use of cessation therapies as part of Objective 3 of the protocol. This data is needed to understand if cessation therapies are being used alongside tobacco products including IQOS and to assess the overall history of cessation therapy use among IQOS users captured in these protocols.

RESPONSE A-4

Data Quality Checks. We revised the Cross-Sectional Study SAP to now include well-defined *a priori* criteria to identify records that contain potential data falsification, including "speeding," nondifferentiation, and gibberish/non-sensical verbatim response (Section 6.3, Appendix B3). We will report the number of respondents flagged in the study report. We will conduct our main analysis using the full dataset and conduct sensitivity analyses without flagged responses to determine if the potentially invalid data substantially influence the results. With respect to outliers, the Cross-sectional Study questionnaire is designed to minimize outliers by defining ranges for numeric responses. Therefore, we do not expect outliers to be a relevant concern in the planned analyses and expect to use all response values provided by participants.

Menthol vs. Non-Menthol (Regular) *HeatSticks*. We revised the Cross-sectional Study protocol (Appendix B1) and SAP (Appendix B3) to stratify several outcomes, including initiation, complete switching from cigarettes to *IQOS*, dual use of *IQOS* and cigarettes, and quit attempts/complete quitting, by users of menthol and non-menthol *HeatSticks*. The following SAP table shells have been revised to report outcomes stratified by *HeatSticks* flavor preference (see Section 11, Appendix B3 for the tables specified below):

- Exclusive or dual/poly tobacco use with *IQOS* (Table 3)
- Dual use of *IQOS* and cigarettes (Table 3)
- *IQOS* use behavior (number of days/*HeatSticks*) (Table 4)
- Initiation – first tobacco product ever tried/used on a consistent basis (Table 10)
- Initiation of *IQOS* among long-term former smokers/tobacco users (Table 11)
- Complete switching to *IQOS* (Table 12)
- Relapse, re-initiation and initiation of smoking after first trying *IQOS* (Table 13)

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- Complete switching to cigarettes after initiating tobacco use with *IQOS* (Table 14)
- Past 12-month quit attempts, motivation to stop smoking, and completely quitting smoking (Table 15-1, Table 15-2)
- Tobacco cessation treatment use (Table 16)
- Completely quitting *IQOS* (Table 17)
- Demographics and background information (Table 18)
- Cigarette smoker status (Table 24)

Menthol vs. Non-menthol Cigarettes. We added new items to the Cross-sectional Study questionnaire to assess menthol and non-menthol cigarette preference among current and former smokers (see items 43a and 43b, respectively, Appendix B2):

(if current smoker) Are the cigarettes you currently smoke most often menthol or non-menthol?

Menthol..... ❍ 1
Non-menthol..... ❍ 2
Don't Know..... ❍ 3
Refused..... ❍ 4

(if former smoker) When you last smoked cigarettes, were the cigarettes you smoked most often menthol or non-menthol?

Menthol..... ❍ 1
Non-menthol..... ❍ 2
Don't Know..... ❍ 3
Refused..... ❍ 4

We revised the Cross-sectional Study protocol (Appendix B1) and SAP (Appendix B3) to stratify several outcomes, including complete switching from cigarettes to *IQOS* and dual use of *IQOS* and cigarettes, by users of menthol and non-menthol cigarettes. Certain analyses consider current menthol cigarette use status (*e.g.*, among current dual users with *IQOS*), while

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others consider former menthol cigarette use status (*e.g.*, among those who completely switched from cigarettes to *IQOS*). The following SAP table shells have been revised to report outcomes stratified by menthol/non-menthol cigarette preference (see Section 11, Appendix B3 for the tables specified below; the asterisk* indicates inclusion of cross tabulation with menthol/non-menthol *HeatSticks* preference):

- Dual use of *IQOS* and cigarettes (Table 3*)
- Initiation of *IQOS* among long-term former smokers (Table 11*)
- Complete switching to *IQOS* (Table 12*)
- Relapse, re-initiation and initiation of smoking after first trying *IQOS* (Table 13*)
- Complete switching to cigarettes after initiating tobacco use with *IQOS* (Table 14*)
- Tobacco cessation treatment use (Table 16)
- Cigarette smoker status (Table 24*)

Tobacco Cessation Treatments. We added a new item to the Cross-sectional Study questionnaire to assess current (past 30 day), past year and lifetime use of cessation treatments among all study participants (see item 155, Appendix B2):

> When was the last time you used any tobacco cessation treatments to help quit tobacco? Common types of tobacco cessation treatments include nicotine replacement therapy (such as nicotine patch, gum, inhaler, nasal spray, lozenge) and prescription drugs (such as Chantix, varenicline, Zyban, or bupropion).
>
> Within the past 30 days ..... ❍ 1
> More than 30 days ago but within 12 months ..... ❍ 2
> More than 12 months ago ..... ❍ 3
> Never ..... ❍ 4
> Don't Know ..... ❍ 5
> Refused ..... ❍ 6

We revised the Cross-sectional Study protocol (*e.g.*, see outcome measures within Objective #3, Section 6, Appendix B1) and SAP (Table 16, Section 11, Appendix B2) to include assessment of cessation treatment use. We evaluate tobacco cessation treatment among all participants and among current established *IQOS* users who switched from cigarettes to *IQOS*.

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B. IQOS® COHORT POSTMARKET ADULT CONSUMER STUDY (PACS) (PROTOCOL ID: (b) (4) [redacted])

FDA REQUEST B-1

Review and respond to the A.1 under the IQOS® Cross-Sectional PACS as it applies to this study as well.

RESPONSE B-1

To support assessments of participants' perceptions of the risks of using *IQOS* over time, we revised the Cohort Study instruments and made corresponding adjustments in the protocol and statistical analyses plan (SAP) as directed by FDA.

With respect to the Cohort Study, we made the following changes to the baseline questionnaire (Appendix C2):

- We eliminated original item 210 (MRTP message)
- We eliminated original items 211-213 (questions related to having seen the MRTP message) and original item 215 (knowledge that exposure reduction is relative to cigarettes)
- We revised original items 214 and 216 (now items 209 and 210) to delete the phrase "Based only on this product message for IQOS…" and replaced it with "Based on what you know or believe…"
- We have conditioned original item 216 (now item 210, "Based on what you know or believe, what do smokers need to do in order to reduce their body's exposure…") to be asked only of those who respond "Have less exposure…" to original item 214 (now item 209, "Based on what you know or believe, please complete the following: Smokers who switch completely from cigarettes to IQOS…")
- For original items 214 and 216 (now items 209 and 210) we have counterbalanced the response options such that half of respondents will be presented the response order as shown in the questionnaire and half will see the options in reverse order (excluding "Don't know" which will always be presented last).

In addition, we made the following change to the Cohort follow-up survey (Appendix C3):

- We added these two questions about perception and understanding of *IQOS* and exposure reduction (see now item 61, "…please complete the following: Smokers who switch completely from cigarettes to IQOS…" and now item 62, "…what do smokers need to do in order to reduce their body's exposure…", Appendix C3). These questions will be asked in all follow up waves of the study (Surveys 2-6).

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We adjusted study Objective #4 to focus only on risk perceptions (which includes the two items discussed above), reflecting the removal of the message awareness and comprehension elements. This and corresponding changes were made in the protocol (Appendix C1) and SAP (Appendix C4).

We revised the Cohort SAP to show results for each response option separately and at each survey time point to the questions: "…please complete the following: Smokers who switch completely from cigarettes to IQOS…" (Table 39, Section 10, Appendix C4) and "…what do smokers need to do in order to reduce their body's exposure…" (Table 41, Section 10, Appendix C4). In addition, Tables 40 and 42 (Section 10, Appendix C4) were added to the SAP to report results of the inferential statistics to assess change over time compared to baseline on these measures.

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FDA REQUEST B-2

In your cohort study protocol, HeatStick flavors tried and regularly used are only collected as basic demographics and not reported in the table shells presented (see page 13, Appendix C4). To better understand the role flavors, in particular menthol flavors compared to regular flavor, play in use behaviors, certain questions should be further stratified by users' flavor preferences. Analyses of tobacco use trajectories should be stratified by predominant use of menthol vs. regular HeatStick flavors. These include the endpoints of complete switching to the product, relapse, re-initiation, initiation, or complete switching to cigarettes, quitting, and quit attempts. These contrasts should identify, in adults, if menthol or regular tobacco flavors are associated with increased quit attempts or complete switching. Your statistical analysis plan should also pre-specify regression models that assess HeatStick flavor preferences as a predictor of complete switching, dual use, quitting cigarettes, and ≥50% changes in cigarette smoking. Revise the protocol to include these changes and provide updated power and sample size calculations to account for additional analyses of regular and menthol HeatStick flavors.

RESPONSE B-2

We revised the Cohort Study protocol (Appendix C1) and SAP (Appendix C4) to stratify several outcomes, including current use, complete switching from cigarettes to *IQOS*, relapse, re-initiation, initiation, complete switching from *IQOS* to cigarettes, dual use of *IQOS* and cigarettes, and quitting, by users of menthol and regular *HeatSticks*. The following SAP table shells have been revised to report outcomes stratified by *HeatSticks* flavor preference (see Section 10, Appendix C4 for the tables specified below):

- Current use of tobacco products (Table 4, 11 - 12)
- Changes in cigarettes per day among dual users (Table 5)
- Cigarettes per day over time among dual users (Table 7)
- Transitions of dual users (Table 14)
- Average number of days used *IQOS*/Cigarettes per 30 days (Table 9)
- Median number of *HeatSticks*/Cigarettes used per day (Table 10)
- Complete switching from cigarettes to *IQOS* (Table 15)
- Complete switching from *IQOS* to cigarettes (Table 17)
- Initiation – ever/established use of a product never used at baseline (Table 19, 21)
- Smoking relapse and re-initiation (Table 23, 25)

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- Quitting smoking after first trying *IQOS* (Table 27)
- Quit attempts (Table 28)
- Completely quit smoking, *IQOS*, all tobacco (Table 32)

In addition, we also revised regression models to assess *HeatSticks* flavor preferences as a predictor of the following study outcomes:

- Current use of cigarettes (Table 13)
- Changes in cigarettes per day among dual users (Table 6)
- Cigarettes per day over time among dual users (Table 8)
- Complete switching from cigarettes to *IQOS* (Table 16)
- Complete switching from *IQOS* to cigarettes (Table 18)
- Initiation – ever/established use of a product never used at baseline (Table 20, 22)
- Smoking relapse and re-initiation (Table 24, 26)
- Quit attempts (Table 29)
- Completely quit smoking, *IQOS*, all tobacco (Table 33 - 35)

An updated power analysis was performed to account for additional analyses of menthol and non-menthol *HeatSticks* variety. The updated power analysis led to an increase in the *IQOS* group sample size from $n=$(b) (4) to $n=$(b) (4) The power analysis was conducted for a two-sided Pearson Chi-square Test for Proportion Difference with a power of 80%.

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FDA REQUEST B-3

Your protocol does not include any information on the use of menthol cigarettes by study participants. This information is necessary to evaluate the role of menthol HeatSticks in increasing IQOS adoption and complete switching in menthol cigarette smokers. In order to study these possible behaviors, add additional items concerning menthol cigarette use to the tobacco use module of this protocol. Revise the protocol to report on use behavior patterns by predominant HeatStick flavor used, stratified by current or former menthol cigarette status, as sample size allows. This information can help us determine, for example, if menthol HeatSticks would increase the likelihood of complete switching among menthol cigarette smokers, compared to the tobacco variety.

RESPONSE B-3

We added new items to the Cohort Study questionnaire to assess menthol and non-menthol cigarette preference among current and former smokers (see items 33a and 33b, respectively, Appendix C2 and 14c and 14d, respectively, Appendix C3):

(If current smoker) Are the cigarettes you currently smoke most often menthol or non-menthol?

Menthol..... ❍ 1
Non-menthol..... ❍ 2
Don't Know ..... ❍ 3
Refused ..... ❍ 4

(If former smoker) When you last smoked cigarettes, were the cigarettes you smoked most often menthol or non-menthol?

Menthol..... ❍ 1
Non-menthol..... ❍ 2
Don't Know ..... ❍ 3
Refused ..... ❍ 4

We revised the Cohort Study protocol (Appendix C1) and SAP (Appendix C4) to stratify several outcomes related to tobacco use patterns by menthol or non-menthol cigarette

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preference. The following SAP table shells have been revised to report outcomes stratified by menthol or non-menthol cigarette preference (see Section 10, Appendix C4 for the Tables specified below):

- Changes in cigarettes per day among dual users (Table 5)
- Cigarettes per day over time among dual users (Table 7)
- Average number of days used *IQOS*/Cigarettes per 30 days (Table 9)
- Median number of *HeatSticks*/Cigarettes used per day (Table 10)
- Transitions of dual users (Table 14)
- Complete switching from cigarettes to *IQOS* (Table 15)
- Complete switching from *IQOS* to cigarettes (Table 17)

In addition, we also revised regression models to assess by menthol or non-menthol cigarette preference as a predictor of the following study outcomes:

- Current use of cigarettes (Table 13)
- Changes in cigarettes per day among dual users (Table 6)
- Cigarettes per day over time among dual users (Table 8)
- Complete switching from cigarettes to *IQOS* (Table 16)
- Complete switching from *IQOS* to cigarettes (Table 18)

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FDA REQUEST B-4

Your analysis of dual use focuses on tobacco use status at each wave (see Table 9, Appendix C4). However, the changes in cigarettes per day among dual users of IQOS and cigarettes are not evaluated. Revise the protocol to include an analysis of changes in CPD among the subset of dual users. Specifically, among dual users of IQOS and cigarettes at each wave, assess what proportion reduced their CPD by at least 50%, increased their CPD by at least 50%, or stayed the same at a subsequent wave. Additionally, the measures for cigarettes used on use days and days used per 30- days should be combined by taking their product and dividing by 30 to obtain a CPD for both daily and non-daily smokers. Understanding changes in smoking behavior among dual users will help us to better interpret the public health implications.

RESPONSE B-4

We revised the Cohort Study protocol (Appendix C1) and SAP (Appendix C4) to include several outcomes related to smoking behavior among dual users. The following outcomes and SAP table shells have been revised to include descriptive statistics and generalized estimating equations (see Section 10, Appendix C4 for the tables specified below):

- Changes in cigarettes per day among dual users (Table 5, 6)
- Cigarettes per day over time among dual users (Table 7, 8)

A standardized cigarettes per day calculation was developed for these analyses by taking the product of cigarettes used per days on days used in the past 30 days and days used in the past 30 days and dividing by 30.

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FDA REQUEST B-5

Your cohort study protocol (Appendix C) does not capture the use of tobacco cessation treatments (including, but not limited to, Nicotine Replacement Therapy (NRT), varenicline, or bupropion) in quitting attempts. This information can capture participants' attempts to quit cigarettes with such therapies, which is needed to control for their effects, and to understand IQOS' independent impact on use behaviors. In particular, the data is needed to understand if cessation therapies are being used alongside tobacco products including IQOS and to assess the overall history of cessation therapy use among IQOS users captured in these protocols. In the cohort study protocol, assess cessation therapy use history at baseline, as well as incident use at each study timepoint. Report outcomes such as complete switching, quitting, and dual use stratified by cessation therapy use. Also adjust for cessation therapy use in your regression models.

RESPONSE B-5

We added a new item to the Cohort Study questionnaire to assess current (past 30 day), past year and lifetime use of a cessation treatment among all study participants at baseline (see item 204, Appendix C2) and current and incident use of a cessation treatment at each follow-up survey (see item 57, Appendix C3):

Item 204, Appendix C2:

> When was the last time you used any tobacco cessation treatments to help quit tobacco? Common types of tobacco cessation treatments include nicotine replacement therapy (such as nicotine patch, gum, inhaler, nasal spray, lozenge) and prescription drugs (such as Chantix, varenicline, Zyban, or bupropion).
>
> Within the past 30 days ..... ❍ 1
> More than 30 days ago but within 12 months ..... ❍ 2
> More than 12 months ago ..... ❍ 3
> Never ..... ❍ 4
> Don't Know ..... ❍ 5
> Refused ..... ❍ 6

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Item 57, Appendix C3:

> During the past (INSERT: 3/6 DEPENDING ON WAVE) months, have you used any tobacco cessation treatments to help quit tobacco? Common types of tobacco cessation treatments include nicotine replacement therapy (such as nicotine patch, gum, inhaler, nasal spray, lozenge) and prescription drugs (such as Chantix, varenicline, Zyban, or bupropion).
>
> Yes, in the past 30 days.....❍ 1
>
> Yes, more than 30 days to (INSERT: 3/6 DEPENDING ON WAVE) months ago....❍ 2
>
> No.....❍ 3

We revised the Cohort Study protocol (Outcome measures within Objective #2, Section 6, Appendix C1) and SAP (Use of Cessation Treatment, Table 30 - 31, Section 5, Appendix C4) to include assessment of cessation therapy use history at baseline, as well as incident use at each study timepoint. The following SAP table shells have been revised to report outcomes stratified by use of a cessation therapy (see Section 10, Appendix C4 for the tables specified below):

- Current use of tobacco products (Table 4, 11)
- Changes in cigarettes per day among dual users (Table 5)
- Cigarettes per day over time among dual users (Table 7)
- Transitions of dual users (Table 14)
- Complete switching from cigarettes to *IQOS* (Table 15)
- Complete switching from *IQOS* to cigarettes (Table 17)
- Smoking relapse and re-initiation (Table 23, 25)
- Quitting smoking after first trying *IQOS* (Table 27)
- Completely quit smoking, *IQOS*, all tobacco (Table 32)

In addition, we also revised regression models to assess use of a cessation therapy as a predictor of the following study outcomes (see Section 10, Appendix C4 for the tables specified below):

- Current use of cigarettes (Table 13)
- Changes in cigarettes per day among dual users (Table 6)
- Cigarettes per day over time among dual users (Table 8)

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- Complete switching from cigarettes to *IQOS* (Table 16)
- Complete switching from *IQOS* to cigarettes (Table 18)
- Smoking relapse and re-initiation (Table 24, 26)
- Completely quit smoking, *IQOS*, all tobacco (Table 33 - 35)

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FDA REQUEST B-6

The cohort study protocol describes an approach to address missing data, but this is lacking sufficient details regarding participant censoring (section 5.5, Appendix C1; section 9.2, Appendix C4). Clarify if participants are censored at the time of their first missed survey. Describe the methods that will be used to assess missing data randomness and informative censoring in greater detail. Describe the possible imputation approaches to be used in greater detail. In order to ensure study validity, describe an a priori approach to address potential biases due to missing data and loss to follow-up.

RESPONSE B-6

We revised the Cohort SAP to include well-defined *a priori* criteria for handling missing data (Section 9.2, Appendix C4). Participants who drop out of the study will not be replaced. If a participant misses a survey, he/she will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation from the study schedule. Only completed surveys will be used for analysis and reporting.

Missing data or surveys will not be imputed and results will be analyzed using available complete data which may include weighting as detailed by a well-defined *a priori* criteria. A comprehensive analysis of attrition and its possible consequences for introducing bias in the results will be carried out. At each time point, those who complete the survey versus those who do not will be compared on the basis of demographics (age, race, education, income) and study group (*IQOS* versus cigarette smokers). A logistic regression will be performed with survey completion as the dependent variable; the demographics and study group variables will be the independent variables. A significant omnibus chi-squared test and any significant estimates for the individual variables would indicate potential bias for that wave. If the model and any estimates are significant, post-stratification weights will be created based on iterative proportional fitting to make the respective wave's sample more similar to the baseline sample. Weighting efficiencies will then be examined and, if less than 90%, descriptive statistics based on the weighted data will be provided in the appendix. This analysis will be repeated separately at each time point.

To address the potential bias due to attrition in the GEE models, the weighted GEE estimator originally proposed by Robins, Rotnitzky, and Zhao (Robins et al., 1995)[2] will be performed. This approach uses logistic regression to estimate the probability that a subject's survey is missing at a given wave and reweights the data based on the inverse of these probabilities.

[2] Robins J.M., Rotnitzky A., & Zhao L.P. Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. Journal of the American Statistical Association. 1995;90(429):106–121.

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Results from the weighted and unweighted models will be compared. The unweighted results will be presented, but any changes in inference due to the weighting will be clearly noted in the report.

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FDA REQUEST B-7

In the "IQOS Cohort PACS," you describe data quality checks, treatment of outliers, and responses to missing data (SAP, pp. 30-31). The protocol states that you will conduct a qualitative review of the data to identify outliers on single items and across items, that your method of identifying outliers will not use any a priori specifications, and that you will examine missing data (*i.e.*, participants who discontinue participation or miss one or more surveys [waves]) and consider whether to impute missing data. These methods appear vague and subjective.

a. Include a well-defined a priori criteria for identifying outliers (*e.g.*, greater than 3 standard deviations from the mean on an open-ended item) or, if you seek to identify people who are not paying attention to the survey, propose to exclude "speeders" (*i.e.*, people who complete the survey faster than a predetermined time) or include an *attention check* at the end of the survey such as an *instructed-response item* from Kung, Kwok, and Brown (2018; *Applied Psychology*, 67(2):264-283; *i.e.*, "For this question, please select number two to demonstrate your attention.").

b. Include a priori criteria for determining whether to impute data for participants who discontinue participation or miss surveys (waves). Conduct all descriptive and inferential analyses first with the complete dataset (*i.e.*, all respondents) and no imputation, and follow up with sensitivity analyses in which you exclude respondents based on the pre-specified criteria and impute data, if your a priori criteria are met. Reporting both of these analyses to FDA will enable the agency to understand whether excluding potentially invalid data and imputing missing data influenced results substantively.

RESPONSE B-7

We revised the Cohort SAP to now include well-defined *a priori* criteria to identify records that contain potential data falsification, include "speeding," non-differentiation of rating, and gibberish/non-sensical verbatim response (Section 7.3, Appendix C4). We will report the number of respondents flagged in the study report. We will conduct our main analysis using the full dataset and conduct sensitivity analyses without flagged responses to determine if the potentially invalid data substantially influence the results. With respect to outliers, the Cohort Study questionnaire is designed to minimize outliers through survey programming logic by defining ranges for numeric responses. Therefore, we do not expect outliers to be relevant in the planned analyses and expect to use all response values provided by participants.

We revised the Cohort SAP to now include well-defined *a priori* criteria for handling missing data (Section 9.2, Appendix C4). Participants who drop out of the study will not be replaced. If a participant misses a survey, he/she will have the opportunity to remain in the study and will receive an invitation for the next scheduled survey with no catch-up surveys or deviation

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from the study schedule. Only completed surveys will be used for analysis and reporting. Missing data or surveys will not be imputed and results will be analyzed using available complete data which may include weighting as detailed by a well-defined *a priori* criteria (see prior response for additional detail).

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C. RESEARCH ANALYSIS PLAN: ESTIMATION OF PREVALENCE OF IQOS® USE

FDA REQUEST C-1

The ALCS Adult Tobacco Consumer Tracking (ATCT) study secondary analysis protocol did not describe plans to capture data on the flavors of HeatSticks and cigarettes used. Menthol and regular flavors may be associated with behaviors including dual use, quitting, and complete switching. Revise the protocol to report overall prevalence of menthol vs. regular flavor use by study participants as a demographic variable. Additionally, stratify the analyses corresponding with Objective 4 (Tables 21-24, Appendix D) by primary HeatStick flavor used, comparing menthol flavors to regular flavor, as sample size allows.

RESPONSE C-1

We revised the Research Analysis Plan to include stratified analyses within each study objective to report prevalence, demographics, dual/poly use, use consumption and transition behaviors by *HeatSticks* menthol versus non-menthol variety (Appendix D). In addition, we intend to analyze and report data by menthol status of cigarettes and *HeatSticks* among dual users and among those who completely switch to *IQOS*. Specifically, we adjusted the following table shells in the reporting plan to report outcomes by menthol and non-menthol *HeatSticks* use (see Section 10, Appendix D; *indicates inclusion of stratifications by menthol and non-menthol cigarette use as well):

- Prevalence of current (Tables 7, 8) and past year use of *IQOS* (Table 9)
- *Heatstick* variety among *IQOS* users (Table 14)
- Demographic characteristics of *IQOS* menthol and non-menthol users (Table 15)
- Exclusive, dual/poly use with *IQOS* (Tables 17, 18)
- Menthol use status among *IQOS* and cigarette dual users (Table 21*)
- Number of days and *HeatSticks* used among *IQOS* users (Tables 19, 20)
- Consumption behavior with other tobacco products among *IQOS* users (Tables 22-25)
- Past year initiation of *IQOS* (Table 26, formerly Table 21 noted in the above request)
- Complete switching to *IQOS* (Table 27*, formerly Table 22)
- Complete switching from *IQOS* (Table 28, formerly Table 23)
- Quitting tobacco (Table 29, formerly Table 24)

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FDA REQUEST C-2

No data cleaning, quality control, or other techniques to address outliers is described in the protocol for the ATCT study analysis (Appendix D). Revise the protocol to include well-defined a priori criteria for identifying outliers (*e.g.*, greater than 3 standard deviations from the mean on an open-ended item). Conduct all descriptive and inferential analyses first with the complete dataset (*i.e.*, all respondents), and follow up with sensitivity analyses in which respondents are excluded based on the pre-specified criteria. Reporting both of these analyses to FDA will enable the agency to understand whether excluding potentially invalid data influenced results substantively.

RESPONSE C-2

The ATCT data quality control process has been added to the Research Analysis Plan (Section 6, Appendix D). The process includes data recoding, data cleaning, creation of specific metric variables, weighting and exception reporting. Potential outliers and invalid responses are checked and cleaned during the data management process. These steps occur before the data are transmitted to ALCS. The analyses described in the ATCT Analysis Plan will be conducted on the data file received. As a result, we do not plan to run additional sensitivity analyses.

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D. REPORTING PLAN – U.S. IQOS® OWNERS PANEL

FDA REQUEST D-1

No data cleaning, quality control, or other technique to address outliers is described in the protocol for the *IQOS* owners panel study (Appendix E).

a. Revise the protocol to include well-defined a priori criteria for identifying outliers (*e.g.*, greater than 3 standard deviations from the mean on an open-ended item) or, if you seek to identify people who are not paying attention to the survey, propose to exclude "speeders" (*i.e.*, people who complete the survey faster than a predetermined time) or include an attention check at the end of the survey such as an instructed-response item from Kung, Kwok, and Brown (2018; Applied Psychology, 67(2):264-283; *i.e.*, "For this question, please select number two to demonstrate your attention.").

b. Conduct all descriptive and inferential analyses first with the complete dataset (*i.e.*, all respondents), and follow up with sensitivity analyses in which respondents are excluded based on the pre-specified criteria. Reporting both of these analyses to FDA will enable the agency to understand whether excluding potentially invalid data influenced results substantively.

RESPONSE D-1

We revised the *IQOS* Owners Panel reporting plan to include a summary of the data quality control checks currently employed in this ongoing consumer research study (Section 3.5, Appendix E). These checks are primarily focused on identifying records that contain potential data falsification through fraudulent respondents conducting several interviews from the same device. We will conduct our main analysis using the full dataset and conduct sensitivity analyses without flagged responses to determine if the potentially invalid data substantially influence the results. The study also does not currently track "speeding" due to the level of routing on the survey instrument that makes the average length of interview vary greatly between respondents.

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FDA REQUEST D-2

The IQOS owners panel protocol (Appendix E) does not capture use of tobacco cessation treatments (including, but not limited to, Nicotine Replacement Therapy (NRT), varenicline, or bupropion) in quitting attempts. Capture of attempts to quit cigarettes with such therapies, which is needed to control for their effects, and to understand IQOS' independent impact on use behaviors. In particular, this data is needed to understand if cessation therapies are being used alongside tobacco products including *IQOS*. Revise the protocol to capture current use of cessation therapies or treatments in the owner's panel protocol and report additional tables stratified by cessation therapy use. Additionally, quantify the lifetime history of cessation therapy use among IQOS users captured in these protocols. Your analysis plan should assess and report history of cessation therapy use similarly to the other demographics (as in tables 2-7, Appendix E).

RESPONSE D-2

Following review of this request, Dr. Jeffrey Walker, Teton Regulatory Sciences, on behalf of PMP S.A. and ALCS, asked a clarifying question to FDA. This question was asked via an email on October 13, 2020 entitled "Clarifying questions from Altria regarding October 5, 2020 Information Request pertaining to Modified-Risk Granted Order for IQOS" which was sent to Rose Bianchi M.S., Regulatory Counsel, FDA Center for Tobacco Products.

The question was posed as follows:

"We will amend the protocol for the IQOS® Cross-Sectional Postmarket Adult Consumer Study (PACS) and the IQOS® Cohort PACS to capture use of cessation therapies or treatments. However, the IQOS owners panel is an existing marketing consumer research panel consisting of current adult IQOS users. Altria Client Services (ALCS), on behalf of Philip Morris USA, uses this panel to understand potential drivers and barriers to conversion from traditional cigarettes to IQOS®. Information learned from the panel is used to provide insight for marketing plans. While we described our reporting plan for data from this existing longitudinal consumer panel in the PMSS, it is primarily a tool to understand IQOS consumers and shape marketing to facilitate conversion. As such, this ongoing consumer panel study does not collect medical information about the use of cessation therapies or treatments. Given this, and since we will be collecting information about use of tobacco cessation treatments in the IQOS® Cross-Sectional PACS and the IQOS® Cohort PACS, is it sufficient to provide this information through these studies only and not the IQOS owners panel consumer study?"

In response to the clarifying question, Rose Bianchi replied on October 14, 2020 stating that "The FDA believes the approaches expressed on your email regarding data collection and reporting is adequate."

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Therefore, use of cessation therapies or treatments will not be included in the data collection and as a result will not be reported for the *IQOS* Owners Panel.

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E. SECONDARY ANALYSIS: ESTIMATION OF AWARENESS AND USE OF IQOS® AMONG UNDERAGE INDIVIDUALS

FDA REQUEST E-1

In the research on "Estimation of Awareness and Use of IQOS among Underage Individuals 13- 20 Years of Age: ALCS Underage Tobacco Use Survey (UTUS)," you plan to ask minors if they have seen or heard of IQOS and if they have ever used IQOS (pp. 18-20). Your study items use an approach that may underestimate minors' awareness and use of IQOS. Specifically, participants are first asked if they have ever seen or heard of heated tobacco products before the study (Item 3h) and, among participants who respond affirmatively, if they have ever used a heated tobacco product (Item 4h). Participants who report that they have seen or heard of heated tobacco products are then shown a list of heated tobacco products (Eclipse, Glo, IQOS, PAX, Ploom Tech, Some other brand not listed here) and are asked to select all of the products that they have seen or heard of before the study (*i.e.*, a "select-all-that-apply" format). Participants who report that they have ever seen or heard of a heated tobacco product are also asked if they have ever used one before. Participants who respond affirmatively are then shown a list of the products they reported being aware of and are asked to select all of the products they have used. This approach to asking about minors' awareness and use of IQOS may fail to identify participants who are aware of IQOS or use it if they do not consider it to be a "heated tobacco product" (or "heat-not-burn" product) or if they fail to examine and consider every brand listed in the select-all-that-apply items. Reformat the study items about awareness and use of IQOS on pp. 18-20 so that they are all forced-choice questions about IQOS specifically (*e.g.*, "Have you ever seen or heard of IQOS before?" [yes/ no/ don't know]; "Have you ever used IQOS before, even just one time"? [yes/ no/ don't know]). Reformatting these questions about minors' awareness and use of IQOS is necessary to enable the agency to accurately understand minors' awareness and use of IQOS.

RESPONSE E-1

While we originally designed the survey questions to avoid overestimation, we appreciate FDA's concerns about the prospects for underestimation and have revised our approach in accordance with the agency's direction. Specifically, we made the following changes (Section 10, Appendix F):

- We have revised the awareness question to be: "Have you ever seen or heard of IQOS before this study?" [yes/no/don't know] (item 3h1). All respondents will be asked this question; it will not be conditioned on awareness of heated tobacco products (HTP).
- We have revised the ever use question to be: "Have you ever used IQOS before this study, even just one time?" [yes/no/don't know] (item 4h1). This question will only be

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conditioned on being aware of *IQOS* (item 3h1).

- We have inserted a direct question for current use: "During the past 30-days, did you use IQOS?" [yes/no/don't know] (item 23hi). This question will only be conditioned on having ever used *IQOS* (item 4h1). Additionally, those who report ever use of *IQOS* and don't identify *IQOS* as brand used in the past 30 days in the HTP module (item 12h) will be asked the current use of *IQOS* question (item 23hi) in the *IQOS*-specific module.

In addition, we removed correct identification of *IQOS* as a condition for the awareness, ever and current use of *IQOS* in the outcome measures (Section 5, Appendix F).

We had developed the original proposed items and sequence to assess *IQOS*-specific awareness, ever use and current use while trying to minimize respondent burden and potential misreporting. The Underage Tobacco Use Survey (UTUS) monitors tobacco use at the product category level while also assessing brands used in the past 30-days (current use). We sought to add a minimal number of new items to obtain the additional needed information: awareness and ever use of *IQOS*. We also sought to address potential confusion and misreporting that is likely with new products. For example, data from wave 1 of the International Tobacco Control Youth Tobacco and E-cigarette Survey show that 9.1% of US 16-19 year-olds indicated awareness of *IQOS* in 2017 (Czoli et al., 2020),[3] well in advance of its commercialization in the second half of 2019. Likewise, data from the 2019 National Youth Tobacco Survey, fielded in the winter and spring, show that 12.8% of middle and high school students indicated awareness of HTPs (Dai, 2020).[4] In addition, 2.4% and 1.6% of students overall reported ever use and current use of HTPs, respectively (Dai, 2020). Findings from these national surveys conducted before *IQOS* was available in the US and when other HTPs were in very limited distribution suggest a degree of misreporting. Based on this evidence, we propose retaining item 3h9 ("Which of the following best describes *IQOS*?") as a means of understanding potential misreporting given the newness of this product and category.

The UTUS is administered quarterly, and we plan to incorporate the *IQOS*-specific questions proposed in Section 10 of Appendix F in the next earliest quarter following FDA approval of this research plan. Accounting for time needed for IRB submission and survey programming, should we received approval by December 15, 2020, we expect that we will be able to introduce the new questions in the quarter 1, 2021 administration.

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[3] Christine D Czoli , Christine M White, Jessica L Reid, et al. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 2020;29(1):89-95.

[4] Dai H. Heated tobacco product use and associated factors among U.S. youth, 2019. Drug Alcohol Depend. 2020;214:108150.

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FDA REQUEST E-2

In the research on "Estimation of Awareness and Use of IQOS among Underage Individuals 13- 20 Years of Age: ALCS Underage Tobacco Use Survey (UTUS)," you plan to ask minors about the source of their awareness of IQOS ("How did you first see or hear of IQOS?"). You plan to only ask this question if the participant correctly identifies IQOS (*i.e.*, responds, "This device only uses sticks containing actual tobacco," when asked "Which of the following best describes IQOS?"). This approach will overlook people who are aware of IQOS but do not fully understand its functionality (*i.e.*, that it cannot function with a pod, cartridge, or capsule).

Revise the survey logic such that it does not require that participants correctly answer the question about "Which of the following best describes IQOS" (p. 19; "This device only uses sticks…") in order to be asked questions about the source of their IQOS awareness. Making this change is necessary to understand where minors are first seeing or hearing about IQOS.

RESPONSE E-2

We revised the survey logic to ask source of awareness ("How did you first see or hear of IQOS?" item 3h8) of all respondents who are aware of *IQOS* (item 3h1). In addition, we moved this question, source of awareness, to follow directly after the *IQOS* awareness question. Source of awareness is no longer conditioned on correctly identifying *IQOS* (item 3h9).

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FDA REQUEST E-3

In the "Heated Tobacco Product Section" of the UTUS protocol (see page 20, Appendix F), you capture overall HTP use, sticks, and brands used. However, you do not assess recent use of IQOS and quantity of HeatSticks used specifically.

Revise the protocol to capture specific IQOS and HeatStick underage use, separate from overall HTP use, as described in the order letter. The protocol should also assess past 30-day use of IQOS, including the quantity of HeatSticks used. These questions should only be conditioned on ever use of IQOS, and should not be conditioned on use or awareness of HTPs, or correct identification of IQOS.

RESPONSE E-3

We have created an *IQOS*-Specific Section (module) to be inserted into UTUS to provide additional *IQOS*-specific lifetime and current use information (Section 10, Appendix F). Participants who report ever use of *IQOS* will complete the *IQOS*-Specific Section. The *IQOS*-Specific Section is not conditioned on awareness or use of HTPs or correct identification of *IQOS*.

The *IQOS*-Specific Section will include the following:

- "During the past 30 days, did you use IQOS?" (item 23hi). This question is conditioned on having ever used *IQOS* (item 4h1). Additionally, as described in an earlier response, those who report ever use of *IQOS* and don't identify *IQOS* as a brand used in the past 30 days in the HTP module (item 12h) will be asked the current use of *IQOS* question in this module. Those who answered *IQOS* as a brand used in the past 30 days in the HTP module will automatically be counted as having used *IQOS* in the past 30 days in the *IQOS*-specific module.
- "During the past 30 days, on how many days did you use IQOS?" (item 24hi). This question is conditioned on using *IQOS* in the past 30 days (item 23hi or *IQOS* identified in 12h).
- "During the past 30 days, on the days you used IQOS, about how many HeatSticks did you use with IQOS per day?" (item 25hi). This question is conditioned on using *IQOS* in the past 30 days (item 23hi or *IQOS* identified in 12h).

In addition, the following items will also be included in the *IQOS*-Specific Section:

- "How many HeatSticks have you used with IQOS in your entire life?" (item 21hi). This question is conditioned on having ever used *IQOS* (item 4h1).

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- "…Was the first IQOS HeatStick you used menthol or non-menthol (regular)?" (item 22hi). This question is conditioned on having ever used *IQOS* (item 4h1).
- "During the past 30 days, was the HeatStick you usually used with IQOS menthol or non-menthol?" (item 26hi). This question is conditioned on using *IQOS* in the past 30 days (item 23hi or *IQOS* identified in 12h).

We revised the outcome measures to report lifetime and current quantity of *HeatSticks* consumed and current number of days used specific to *IQOS*. We also have revised the analysis plan to report outcomes overall and by menthol and non-menthol *HeatSticks* use (Section 5, Appendix F).

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FDA REQUEST E-4

The secondary analyses of UTUS (Appendix F) did not assess the flavors of HeatStick first used and currently used by IQOS users. Given the role flavors may play in youth initiation and other behaviors, HeatStick flavors ever-used and currently used should be assessed and reported at each wave, comparing menthol to regular flavors. Certain analyses should be further stratified by flavor preferences, including demographics and use behaviors as outlined in objectives 2-4 of the protocol (see pages 15-16 and 24-26, Appendix F). Present these demographics and use behavior patterns by predominant use of menthol or regular HeatStick flavors as sample size allows.

RESPONSE E-4

We have added questions and adjusted our analysis plan to provide information related to menthol and non-menthol *IQOS Heatstick* use. Specifically, as indicated in the prior response, we added questions to assess menthol/non-menthol status of *IQOS HeatStick* first used (item 22hi) and currently used (26hi). We specify stratified analysis by menthol and non-menthol *HeatSticks* use for outcomes under objectives 2 to 4 when sample size allows (Section 5, Appendix F).

We revised the table shells to show:

- *IQOS* ever use and quantity of lifetime *IQOS HeatSticks* used will be reported overall and stratified by menthol/non-menthol status of first *IQOS HeatStick* used (Table 3 and Table 4, Section 11, Appendix F).
- *IQOS* past 30-day use and behaviors (*e.g.*, number of days, number of *HeatSticks*) will be reported overall and stratified by menthol/non-menthol status of *IQOS HeatSticks* currently used (Table 3 and Table 6, Section 11, Appendix F).
- Demographics of ever and past 30-day *IQOS* users will be reported overall and stratified by menthol/non-menthol *IQOS HeatStick* use (Table 5 and Table 7, Section 11, Appendix F).

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FDA REQUEST E-5

The "Research Analysis Plan – Estimation of Awareness and Use of IQOS among Underage Individuals 13-20 Years of Age," did not describe data quality checks or treatment of outliers. If you plan to review the study data to identify and exclude outliers on single items or across items, add well-defined a priori criteria for identifying the outliers in the Research Analysis Plan (*e.g.*, greater than 3 standard deviations from the mean on an open-ended item, or, if you seek to identify people who are not paying attention to the survey, exclusion of "speeders" or inclusion of an attention check at the end of the survey such as an *instructed-response item* from Kung, Kwok, and Brown; 2018; *Applied Psychology*, 67(2):264-283). Conduct all descriptive and inferential analyses first with the complete dataset (i.e., all respondents), and follow up with sensitivity analyses in which you exclude respondents based on the pre-specified criteria. If you plan to identify and exclude outliers, proposing well-defined a priori criteria and reporting the analyses to FDA with and without the outliers will enable the agency to understand whether excluding potentially invalid data influenced results substantively.

RESPONSE E-5

We have revised the Research Analysis Plan to include *a priori* criteria for identifying potential data falsification, including "speeding" and inattentiveness (Section 6, Appendix F). The main analysis will be conducted using the full data set, and sensitivity analysis will be conducted without flagged respondents to assess the influence of potentially invalid data.

The questionnaire is designed to minimize outliers by defining specific ranges for numeric responses and the use of categorical responses. Therefore, we do not expect outliers to be relevant in this analysis plan.

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F. REPORTING PLAN – U.S. IQOS® SALES AND DISTRIBUTION DATA

FDA REQUEST F-1

The sales/distribution of the IQOS system and HeatSticks will be reported by seven retail channels: Total U.S., Company Owned, ECommerce, Convenience Store, Super Market/Grocery, Drug, and Gas. The protocol does not provide enough details on sales by retail channel as described in the sales reporting section of the order letter under Appendix B. Revise the protocol to report the sales/distribution of IQOS and HeatSticks by detailed retail channel, such as PM USA-owned Retail Outlets, IQOS Trained Experts, PM USA-owned ECommerce, Third Party-owned ECommerce, Third Party-owned Tobacco Specialty Shops, Convenience Store, Super Market/Grocery, Drug, and Gas. If IQOS systems and/or HeatSticks have not been sold from a certain retail channel during the reporting time period, report zero dollar and volume sales in PMSS. In addition to reporting volume and dollar sales/distribution by major retail market and census region, revise the protocol to report total U.S. sales/distribution by MRTPA STN and retail channel and follow the retail channels in the attached Appendix B - Reporting Template as closely as possible. Assessing where consumers are purchasing their MRTPs and how it changes over time can help FDA understand the impact of the MRTPA order on tobacco consumption at the population level.

RESPONSE F-1

In accordance with the direction provided in FDA's October 5, 2020, Information Request letter, Altria/PMPSA will revise the Reporting Plan (Appendix G) to include total US sales and distribution of *IQOS* devices and *HeatSticks* utilizing the Reporting Template attached as Appendix B to the Information Request letter, with the exception of a classification for "*IQOS* Trained Experts."

In the Information Request letter, FDA stated that we should revise the sales and distribution data protocol to report by detailed retail channels "such as PM USA-owned Retail Outlets, *IQOS* Trained Experts, PM USA-owned ECommerce, Third Party-owned ECommerce, Third Party-owned Tobacco Specialty Shops, Convenience Store, Super Market/Grocery, Drug, and Gas". Following review of this request, Dr. Jeffrey Walker, Teton Regulatory Sciences, on behalf of PMP S.A. and ALCS, asked a clarifying question to FDA. This question was asked via an email on October 13, 2020 entitled "Clarifying questions from Altria regarding October 5, 2020 Information Request pertaining to Modified-Risk Granted Order for IQOS" which was sent to Rose Bianchi M.S., Regulatory Counsel, FDA Center for Tobacco Products. The question was posed as follows:

"We plan to report sales and distribution data by detailed channels as FDA has directed. However, we have a concern with one of the "channels" that FDA enumerated in its information request. FDA requests that we revise the sales and distribution protocol to report

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sales from IQOS Trained Experts as a separate channel. However, IQOS Trained Experts serve multiple functions, covering IQOS consumer education and sales in various PM USA-owned Retail Outlets and in one-to-one engagements with adult consumers. Therefore, sales made with the assistance of IQOS Trained Experts are tracked through the PM USA-owned Retail Outlet channel and the store with which the Trained Expert is tied. We do not have in place a system for separately tracking sales made with the assistance of Trained Experts. We propose to continue reporting sales involving IQOS Trained Experts as part of the PM USA-owned Retail Outlet channel. Is this acceptable?"

In response to the clarifying question, Rose Bianchi replied on October 14, 2020 stating that "The FDA believes the approaches expressed on your email regarding data collection and reporting is adequate." Therefore, Altria/ PMPSA will report sales for the following eight mutually exclusive and comprehensive retail channel categories: PM USA-owned Retail Outlets, PM USA-owned ECommerce, Third Party-owned ECommerce, Third Party-owned Tobacco Specialty Shops, Convenience Store, Super Market/Grocery, Drug, and Gas.

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FDA REQUEST F-2

The sales/distribution of the IQOS system and HeatSticks will be reported by U.S. census region and major retail markets. As such, the protocol does not provide enough details on major retail markets to be included in PMSS. The sales reporting section of the order letter under Appendix B (page 7) specifically states "total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold." Revise the protocol to provide operational definitions of major retail markets, including a list of major retail markets (*i.e.*, major metropolitan areas) will be included in the PMSS.

RESPONSE F-2

We have revised the Reporting Plan (Appendix G) to provide our approach to defining and listing major retail markets as part of our annual submission for *IQOS* PMSS. Currently, we define major retail markets as a cluster of counties where *HeatSticks* are in distribution. These counties are typically contiguous and surround a major U.S. city. The geographical limits of the major retail market may grow over time as *HeatSticks* distribution expands. In each reporting period, ALCS will provide a list of counties which define the area for every reported major retail market. Additionally, the number of major retail markets will expand as *IQOS* continues to gain distribution in new U.S. markets. Our first annual report for *IQOS* PMSS will include county definitions for the current Atlanta, Richmond and Charlotte major retail markets, as well as any additional major retail markets in which *IQOS* is launched.

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FDA REQUEST F-3

The growth rate or percent change comparing each quarter/annual unit volume versus the prior time period will be reported. The reporting tables included in the protocol under Appendix G do not contain columns to report annual and quarterly growth rates. Revise the protocol to report growth rates in reporting tables under Appendix G. In order to adequately assess the trend in sales/distribution of IQOS and HeatSticks as proxies for tobacco consumption at the population level, it is necessary to compare growth rates in volume and dollar sales by Submission Tracking Number and retail channel after the MRTP order.

RESPONSE F-3

We have revised the Reporting Plan (Appendix G) to include the following in order to adequately assess the trend in sales and distribution of *IQOS* and *HeatSticks*:

- (Dollars) Percent Change from Prior Reporting Calendar Year
- (Dollars) Percent Change from Prior Reporting Quarter
- (Units) Percent Change from Prior Reporting Calendar Year
- (Units) Percent Change from Prior Reporting Quarter

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FDA REQUEST F-4

The protocol includes reporting table shells with product descriptions of IQOS systems and HeatSticks, but it does not include the relevant MRTPA Submission Tracking Number (STN). Revise the protocol to include STN in reporting tables. Inclusion of FDA Submission Tracking Numbers provides information to help evaluate changes in the sales/distribution (used as a proxy for product use) by product after MRTPA order. In order to ensure standardized reporting of IQOS sales and distribution data, utilize the attached Appendix B - Reporting Template provided by FDA.

RESPONSE F-4

We revised the reporting template (Table 1, Appendix G) to include MRTPA Submission Tracking Numbers (STN) per the Reporting Template provided in Appendix B of FDA's October 5, 2020 Information Request Letter.

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G. COMPUTATIONAL APPROACH TO ASSESS THE CANCER RISK FROM THE EXPOSURE TO CHEMICALS INCREASED IN THS2.2 AEROSOL COMPARED TO 3R4F SMOKE

FDA REQUEST G-1

You propose to perform hazard identification for genotoxicity potential following IST/GIST protocols described in Myatt et al., 2018 and Hasselgren et al., 2019, and integrate experimental data, statistical model results, expert alert results, and read-across results to generate a combined assessment with a reliability score. The methods described in the protocols are appropriate for the purpose of parent compound assessment. However, reactive and toxic metabolites from the parent compounds are not addressed in this protocol. If all the data recommended in the two articles are obtained and properly interpreted, it will be necessary for you to address reactive and toxic metabolites. It is also necessary to describe why each specific QSAR model and SAR knowledge base used and the corresponding prediction data are applicable to predicting the genotoxicity and carcinogenicity potential of inhaled tobacco product constituents.

FDA needs additional information to evaluate the quality of *in silico* prediction results of the chemicals increased in THS2.2. aerosol compared to 3R4F smoke. To accomplish this, FDA requests that PMP revise the protocol to include the following information:

a. Reactive or toxic metabolites from the chemicals increased in THS2.2 aerosol compared to 3R4F smoke: Priority for your analysis of reactive or toxic metabolites needs to be based upon known human metabolites first, followed by metabolites known from animal models, then *in silico* predicted metabolites. Any known species-specific differences in metabolite formation needs to be addressed in your assessment.

b. A narrative justifying for the selection of the metabolites for *in silico* analysis for the hazard identification.

c. A narrative explaining how the computational toxicology model prediction results are applicable to the toxicity evaluation of inhaled tobacco product constituents.

RESPONSE G-1

The protocol for computational toxicology assessment has been revised to reflect additional information requested by the Agency:

a. Assessment plan for reactive or toxic metabolites from the parent compounds has been added to the protocol. This information is provided under Section 2.2.3 *Metabolites from the parent compounds,*

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b. A narrative justifying for the selection of the metabolites for *in silico* analysis for the hazard identification is included in the narrative within Section 2.2.3,

c. A narrative explaining how the computational toxicology model prediction results are applicable to the toxicity evaluation of inhaled tobacco product constituents has been provided under Section 2.2.4 *Applicability of the computational model predictions to inhaled tobacco product constituents*.

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FDA REQUEST G-2

You propose to predict points of departure for data-poor chemicals based on read-across methods and QSAR models. However, you did not elaborate on how the toxicity values will be derived from available exposure limits of structural analogs and metabolites. For the QSAR models, you propose to use the Conditional Toxicity Value (CTV) predictor to predict quantitative toxicity values, specifically CTV-OSF, CTV-CPV, and CTV-IUR.

Collecting information on hazard characterization is beyond the scope of the PMSS requirements of your order. Consequently, it is up to you whether you choose to proceed with this step. If you do decide to proceed, we recommend that you provide the following information in your protocol to ensure that FDA will have the necessary information to evaluate the quantitative prediction results:

a. A detailed plan on how a read-across approach will be performed to derive toxicity values.

b. Compiled lists of individual CTV values predicted from multiple alternative CTV models that can be built with different machine learning approaches and molecular descriptors.

c. IQOS aerosol constituent-specific domain of applicability coverage for each database/model (i.e., CTV-OSF, CTV-CPV, and CTV-IUR) and a list of the IQOS chemicals that are outside of the applicability domain of each CTV-model.

d. Mechanistic interpretation of the models including any relationship between the molecular descriptors selected in the CTV model and the predicted endpoints (CTV-OSF, CTV-CPV, and CTV-IUR) wherever such an interpretation can be made.

RESPONSE G-2

As recommended by the Agency, the hazard characterization step has been removed from the protocol for computational toxicology assessment.

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FDA REQUEST G-3

Collecting information on exposure assessment and QRA is beyond the scope of the PMSS requirements of your order. FDA recommends removing these steps from the protocol.

RESPONSE G-3

As recommended by the Agency, the collection of information on exposure assessment and QRA have been removed from the protocol for computational toxicology assessment.

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H. DEVELOPMENT OF POPULATION HEALTH IMPACT MODEL (PHIM) V.8

FDA REQUEST H-1

At this time, your PHIM protocol does not require a revision. However, FDA reminds you of the following.

a. Appendix J Section 1 of your PMSS protocol acknowledges specifics for data and information required for computational modeling of the impact of the MRTPs on population health, and specific characterizations required for description of such modeling, in accordance with FDA's MRGO. Your description of these requirements suggests that they might be optional (*e.g.*, by referring to them as recommendations or by using the terms "should" instead of "must"). FDA reminds you that the requirements for computational modeling, as indicated in the MRGO, are not optional.

b. You are proposing a new version of your Population Health Impact Model (PHIM, v.8). As such, when you report on the results from your PHIM in PMSS annual reports, it is important that you provide all information necessary for FDA to perform a thorough evaluation of the new version of the model, including statistical, mathematical, and computational components of the model, and other features associated with input parameters as described in Appendix J of your submitted postmarketing plan. Documentation directly related to model development and implementation, including scientific literature, is indispensable for evaluating the relevant features of the model.

c. Since you are proposing to implement the model using the open source software environment R, FDA recommends that you consider using many of the available R packages to develop a Graphical User Interface (GUI) directly from R, including Unified Modeling Language (UML) diagrams. These recommendations will strengthen the efficiency of the review process at FDA.

RESPONSE H-1

a. Appendix J has been amended to make clear our understanding that the requirements are not optional.

b. We will provide all the requested information necessary for the FDA evaluate the new version of the model, including statistical, mathematical, and computational components of the model, and other features associated with input parameters as described in Appendix J, and documentation directly related to model development and implementation, including scientific literature.

c. We will develop a Graphical User Interface (GUI) and Unified Modelling Language (UML) diagrams to facilitate the review process. All code and materials relating to such development will be provided in addition to the materials specified in (a) and (b) above.

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