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Version 1.0

RESPONSE TO DECEMBER 11, 2020 INFORMATION REQUEST LETTER for PS0000042 and PS0000078 - responses to sections I, II, III and IV.

December 22, 2020

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I. APPENDIX B. *IQOS* CROSS-SECTIONAL POSTMARKET ADULT CONSUMER STUDY (PACS) (PROTOCOL ID: (b) (4)

FDA REQUEST I-1

Edit the "*IQOS* Cross-Sectional PACS," correct the skip logic and programming text (Cross-Sectional PACS Instrument, p. 51) as follows:

a. Revise the skip logic text before item 161 to state, "Continue with Q.161 if 'Have less exposure…' selected in Q.160; otherwise skip to instruction before Q.162."

b. Revise the programming text before item 162 to state, "Ask Q.162 – Q.163 for current cigarette smokers and *IQOS* users, respectively…"

c. Check the formatting of all other skip logic and programming text throughout the rest of the study instrument to ensure that it is correct, given that the item numbering has changed because you have deleted or added items.

These changes are necessary to ensure that study participants are correctly routed to the appropriate survey items.

RESPONSE

I-1: We have revised the "IQOS Cross-Sectional PACS" survey instrument (Appendix B2) as follows:

I-1-a: We have revised the skip logic text before item 161 to state, "CONTINUE WITH Q.161 IF "HAVE LESS EXPOSURE…" SELECTED IN Q.160; OTHERWISE, SKIP TO INSTRUCTION BEFORE Q.162" This change will ensure that participants are routed to the appropriate items.

I-1-b: We have revised the programming text before item 162 to state, "ASK Q. 162 – Q. 163 FOR CURRENT CIGARETTE SMOKERS AND IQOS USERS." This change will ensure that participants are routed to the appropriate items.

I-1-c: We examined the remaining programming and skip logic language in the "IQOS Cross-Sectional PACS" survey instrument to ensure that participants are accurately routed to appropriate survey items. While no other issues with the programming notes or skip logic were identified, the following additional change was made:

- Item 118 was missing part of the question stem and was revised to "*Before you first tried* IQOS, had you EVER used an oral tobacco-derived nicotine product EVEN ONCE?" (The italics indicate the added verbiage.)

In addition to the requested changes noted above and in response to requests III-3-a and IV-1 to "…revise all protocols so that quantities of use are also reported as a one-item measure of *HeatSticks* per day, comparable to typical measures of cigarettes per day…" we added additional measures of *HeatSticks* per day and cigarettes per day to the "IQOS Cross-Sectional PACS" protocol (Appendix B1) and statistical analysis plan (SAP) (Appendix B3). The measures of *HeatSticks* per day and cigarettes per day are included in addition to *HeatSticks* per day on days used and cigarettes per day on days used. These changes affected Section 6, Objective 1 of the "IQOS Cross-Sectional PACS" protocol and Section 4.1.3 and Tables 4 and 5 of the "IQOS Cross-Sectional PACS" SAP.

Revised Appendices included with this Response

- Appendix B1 – Cross-sectional Protocol
- Appendix B2 – Cross-sectional Questionnaire
- Appendix B3 – Cross-sectional SAP

II. APPENDIX C. *IQOS* COHORT POSTMARKET ADULT CONSUMER STUDY (PACS) (PROTOCOL ID: (b) (4)

FDA REQUEST II-1

Table 15 of Appendix C4 of the updated protocol for the PACS Cohort Study describes 'complete switching from cigarettes to *IQOS*.'

a. Revise your protocol to also report on total complete switching to *IQOS* stratified by the four possible flavor transitions (Regular CC à Regular *IQOS*, Regular CC à Menthol *IQOS*, Menthol CC à Regular IQOS, Menthol CC à Menthol *IQOS*) across the study groups and survey waves.

One way to construct this table would be to duplicate Table 15, replacing the rows currently stratifying by flavor preferences and cessation treatment with rows stratifying by the 4 possible flavor transitions (see below).

Measure	Survey Wave					
	Baseline % (CI)	Month 3 % (CI)	Month 6 % (CI)	Month 12 % (CI)	Month 18 % (CI)	Month 24 % (CI)
Base: Test Group Participants	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx
Total switched from cigarettes to IQOS						
To regular IQOS						
Regular CC to regular IQOS						
Menthol CC to regular IQOS						
To menthol IQOS						
Menthol CC to menthol IQOS						
Regular CC to menthol IQOS						
Base: Reference Group Participants	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx
Total switched from cigarettes to IQOS						
To regular IQOS						
Regular CC to regular IQOS						
Menthol CC to regular IQOS						
To menthol IQOS						
Menthol CC to menthol IQOS						
Regular CC to menthol IQOS						

Understanding the prevalence of same-flavor and switched-flavor complete switching is important for FDA to assess the overall impact of menthol flavored products.

RESPONSE

II-1: We have revised the "IQOS Cohort PACS" protocol (Appendix C1) and SAP (Appendix C4) as follows:

II-1-a: We have added total complete switching to IQOS stratified by transitions between product variety (Regular CC to IQOS Regular, Regular CC to IQOS Menthol, Menthol CC to IQOS Regular, and Menthol CC to IQOS Menthol) as an outcome measure in the "IQOS Cohort PACS" study protocol, Section 6-Product Use Transitions (Appendix C1). We have also updated the "IQOS Cohort PACS" study SAP to include complete switching to IQOS stratified by transition between product varieties (regular and menthol) as an outcome in Section 4.2 and 5.2 (Appendix C4). We have revised SAP Table 15 to include descriptive information regarding complete switching to IQOS stratified by transitions between product varieties.

In addition to the requested changes noted above and in response to requests III-3-a and IV-1 to "…revise all protocols so that quantities of use are also reported as a one-item measure of *HeatSticks* per day, comparable to typical measures of cigarettes per day…" we added additional measures of *HeatSticks* per day and cigarettes per day to the "IQOS Cohort PACS" protocol and SAP. (In the prior version of these study materials, we only incorporated the cigarettes per day measure to assess change in CPD among dual users, as requested in FDA's information request letter dated October 5, 2020.) The measures of *HeatSticks* per day and cigarettes per day are included in addition to *HeatSticks* per day on days used and cigarettes per day on days used. These changes affected Section 6-Tobacco Use of the "IQOS Cohort PACS" protocol (Appendix C1). We have also revised Section 4.1 and 5.2 and Table 10 of the "IQOS® Cohort PACS" SAP (Appendix C4) to include measures of *HeatSticks* used per day and Cigarettes per day in addition to *HeatSticks* or Cigarettes per day on days used.

Finally, we note a revision to Figure 1 of the "IQOS® Cohort PACS" protocol (Appendix C1). The previously submitted "IQOS® Cohort PACS" protocol did not include the final updated figure that reflected the changes made in response to the previous information request letter dated October 5, 2020. We have updated Figure 1 to accurately reflect the sample sizes and survey modules administered in the "IQOS® Cohort PACS."

Revised Appendices included with this Response

- Appendix C1 – Cohort Protocol
- Appendix C4 – Cohort SAP

III. APPENDIX D. SECONDARY ANALYSIS: ESTIMATION OF PREVALENCE OF *IQOS* USE

FDA REQUEST III-1

Table 27, Appendix D of the updated protocol for the ATCT study secondary analysis describes both cigarette flavors used and *IQOS* flavors used but does not describe like-flavor or switched flavor transitions between products.

a. Ensure that complete switching—in either direction—between cigarettes and *IQOS* is reported with stratification by flavors of both products simultaneously.

b. Add two new tables based on the table below (a similar design may be used to describe complete switching from *IQOS* to cigarettes). Note in these tables if sample size issues preclude reporting of specific transitions.

Complete Switching Measure	Base Sample Size	Unweighted Count	Weighted Frequency	Proportion (95% CI)
Complete switching from cigarettes to IQOS within the past year				
To regular IQOS				
Regular CC to regular IQOS				
Menthol CC to regular IQOS				
To menthol IQOS				
Menthol CC to menthol IQOS				
Regular CC to menthol IQOS				
Complete switching from cigarettes to IQOS within the past year among past year established smokers				
To regular IQOS				
Regular CC to regular IQOS				
Menthol CC to regular IQOS				
To menthol IQOS				
Menthol CC to menthol IQOS				
Regular CC to menthol IQOS				
Complete switching from cigarettes to IQOS within the past year among current established IQOS users				
To regular IQOS				
Regular CC to regular IQOS				
Menthol CC to regular IQOS				
To menthol IQOS				
Menthol CC to menthol IQOS				
Regular CC to menthol IQOS				

These results can be used to quantify the utility of flavor parity between *IQOS* and other cigarettes.

RESPONSE

III-1: We have revised the Research Analysis Plan (RAP) for "Estimation of Prevalence of IQOS® Use" (Appendix D) as follows:

III-1-a: We have revised Section 5-Objective 4 of the RAP for "Estimation of Prevalence of IQOS® Use" (Appendix D) to include all switching behaviors between cigarettes and

IQOS®. The revised objective now states: "Describe initiation, quitting and complete switching behaviors relative to IQOS® use… Complete switching behaviors between cigarettes and IQOS® are reported with stratification by menthol and non-menthol variety for both products and includes descriptive statistics for switching within and between menthol and non-menthol product."

III-1-b: Table 27 of the "Estimation of Prevalence of IQOS® Use" RAP (Appendix D) has been updated to further characterize complete switching from cigarettes to IQOS® within the past year among past year established smokers and complete switching from cigarettes to IQOS® within the past year among current established IQOS® users. Each behavior change now also includes information on Switch from Menthol Cigarettes to IQOS® Menthol, Switch from Menthol Cigarettes to IQOS® Non-Menthol, Switch from Non-Menthol Cigarettes to IQOS® Menthol, and Switch from Non-Menthol Cigarettes to IQOS® Non-Menthol. We made a similar revision to Table 28 for outcomes associated with completely switching from IQOS© to cigarettes.

FDA REQUEST III-2

Add cigarette smoking history (as 'Never,' 'Former,' and 'Current') to the 'Major Demographics' that are used to stratify results in Tables 10-15 of the protocol for ATCT study secondary analysis.

This is necessary for FDA to understand *IQOS'* appeal by smoking status.

RESPONSE

III-2: We have revised Section 5-Objective 1 of the RAP for "Estimation of Prevalence of IQOS® Use" (Appendix D) to include prevalence by never, current, and former smoking status. The revised objective now states: "Estimate prevalence of IQOS® use, in total and by demographic characteristics…Prevalence will also be evaluated based on cigarette smoking status (having never smoked cigarettes as "never", having smoked cigarettes in the past 30 days as "current", and having ever smoked cigarettes but not smoked in the past 30 days as "former")."

Tables 10-15 have been updated with rows reporting cigarette smoking status (never, current, former) and the table and column titles have been updated to reflect the expansion of information beyond demographics.

FDA REQUEST III-3

Tables 19, 20, 22, and 23, Appendix D of the revised protocol for the ATCT study, past 30-day *HeatSticks* use is assessed using the two-item measure used elsewhere in your submitted protocols (for example, "During the past 30 days, on how many days did you use *IQOS*?" and "During the past 30 days, on the days you used *IQOS*, about how many *HeatSticks* did you use with *IQOS* per day?").

a. In addition to these metrics, revise all protocols to report quantities of use as a one-item measure of *HeatSticks* per day, comparable to typical measures of cigarettes per day (CPD) as follows (emphasis added):

   (Use days in past 30 days * *HeatSticks* used on use days) / 30 = *HeatSticks* Per Day (HPD)

   Use of this measure, reported as a median, allows the FDA to compare cigarette and *IQOS* use using simpler, one-item metrics.

b. Report cigarette use (Tables 22 and 23) as a 1-item measure of Cigarettes Per Day (CPD) in a similar fashion. As a reference, see revisions that have been made to the PACS Cohort Study protocol (Appendix C4).

RESPONSE

III-3: We have revised the RAP for "Estimation of Prevalence of IQOS® Use" (Appendix D) to address FDA's request as follows:

III-3-a: We have revised Section 5-Objective 3 of the RAP for "Estimation of Prevalence of IQOS® Use" to include *HeatSticks* per day (HPD) using FDA's suggested formula for calculation. Table 19 (Appendix D) has also been updated to show *HeatSticks* per day in addition to *HeatSticks* per day on days used.

III-3-b: We have revised Section 5-Objective 3 of the RAP for "Estimation of Prevalence of IQOS® Use" to include Cigarettes per day (CPD) using FDA's suggested formula for calculation. Table 22 (Appendix D) has also been updated to show Cigarettes per day in addition to Cigarettes per day on days used.

Revised Appendix included with the Responses to Request III

- Appendix D – Research Analysis Plan: Estimation of Prevalence of IQOS® Use

IV. APPENDIX F. SECONDARY ANALYSIS: ESTIMATION OF AWARENESS AND USE OF *IQOS* AMONG UNDERAGE INDIVIDUALS

FDA REQUEST IV-1

In the revised *IQOS*-Specific Section to the UTUS study (Section 10, Appendix F), the quantity of *HeatSticks* used in the past 30 days is assessed using the two-item measure used elsewhere in your submitted protocols (for example, "During the past 30 days, on how many days did you use *IQOS*?" and "During the past 30 days, on the days you used *IQOS*, about how many *HeatSticks* did you use with *IQOS* per day?").

In addition to these metrics, revise all protocols so that quantities of use are also reported as a one-item measure of *HeatSticks* per day, comparable to typical measures of cigarettes per day (CPD), as follows (emphasis added):

(Use days in past 30 days * *HeatSticks* used on use days) / 30 = *HeatSticks* Per Day (HPD)

Use of this measure, reported as a median, allows the FDA to compare cigarette and *IQOS* use using a simpler, one-item metric.

RESPONSE

IV-1: We responded to FDA with the following clarifying question on December 15, 2020:

> "We created the IQOS consumption question in UTUS to closely align with other national surveys which use categorical responses to capture amount of tobacco product use (Table 1). The FDA's request for a one-item measure of *HeatSticks* per day (HPD) and suggested equation for calculating HPD would require a continuous response option for the HPD item. To preserve consistency with the national surveys, we prefer to retain the IQOS consumption question as proposed and to characterize use patterns by reporting on frequency (days used) and amount (number of *HeatSticks* used on days used) as two separate measures. Does FDA agree with our request to use two separate measures to describe use of IQOS to remain aligned with other national surveys and not incorporate the one-item metric?"

FDA replied to our question on December 17, 2020 saying that they agreed with our request to maintain the two separate outcome measures: *HeatSticks* per day on days used with categorical response options and number of days used in the past 30 days. Therefore, we will maintain the original plan to align with existing national surveys of underage populations by

providing categorical response options for the *HeatSticks* per day on days used question. We will not include the one-item metric.

FDA REQUEST IV-2

In the revised protocol describing the UTUS study (Table 6, Appendix F), polytobacco use of current IQOS users is reported at the level of other combusted and non-combusted products but does not explicitly describe dual use of *IQOS* and cigarettes.

a. Report dual use of cigarettes and *IQOS* specifically in the categories of 'Tobacco Use History'.

Detailed information on dual use of cigarettes and *IQOS* allows the FDA to better compare youth *IQOS* users to youth cigarette smokers.

RESPONSE

IV-2: We have revised Section 5-Objective 4 of the "Estimation of Awareness and Use of IQOS® among Underage Individuals" RAP (Appendix F) to include percentages of respondents who used both IQOS® and cigarettes (regardless of other tobacco product use). We have revised Table 6 of the "Estimation of Awareness and Use of IQOS®" RAP to include use of both IQOS® and cigarettes as an outcome.

FDA REQUEST IV-3

In Table 7 of the revised UTUS Study protocol describing demographics of current *IQOS* users (page 30, Appendix F):

a. Stratify by combusted cigarette history (as either Never- and Ever-smokers). Describe the proportion of current *IQOS* users who are daily *IQOS* users, and the proportion who are daily cigarette smokers as simple demographic variables.

This allows the FDA better understand *IQOS'* appeal among underage populations.

RESPONSE

IV-3: We have updated Section 7-Data Analysis and Table 7 of the "Estimation of Awareness and Use of IQOS®" RAP to include History of Cigarette Smoking (Never and Ever), Daily

IQOS® use (Yes or No), and Daily Cigarette Smoking (Yes or No) as demographic variables. We also expanded Table 7 to stratify demographic information (sex, age, race/ethnicity, daily IQOS® use, daily cigarette smoking) by history of cigarette smoking (Never and Ever).

Revised Appendix included with the Responses to Request IV

- Appendix F – Research Analysis Plan, Estimation of Awareness and Use of IQOS® Among Underage Individuals