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RESPONSE TO NOVEMBER 22, 2017 INFORMATION REQUEST for PM0000424-PM0000426

December 22, 2017

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FDA QUESTION 1:

Section 3.1, "Product Description and Formulation," pages 7-8, describe the Polylactic Acid (PLA) Filter and Mouth Piece Filter (MPF) of the Heatstick. The PLA filter function is given as "…condenses the water in vapor phase, thus reducing the perceived aerosol temperature as well as maintaining the mouth piece filter (MPF) integrity." The MPF is described as "…a cellulose acetate filter designed to act as a mouth piece similar to the filter of a conventional cigarette." No information is provided regarding the filtration characteristics and functions of the MPF and PLA filters. For the MPF and PLA filters, provide the target specifications and upper and lower range limits of filter efficiency (%), pressure drop (mm H_2O), and ventilation (%). In addition, provide test data (i.e. measured values of design parameters) for these three parameters, including test protocols, quantitative acceptance criteria, and a summary of the results. If the testing was performed according to national or international standards, identify the standards and state what deviations, if any, from the standards occurred. This information is necessary to fully characterize the performance characteristics of the product.

PMP S.A. RESPONSE:

Background: Filtration characteristics and functions of the MPF and PLA filters (CMC sections 3.1 & 3.2.2)

In conventional cigarettes the smoke deliveries are controlled through various design components including filter efficiency, and ventilation. In THS 2.2, neither filter efficiency and nor ventilation are design parameters to control aerosol deliveries (product performance); reduced formation is achieved due to heating rather than burning of the tobacco.

The Filters (Mouth Piece Filter, MPF and Poly Lactic Acid, PLA) of THS 2.2 were designed to mimic a similar look and comfort feel of a conventional cigarette filter. During the design of the THS 2.2, the consumer acceptability of the product was considered as part of the verification of the design. Including:

- Acceptable resistance to draw of the THS 2.2 system,
- Comfortable perceived aerosol temperature (through condensation of the water in vapor phase in the PLA)
- Familiar sensation of use with the MPF, to mimic the sensation of the filter of a conventional cigarette.

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Filter Efficiency

In conventional cigarettes, filter efficiency controls the deliveries and is measured and expressed through the reduction of nicotine in the smoke. For THS 2.2, filter efficiency for the two components has not been performed and no target specifications or manufacturing limits are considered for the filter efficiency (%) of the MPF and PLA, therefore, the filter efficiency is not a design parameter.

The performance of the THS 2.2 is evaluated through the aerosol composition of the finished goods; the influence of the filtration characteristics of PLA and MPF are not primary in their contribution to the reduced formation.

(b) (4)

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(b) (4)

Results

For the batches of PMI product provided in Section 3.3, the values of the RTD of the PLA and MPF filter rods can be found in Table 2.

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Table 2 Production batch record results of RTD from PLA and MPF filter rods for Batches in Section 3.3

Product	Batch # PMI	Batch # PMMTB	RTD of PLA Rod	RTD of MPF Rod
Regular Dorado II Ron	B-25904	41-2397948	Appendix SRP1_Q01-A1	Appendix SRP1_Q01-A5
	B-25905	41-2397950	Appendix SRP1_Q01-A1	Appendix SRP1_Q01-A5
	B-25906	41-2382704	Appendix SRP1_Q01-A1	Appendix SRP1_Q01-A5
Menthol 1 Dorado I Mint Vinny	B-25900	41-2381531	Appendix SRP1_Q01-A2	Appendix SRP1_Q01-A5
	B-25901	41-2374718	Appendix SRP1_Q01-A2	Appendix SRP1_Q01-A5
	B-25902	41-2379112	Appendix SRP1_Q01-A3	Appendix SRP1_Q01-A6
Menthol 2 Dorado I Mint Vinny	B-31061	41-2572271	Appendix SRP1_Q01-A4	Appendix SRP1_Q01-A7
	B-31062	41-2572272	Appendix SRP1_Q01-A4	Appendix SRP1_Q01-A7
	B-31063	41-2572273	Appendix SRP1_Q01-A4	Appendix SRP1_Q01-A7

Ventilation

In conventional cigarettes ventilation is used for dilution of the smoke and to adjust the smoke to air ratio. In THS 2.2 there is no dilution of the aerosol through the filter in the product design, therefore ventilation is not a design parameter for the THS 2.2 system. Consequently, there are no target specifications and upper and lower range limits for ventilation in the product, including in the semi-finished products of MPF and PLA.

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FDA QUESTION 2:

Report 15006 THS SR Part 3.pdf contains several amendment attachments with redacted sections:

a. Amendment 9 Attachment 1 (page 66) – section 7 STUDYANA\72 PRECLIN\InVivo\90dReg\Report
b. Amendment 17 Attachment 1 (pages 128-129) – section 7 STUDYANA\72 PRECLIN\InVivo\90dMenth\Report
c. Amendment 26 Attachment 1 (pages 192-193) – section 7 STUDYANA\72 PRECLIN\InVivo\AJ MOUSE\Report
d. Amendment 26 Attachment 1 (pages 197) – section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW

To complete a thorough review of the studies, all documents need to be unredacted. Provide an unredacted copy of 15006 THS SR Part 3.pdf.

PMP S.A. RESPONSE:

The redacted versions of the amendments were distributed to the Test Sites in the study 15006. [In OECD GLP terms, a Test Site is defined as a laboratory where parts of the study are executed under control of the Test Facility where the Study Director resides. Amendments relevant to the Test Site's work are distributed by the Study Director to the Test Site, and may be redacted if the Test Site doesn't need to see all information in an amendment.] However, in the documents submitted in the original MRTP applications, the non-redacted copies were also included in the respective amendments:

a. Refer to page 64 for the non-redacted version - in Amendment 9 Attachment 1
b. Refer to pages 119-120 for the non-redacted version – in Amendment 17 Attachment 1
c. Refer to page 190 for the non-redacted version - Amendment 26 Attachment 1
d. Refer to page 190 for the non-redacted version - Amendment 26 Attachment 1 (Amendment 26 was sent to two Test Sites and therefore there are two redacted copies in the same document; the non-redacted copy is in page 190)

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FDA QUESTION 3:

Studies 15006, 15025, 15020, and 15015 contain urine or plasma biomarkers of exposure levels measured by Analytisch-Biologisches Forschungslabor (ABF). The data are contained in the following reports:

- 15006 THS SR Part 4.pdf (pages 836-840) – section 7 STUDYANA\72 PRECLIN\InVivo\90dReg\Report
- 15025 THS SR Part 4.pdf (pages 3028-3031) – section 7 STUDYANA\72 PRECLIN\InVivo\90dMenth\Report
- 15020 THS SR Part 6.pdf (pages 4-19) – section 7 STUDYANA\72 PRECLIN\InVivo\AJ MOUSE\Report
- 15015_CVD_Resp_ApoE_SW_SR_Part 7.pdf (pages 12-20) – section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW

However, the data are blinded. For example, 15006 THS SR Part 4.pdf (pages 836-840) contains a column with a number indicating the exposure group (column 3) and a column with the week (column 5), however sex is not indicated.

Provide the table columns indicating:

a. Exposure group (e.g., sham, 3R4F low, medium, or high, IXMIS, 2XMIS, THS2.2 low, medium or high, or if they are part of the recovery section)
b. Sample collection time point (e.g., day 6, week 8)
c. Sex

This complete un-blinded information is necessary for a full evaluation of the data.

PMP S.A. RESPONSE:

To address the above question, we are providing the cross-reference tables for the following studies:

- 15006 : SRP1_Q03-A1_15006-XReference-list
- 15025 : SRP1_Q03-A2_15025-XReference-list
- 15020 : SRP1_Q03-A3_15020-XReference-list
- 15015 : SRP1_Q03-A4_15015-XReference-list

These tables contain UAN (unique animal number) and CAN (codified animal number). The UAN numbering system consists of 7 digits which contains the information of each specific animal: The first 3 digits refers to the group number (this information is also provided in the Study Plan/Reports; the fourth digit refers to the gender (i.e. 1=male, 2=female); last three digits refer to the specific animal in the group.

For example:

UAN 1011001: Animal belongs to group 101

UAN 1011001: The digit 1 indicates the gender (i.e. male)

UAN 1011001: These digits identify the specific animal in the group.

The CAN consists of 6 digits and it is provided by the *in vivo* LIMS – Provantis to a specific animal upon implantation of the microchip; each animal will have both numbers UAN and CAN (i.e. one CAN will have a corresponding unique UAN). The first digit of the CAN will be always a 9 and it will be followed by the gender specific digit (i.e 1=male, 2=female) the last 4 digits will be assigned by the in vivo LIMS – Provantis. This CAN number is used when blinding of the animals is deemed necessary in order to avoid any potential bias that could arise during the analysis of a specific endpoint and therefore, CAN is provided to the Test Sites. Once the results are back from the Test Sites, the CAN numbers are translated to UAN for further data analysis.

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FDA QUESTION 4:

Studies 15006, 15025, 1502, and 15015 contain biomarkers in the bronchioalveolar lavage fluid (BALF) measured by Myriad RBM using RodentMAP. The data are contained in the following reports:

- 15006 THS SR Part 6.pdf – section 7 STUDYANA\72 PRECLIN\InVivo\90dReg\Report
- 15025 THS SR Part 6.pdf – section 7 STUDYANA\72 PRECLIN\InVivo\90dMenth\Report
- 15020 THS SR Part 7.pdf – section 7 STUDYANA\72 PRECLIN\InVivo\AJ MOUSE\Report
- 15015_CVD_Resp_ApoE_SW_SR_Part 6.pdf – section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW

However, the data are blinded. Provide the table columns indicating:

a. Exposure group (e.g., sham, 3R4F low, medium, or high, IXMIS, 2XMIS, THS2.2 low, medium or high, or if they are part of the recovery section)
b. Sample collection time point (e.g., day 6, week 8)
c. Sex

In addition, for study 15015, only consolidated results and statistical tables are provided in 15015_CVD_Resp_ApoE_SW_SR_Part 6.pdf; a report from Myriad RBM was not included. Provide the Myriad RBM report with the data un-blinded.

Providing the complete and un-blinded information for these studies is necessary for a full evaluation of the data.

PMP S.A. RESPONSE:

To address the above question, we are providing the cross-reference tables for the following studies:

- 15006 : SRP1_Q03-A1_15006-XReference-list
- 15025 : SRP1_Q03-A2_15025-XReference-list
- 15020 : SRP1_Q03-A3_15020-XReference-list
- 15015 : SRP1_Q03-A4_15015-XReference-list

These tables contain UAN (unique animal number) and CAN (codified animal number). The UAN numbering system consists of 7 digits which contains the information of each specific animal: The first 3 digits refers to the group number (this information is also provided in the Study Plan/Reports; the fourth digit refers to the gender (i.e. 1=male, 2=female); last three digits refer to the specific animal in the group.

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For example:

UAN 1011001: Animal belongs to group 101

UAN 1011001: The digit 1 indicates the gender (i.e. male)

UAN 1011001: These digits identify the specific animal in the group.

The CAN consists of 6 digits and it is provided by the *in vivo* LIMS – Provantis to a specific animal upon implantation of the microchip; each animal will have both numbers UAN and CAN (i.e. one CAN will have a corresponding unique UAN). The first digit of the CAN will be always a 9 and it will be followed by the gender specific digit (i.e. 1=male, 2=female) the last 4 digits will be assigned by the in vivo LIMS – Provantis. This CAN number is used when blinding of the animals is deemed necessary in order to avoid any potential bias that could arise during the analysis of a specific endpoint and therefore, CAN is provided to the Test Sites. Once the results are back from the Test Sites, the CAN numbers are translated to UAN for further data analysis.

With regards to Study 15015, the Test Site Myriad RBM provided the data output in form of a data spreadsheet. This was already included in 15015_CVD_Resp_ApoE_SW_SR_Part 6.pdf page 373 – 393, which was submitted in the original MRTP Applications (section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW).

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FDA QUESTION 5:

Page 166 of 15006 THS SR Part 3.pdf in section 7 STUDYANA\72 PRECLIN\InVivo\90dReg\Report indicates that carbon monoxide (CO) levels in the filtered air of the inhalation chambers reached 10 ppm on 21 June 2013. The increase in CO levels resulted in Carboxyhemoglobin (HbCO) measurements on health check animals. The HbCO results were not submitted for the health check animals. Provide all analytical measurements including HbCO and health reports for the health check animals exposed to high levels of CO, and provide these data un-blinded.

PMP S.A. RESPONSE:

This event was captured in the Study Amendment number 26 and further described on page 166 of 15006 THS SR Part 3. This environmental problem (haze) occurred during the Recovery Phase (non-exposure) and blood was collected from animals belonging to health check group as a representative measurement. COHb data from health check animals can be found in attachment SRP1_Q05-A1_15006-HbCO-data, and their respective health reports in attachment SRP1_Q05-A2_15006-HealthCheckAnimals.

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FDA QUESTION 6:

Report 15025 THS SR Part 4.pdf in section 7 STUDYANA\72 PRECLIN\InVivo\90dMenth\Report lists the units for plasma menthol and total p-menthane-3, 8-diol (MI) as µg/mL in Table 1 on page 5. On page 3029 of the same report, the units for menthol and MI in the table are ng/mL. Clarify which are the correct units for menthol and MI in plasma.

PMP S.A. RESPONSE:

Information in Table 1 provided by the Test Site corresponds to the information on the respective methods for plasma menthol and total p-menthane-3, 8-diol (MI). The reported concentration unit depends on the actual exposure dose and therefore, the concentration units for Menthol and MI are ng/ml as indicated.

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FDA QUESTION 7:

Report 15015_CVD_Resp_ApoE_SW_SR_Part 1.pdf in section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW describes the results for the 8-month switching study in ApoE$^{-/-}$ mice (15015). Descriptive statistics were provided for some endpoints including body weight, hematology and clinical chemistry, but not others. Provide descriptive statistics for all endpoints including the flowing:

a. Carboxyhemoglobin (% HbCO)
b. Plasma nicotine and cotinine concentration (ng/mL)
c. Urine nicotine and nicotine metabolite concentrations (µmol/mL)
d. Urine biomarkers of exposure and oxidative stress (HPMA, NNAL, SMPA, CEMA, 8-OHdG, MDA, 4-HNE, t-PGMD, t-PDEM, 2,3-d8-i-PGF2a, 2,3-d-TXB2, 11-dh-TXB2, PGF2a, 8i-PGF2a, LTE4, and 12-HETE) as a mass unit per volume (e.g., µg/mL or ng/mL))
e. Biomarkers in BALF and plasma.

PMP S.A. RESPONSE:

In response to the above question, we are providing the requested descriptive statistics related to the 8-month switching study in ApoE-/- mice (15015). The descriptive statistics were computed separately for each endpoint, study group, and study period. More specifically, Table 3 below provides a list of endpoints contained in each of the files.

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Table 3 List of endpoints

File name	Endpoints or group of endpoints
SRP1_Q07-A1_DescStatsBW.csv	Body weight
SRP1_Q07-A2_DescStats.csv	Carboxyhemoglobin
	Clinical chemistry
	Hematology
	Lung functions and volume
	Plaque size
	Biomarkers of exposure in urine and plasma
	Various cell counts in BALF
	MMP activity in BALF
	Biomarkers in BALF and serum
	Oxysterols
SRP1_Q07-A3_DescStats_Atherotech.csv	Lipoproteins
SRP1_Q07-A4_DescStats_Histo.csv	Morphometry and histopathological related endpoints
SRP1_Q07-A5_DescStats_NictMetSG.csv	Urine nicotine metabolites and urine volume

The endpoints specifically requested can be found in the files described below:

a. Carboxyhemoglobin (% HbCO): SRP1_Q07-A2_DescStats.csv

b. Plasma nicotine and cotinine concentration (ng/mL): SRP1_Q07-A2_DescStats.csv

c. Urine nicotine and nicotine metabolite concentrations (µmol/mL): SRP1_Q07-A5_DescStats_NictMetSG.csv

d. Urine biomarkers of exposure and oxidative stress (HPMA, NNAL, SMPA, CEMA, 8-OHdG, MDA, 4-HNE, t-PGMD, t-PDEM, 2,3-d8-i-PGF2a, 2,3-d-TXB2, 11-dh-TXB2, PGF2a, 8i-PGF2a, LTE4, and 12-HETE) as a mass unit per volume (e.g., µg/mL or ng/mL)): SRP1_Q07-A2_DescStats.csv

e. Biomarkers in BALF and plasma: SRP1_Q07-A2_DescStats.csv

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FDA QUESTION 8:

Report 15015_CVD_Resp_ApoE_SW_SR_Part 9.pdf in section 7 STUDYANA\75 SYSTOX\InVivo\ApoE-THS-SW contains data for oxysterols in plasma. However, the data are blinded.

Provide the table columns indicating:

a. Exposure group (e.g. sham, 3R4F, THS2.2, switch, or cessation)
b. Sample collection time point (e.g., 2M, 3M, 6M, or 8M)
c. Sex

PMP S.A. RESPONSE:

In response to the above question, we are providing the un-blinded data table in the requested format: SRP1_Q08-A1_Oxysterols_P15015.

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FDA QUESTION 9:

Report 15015_CVD_Resp_ApoE_SW_SR_Part 1.pdf (page 14) in section 7 STUDYANA\75

SYSTOX\InVivo\ApoE-THS-SW uses the term pMRTP to refer to THS2.2 and to Smar, MD2 from the platform2 line of products used in a previous study. Report 15015_CVD_Resp_ApoE_SW_SR_Part 8.pdf is a phase report from Numira for MicroCT analyses of ApoE-/- mouse aortas. The Numira report refers to the tested devices as pMRTP. Confirm that the pMRTP listed in the Numira report is for THS2.2 and not a different pMRTP.

PMP S.A. RESPONSE:

In response to the above question, we confirm that the test item "pMRTP" referred to in the Numira report is THS2.2.

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FDA QUESTION 10:

All of your PMTAs contain the draft report "Analysis of the EHTP Features with respect to Biomass/Tobacco Combustion" by Dr. Valerio Cozzani, Professor of Chemical Engineering at the University of Bologna, dated April 4, 2014 (Section A.3.2.1-1). This report is referenced throughout the applications as a key source for statements that no combustion occurs in the new products. Provide the final version of this report for FDA's reference in evaluating this topic.

PMP S.A. RESPONSE:

The final version of the report "Analysis of the EHTP Features with respect to Biomass/Tobacco Combustion" by Prof. Dr. Valerio Cozzani, Professor of Chemical Engineering at the University of Bologna, dated May 8, 2014 is provided in the replacement of the draft report included in the original submission and is provided in attachment SRP1_Q10-A1_PMI_Report_Combustion.

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FDA QUESTION 11:

In the Executive Summary, Section 2.7 (p.151), you provide estimates for IQOS product use from a Japanese Market Research Panel of adult IQOS purchasers. We could not locate any further information about this study in the application. Provide detailed information about the design of this study and all results or data from this study for the use of IQOS and other tobacco products.

This information helps FDA better understand post-marketing IQOS use patterns.

PMP S.A. RESPONSE:

Detailed information about the design of the Japanese Market Research Panel of adult IQOS owners can be found in Appendix SRP1_Q11-A1_MarketResearch-JP_StudyDesign.

Additional study results could be found in Appendix SRP1_Q11-A2_MarketResearch-JP_StudyReport.

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FDA QUESTION 12:

Section 2.7 (p.154) also reports some findings from the Japanese post-market cross-sectional study conducted in September 2016. You previously sent a study report for this survey; however, the report was lacking detailed information about the study population. Provide a more detailed study protocol including information about the source of the study population and recruitment methods. Providing this information helps FDA determine how generalizable these results are to other populations.

PMP S.A. RESPONSE:

Detailed information regarding the study population, including the source of the study population and recruitment methods can be found below.

Sample criteria

Male and female adults 20+ years old recruited living in Japan, from an online panel.

Sample size

2000 adults (38,235 contacts were made to reach the sample size).

Panel recruitment

Several methodologies were used to recruit panelists to the panel, including opt-in email, co-registration, e-newsletter campaigns, traditional banner placements, and social media via both internal and external partner networks. In order to increase the quality of the panel, several panel recruiting 3rd parties were used.

Size of the panel

4,570,000 individuals living in Japan.

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Number of contacts

Table 4 below presents the number of contacts that were made to reach the final sample, considering the predefined quotas on age, gender and region.

Table 4 Number of contacts made to get to the final sample

	Male					Female					Total
Area	**20-29**	**30-39**	**40-49**	**50+**	**Total**	**20-29**	**30-39**	**40-49**	**50+**	**Total**	
Hokkaido / Tohoku	631	385	408	865	2289	564	444	545	538	2091	4380
Koshinetsu	586	324	341	414	1665	672	388	355	442	1857	3522
Shutoken	1527	1057	651	832	4067	1435	1222	1220	1141	5018	9085
Chubu	1592	634	559	781	3566	1103	519	586	753	2961	6527
Kansai	1094	430	419	398	2341	1111	819	767	697	3394	5735
Chugoku / Shikoku	445	288	334	372	1439	557	413	391	438	1799	3238
Kyushu	972	620	414	550	2556	947	1018	614	613	3192	5748
Total	6847	3738	3126	4212	17923	6389	4823	4478	4622	20312	38235

Sample recruitment

The number of invites that were needed to be sent out was determined by carrying out a soft/ small launch. For the soft launch, invites were sent out to a random cross-section of the panel, and the response rates for each of the quotas (age/gender/region) were calculated to determine how many invites were required to meet the final quotas.

Starting from the above estimates, the sample was recruited by randomly sent out invites within the quotas.

Quotas and Weighting

No weighting was applied to the data.

Interlocking quotas were set, and met, on gender, age category and area. Those quotas are presented in Table 5 below.

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Table 5 Sampling by gender, age category and area

Area	Male					Female					Total
	20-29	30-39	40-49	50+	Total	20-29	30-39	40-49	50+	Total	
Hokkaido / Tohoku	1.0%	1.2%	1.4%	2.1%	5.5%	0.9%	1.2%	1.4%	2.2%	5.6%	11.1%
Koshinetsu	0.9%	1.1%	1.3%	1.7%	4.9%	0.8%	1.0%	1.2%	1.7%	4.6%	9.4%
Shutoken	2.9%	3.6%	4.3%	4.7%	15.5%	2.7%	3.4%	4.0%	4.6%	14.7%	30.1%
Chubu	1.3%	1.6%	1.9%	2.4%	7.2%	1.2%	1.5%	1.8%	2.4%	6.9%	14.0%
Kansai	1.5%	1.7%	2.2%	2.6%	7.9%	1.5%	1.8%	2.2%	2.8%	8.2%	16.1%
Chugoku / Shikoku	0.8%	0.9%	1.1%	1.5%	4.2%	0.7%	0.9%	1.1%	1.6%	4.2%	8.4%
Kyushu	1.0%	1.2%	1.3%	2.0%	5.3%	1.0%	1.2%	1.4%	2.1%	5.7%	11.0%
Total	9.2%	11.2%	13.2%	16.8%	50.4%	8.8%	10.9%	12.9%	17.2%	49.7%	100.0%

Source: Population data acquired from Japan Statistics Bureau

The seven geographical areas were defined as described in Table 6.

Table 6 Geographical areas definition

Area definition	
Hokkaido / Tohoku	Hokkaido, Aomori, Iwate, Akita, Miyagi, Yamagata, Fukushima
Koshinetsu	Nagano, Yamanashi, Niigata, Gunma, Tochigi, Ibaraki
Shutoken	Tokyo, Saitama, Chiba, Kanagawa
Chubu	Gifu, Shizuoka, Aichi, Mie, Fukui, Ishikawa, Toyama
Kansai	Kyoto, Osaka, Hyogo, Shiga, Nara, Wakayama
Chugoku / Shikoku	Tottori, Shimane, Hiroshima, Okayama, Yamaguchi, Tokushima, Kagawa, Ehime, Kochi
Kyushu	Fukuoka, Saga, Nagasaki, Kumamoto, Miyazaki, Kagoshima, Oita, Okinawa

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FDA QUESTION 13:

In the study report for the Whole Offer Test (WOT), the methods section states that participants were recruited using databases maintained by market research agencies. The report did not provide information about how people became a part of those databases, aside from having an interest in participating in market research studies. Provide a more detailed study protocol, including information about the sources of participants for the market research databases in each country in the WOT as well as the number of subjects who were initially contacted for screening and breakdown of why contacted individuals were not included in the study (e.g., ineligible, not interested). Providing this information would help FDA evaluate the generalizability of the results of the studies concerning the potential public health impact of marketing the products.

PMP S.A. RESPONSE:

Online, telephone, face-to-face/personal interviews, mailing sent to home address, referrals and consent provided given at the end of market research studies were used to populate market research databases. Detailed information regarding the source of recruitment of participants, the methods used to populate market research databases, the number of adult panel members and the number of adult smokers panel members as well as the percentage of participation in the WOT study for each country can be found in Table 7.

The breakdown of why contacted individuals were not included in the study is not available. Reasons for why contacted individuals were not included in the study were likely to be a) the absence of response due to inaccurate contact information, b) lack of interest in the study and c) ineligibility based on inclusion/exclusion criteria.

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Table 7 Whole Offer Test (WOT) Studies - Additional Information on Databases Used for Participants Recruitment

	JAPAN	ITALY	GERMANY	SOUTH KOREA	SWITZERLAND[1]
Recruitment agency	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Year of study conduct	2013	2013	2014	2015	2014
Database admission / registration	Online followed by a telephone.	Online and telephone.	Face-to-face street interview, online, correspondence sent to home address, referrals from existing panel members and approval given at the end of studies.	Personal interview, random digit dialing, online, email, referrals from existing panel members and approval given at the end of studies.	n/a
Number of adult / adult smokers within database	Adults: Approximately 2,100,000 Adult smokers: Approximately 56,000	n/a	Adults: Approximately 5,000 in Hannover, 5,500 in Munich and 6,000 in Dresden. Adult smokers: At least 1,500 in Munich and Hannover and approximately 2,500 in Dresden	Adults: Approximately 320,000 Adult smokers: Approximately 46,000	n/a
Participation rate to WOT studies	Approximately 10% of adult smokers contacted participated in the study.	Between 7% and 10% of adult smokers contacted participated in the study.	Approximately 90% of adult smokers contacted participated in the study (Dresden only). No information available for Munich and Hannover.	Approximately 70% of adult smokers contacted participated in the study.	n/a

[1] No information available for Switzerland. The recruitment agency, Léger Switzerland, went bankrupt a few months after the study completion.

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FDA QUESTION 14:

The study report for the WOT presents the average daily number of conventional cigarettes plus Heatsticks consumed for each study week. These tables do not provide average number of cigarettes per day by study week. Provide the average number of cigarettes per day for each study week, overall and by the IQOS usage categories at week 4, including the "Exclusive Heatstick use" category. Also, provide the mean number of cigarettes per day and total tobacco use per day (i.e., cigarettes plus Heatsticks) stratified by average number of cigarettes per day smoked at baseline and then further stratified by main IQOS use category at week 4. This information helps FDA evaluate how cigarette consumption changed during the observational period and whether the change in cigarette consumption varied by IQOS use pattern.

PMP S.A. RESPONSE:

For each Whole Offer Test (WOT) study, the information about the average number of cigarettes per day for each study week, overall and by the IQOS usage categories at week 4 is included in Appendix SRP1_Q14-A1_WOT-Studies. This appendix also includes information on the "Exclusive *HeatStick* use" category and the mean number of cigarettes per day and total tobacco use per day (i.e., cigarettes plus *HeatSticks*) stratified by average number of cigarettes per day smoked at baseline and then further stratified by main IQOS use category at week 4 for each country.

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FDA QUESTION 15:

The PBA-07 "ths-pba-07-us-table.pdf" document provides data for the change in daily cigarette and total tobacco (i.e., cigarettes plus Heatsticks) consumption by main usage categories of IQOS and for changes in cigarette and total tobacco consumption stratified by average number of cigarettes smoked per day during the baseline period. This document does not provide results for the changes in daily cigarettes per day or daily total tobacco for the "Exclusive Heatstick user" group at week 6 (i.e., uses ≥95% Heatsticks) or for the main IQOS usage categories by average cigarettes per day at baseline. Provide results for the average number of cigarettes per day and total tobacco per day at baseline and week 6 for participants who were "Exclusive Heatstick users" at week 6. Also, provide the results for the changes in average number of cigarettes and total tobacco per day (provide baseline and week 6 data) by average cigarettes smoked at baseline (1-4, 5-10, 11-20, 20-30, and ≥30) and then further stratified by main usage category of IQOS at week 6. These additional results will help FDA assess how IQOS use may influence changes in cigarette consumption.

PMP S.A. RESPONSE:

In response to the above question, we are providing:

- Results for the average number of cigarettes per day and total tobacco per day at baseline and week 6 for participants who were "Exclusive *HeatStick* users" at week 6 in Appendix SRP1_Q15-A1_PMI-PBA07-FAS-ExclHS-W6

- Results for the changes in average number of cigarettes and total tobacco per day (provide baseline and week 6 data) by average cigarettes smoked at baseline (1-4, 5-10, 11-20, 20-30, and ≥30) and then further stratified by main usage category of IQOS at week 6 in Appendix SRP1_Q15-A2_PMI-PBA07-FAS-ByUsageW6

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FDA QUESTION 16:

In the Executive Summary, Section 2.7 (p.151), data provided from a Japanese Market Research Panel of adult IQOS purchasers suggested that 65% of smokers within this panel converted to exclusive IQOS use. In contrast, based on our analysis of the data you provided from the Japanese post-market cross-sectional study conducted in September 2016 discussed in Section 2.7 (p.154), 85% of IQOS users continued to smoke cigarettes in addition to IQOS. Provide an explanation for the discrepancy in findings and any additional information you have on the extent to which Japanese smokers are switching completely to IQOS versus using IQOS in conjunction with conventional cigarettes. This additional context will help FDA understand the population-level impact of IQOS use in Japan and its relevance to the U.S.

PMP S.A. RESPONSE:

PMI has established sizable continuous Market Research Panels of adult IQOS purchasers in many markets including Japan. PMI has also conducted online pilot cross-sectional studies in Japan.

There are several methodological differences between the two studies.

1) Those studies are designed for different purposes
    a. Cross-sectional study is designed to measure prevalence of tobacco and nicotine-containing products within a representative population of adults, at a given point of time.
    b. IQOS Panel is designed to measure IQOS owners' patterns of use behavior over time by length of device ownership.
2) The reference population are different
    a. The population for cross-sectional study is adults of legal age of smoking.
    b. The population for IQOS Panel is registered IQOS owners, of legal age of smoking + one year (e.g. 21 years old in Japan), who started using IQOS in the three weeks preceding the time of recruitment. For information, in Japan, the registration level of IQOS owners is approximately equal to 60% of the sold IQOS devices.
3) Recruitment methodologies are different
    a. Cross sectional study sample is freshly recruited for every survey. It is stratified by gender, age and geography. Quotas are applied for each stratified variable. The measured behavior refers to the time of the survey.

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b. IQOS Panel sample is cumulative, i.e. each month new IQOS owners are recruited as follows. A random sample is extracted from the database of registered IQOS owners. This sample receives an invitation to enroll into the panel. Then, for first 12 weeks of participation in the panel, behavior is collected on a weekly basis. Following this first 12 week-period, behavior is collected on a monthly basis.

4) Number of IQOS users in the sample is different:

   a. Cross-sectional study only captured 45 daily IQOS users out of 46 daily heated tobacco products users and 71 out of 73 daily or weekly users. This leads to high variability of the study results.

   b. IQOS panel accounted for 14,999 IQOS owners (August 2016). This leads to robust study results, higher precision and much lower variability.

5) The definition of usage categories is different

   a. In the cross-sectional study, the 85% combined use refers to the usage of *HeatSticks* and/or cigarettes irrespective of the quantity of *HeatSticks* and cigarettes used.

   b. In the IQOS owner panel, the 65% "exclusive" usage refers to the proportion of IQOS owners who use *HeatSticks* in a proportion equal or greater than 95% of the total quantity of *HeatSticks* and cigarettes used.

6) Study measurement precision of exclusive IQOS use or combined use with cigarettes is dependent on IQOS device purchase date. The cross-sectional study methodology does not collect information about the length of IQOS device ownership (e.g. purchase date). We know that complete switching from cigarettes to IQOS requires an adaptation period which varies from user to user, usually lasting between one and six weeks. Therefore, the absence of the purchase date information does not allow to assess at what stage of the adaptation period each IQOS user is and whether the cross-sectional overrepresented recent IQOS purchasers (e.g. still in the adaptation phase) as opposed to established IQOS users.

7) Cross-sectional study measurement precision of exclusive IQOS use or combined use with cigarettes is also dependent on the time of the survey. Cross-sectional studies can accurately describe patterns of use after the IQOS penetration has stabilized and its geographic concentration is more evenly distributed.

8) Questionnaire structure and usage questions sequence are different and it is difficult to assess how this affects reported behaviors. For example in the cross-sectional study, question about cigarettes always appear first, while in the IQOS panel question about *HeatSticks* is asked first.

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In conclusion, the above-described differences indicate that the patterns of use measured by the two studies cannot be compared. Japanese publicly available data, such as total industry volume and IQOS share of market, indicate that the market research panel of IQOS owners represents quite accurately the switching rates and patterns of use of IQOS in the country. However, a range of post-market studies is important to provide comprehensive data on the effect IQOS may have on the population as a whole and how IQOS is used in real-life.

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FDA QUESTION 17:

The post-market studies conducted in Japan to assess IQOS use patterns, specifically the Japanese Market Research Panel of adult IQOS purchasers and the Japanese cross-sectional study conducted in September 2016, do not specify whether the IQOS products (e.g., model) used in these studies are the same IQOS products in the PMTAs. Confirm whether the IQOS products used by participants in the Japanese post-market studies are the same as the products in the application, and if not, describe any differences. This information allows FDA to determine whether the IQOS product used by participants in the post-market studies is the same product used in the US PBA-07 study and WOT, since differences across products may influence use patterns.

PMP S.A. RESPONSE:

The product codes corresponding to the individual parts (Tobacco Stick and Holder) of THS 2.2, subject of the applications are listed in Section 3.2.1.2 Table 1 of the original MRTP Applications.

In Section 3.2.1.4.3 Table 3 of the original MRTP Applications, the history of changes to the products tested throughout the assessment program, post-performance lock, are described along with corresponding product codes and reference to the comparability documentation included in the applications. Further information on changes and the evolution of the product can be found in appendices A3.2.1-21 and A3.2.1-20 respectively.

As described in Section 3.2.1.4 of the applications, PMI has a Change Management process overseen by a Change Management Board (CMB) to ensure that any changes implemented are assessed with regards to the product performance, safety, and quality, ensuring that the data generated on the proposed product prior to a change remains equally applicable (Comparable) to the product after the change.

Product performance comparability provides a set of acceptance criteria for HPHC levels in the aerosol of THS 2.2, and for its *in vitro* biological activity. These criteria ensure that the performance of THS 2.2 remains unchanged, i.e. remains within the variability of analytical methods and, most importantly, of the tobacco crop over time.

The data provided in Section 2.7, for the post-market studies conducted in Japan to assess IQOS use patterns, specifically the Japanese Market Research Panel of adult IQOS purchasers and the Japanese cross-sectional study conducted in September 2016 is based upon the products available on the Japanese market since the initial launch in 2014 until the data snapshot submitted in the application (data cut off: Q3 2016).

Table 8 shows the product variants available on the market during this period. The information collected from the consumer does not allow us to identify which particular product was used, only

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that the consumer was using IQOS. At any point in time consumers were equally likely to use any of the products on the market during that period.

Table 8 Tobacco Sticks and Devices available on the Japanese Market from Market Launch (2014) until end of Q3 2016.

Product Code	Variant	Release Date*	Discontinuation date*
6AAAD	Regular	July 2014	April 2015
6AAAE (CONS.01991.RD)	Regular	July 2014	April 2015
6AAKX	Regular	April 2015	Current
6AAKY	Regular	April 2015	Current
6AAAH (CONS.02000.RD)	Menthol 2	July 2014	April 2015
6AAKG	Menthol 2	April 2015	Current
6AAKH	Menthol 2	April 2015	Current
6AAAR (CONS.02061.RD)	Menthol 1	October 2014	August 2015
6AAKE	Menthol 1	August 2015	Current
6AAKF	Menthol 1	August 2015	Current
6AAAX (CONS.02695.RD)	Regular	August 2015	December 2015
6AAKJ	Regular	December 2015	Current
6AAKK	Regular	December 2015	Current
DV.000101.RD	Holder	July 2014	March 2015
DV.000174	Holder	March 2015	Current
DV.000180	Holder	March 2015	Current

*PMPSA System date, not local market date

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The products in Table 8 are representative of the products submitted in the application. Whilst the items represented by these product codes are not identical, due to continuous improvement of the product, and manufacturing site differences, they are comparable in their performance. The methodology and acceptance criteria to deem product performance as comparable are described in Appendix A3.2.1-13 included in the original MRTP applications.

(b) (4)

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(b) (4)

In summary, throughout the development, assessment and commercialization of THS 2.2, the assessments of major product changes performed as part of the change management process and listed in Section 3.2.1.4.3 of the original MRTP applications have demonstrated that none of the product changes impacted the product performance, as assessed through the levels of harmful and potentially harmful constituents in the aerosol of THS 2.2 and/or its biological activity as evaluated in in vitro assays.

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FDA QUESTION 18:

In the PMTA05-NOC study, if the participants were randomly assigned to receive Arm 2 or 3, current and former smokers were presented with either a Regular or Menthol package of Heatsticks depending on their stated cigarette smoking preference. Within the menthol variants they received either "Smooth Menthol" or "Fresh Menthol" by random assignment. However, you have not submitted information on perceptions of IQOS, intention to try or use IQOS, or intention to quit cigarette smoking or quit all tobacco use among current and former smokers by their assigned Heatstick type – Regular, "Smooth Menthol," or "Fresh Menthol." This information would assist FDA in evaluating the likelihood of IQOS use for each product. Submit information about perceptions of IQOS, intention to try or use IQOS, or intention to quit cigarette smoking or quit all tobacco use among current and former smokers by whether the participant was assigned to view a Regular, "Smooth Menthol" or "Fresh Menthol" package in Arm 2 or Arm 3.

Never smokers and legal age to 25-year-old never smokers who were randomized to Arm 2 or Arm 3 were presented with the Regular package of Heatsticks. You have not submitted information on perceptions of IQOS and intention to use or try IQOS among never smokers presented with "Smooth Menthol" or "Fresh Menthol" Heatsticks packages. This information would assist FDA in evaluating the likelihood of IQOS use for each product. Submit any information that describes perceptions of IQOS or intention to try or use IQOS among never smokers and legal age to 25 year-old never smokers. Also, submit any bridging information from Regular to the Menthol packages or from one smoker group to never smokers.

PMP S.A. RESPONSE:

Question 18 can be divided into three parts, which we address separately and in order.

PART 1

The first part of Question 18 was as follows:

"In the PMTA05-NOC study, if the participants were randomly assigned to receive Arm 2 or 3, current and former smokers were presented with either a Regular or Menthol package of HeatSticks depending on their stated cigarette smoking preference. Within the menthol pack types they received either "Smooth Menthol" or "Fresh Menthol" by random assignment. However, you have not submitted information on perceptions of IQOS, intention to try or use IQOS, or intention to quit cigarette smoking or quit all tobacco use among current and former smokers by their assigned HeatStick type – Regular, "Smooth Menthol," or "Fresh Menthol." This information

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would assist FDA in evaluating the likelihood of IQOS use for each product. Submit information about perceptions of IQOS, intention to try or use IQOS, or intention to quit cigarette smoking or quit all tobacco use among current and former smokers by whether the participant was assigned to view a Regular, "Smooth Menthol" or "Fresh Menthol" package in Arm 2 or Arm 3."

Response

At the time of the FDA's request, no analyses addressing the information requested had been undertaken. To address the questions raised new analyses were performed. Outlined below are the methods and results of the analyses.

These analyses included the current and former smokers randomized to study arms 2 and 3 in the THS-PMTA-05-NOC-US study. Table 9 below presents the number of subjects assessed by study arm, subject group and *HeatSticks* Pack type.

Abbreviations

Note, in this document we use the following abbreviations throughout:

S-NIQ	Adult Smokers with no Intention to Quit
S-IQ	Adult Smokers with Intention to Quit
FS	Adult Former Smokers
NS	Adult Never Smokers
LA-25 NS	Legal Age to 25 years old Never Smokers
UCL	upper 95% confidence limit
LCL	lower 95% confidence limit
THS	Tobacco Heating System

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Table 9 Number of Subjects by Arm, *HeatSticks* Pack type and Subject Group

	***HeatSticks* Pack type**	**Subject Group**			**Total**
		S-NIQ	S-IQ	FS	
Arm 2	Regular	49	49	54	152
	Smooth Menthol	22	22	22	66
	Fresh Menthol	24	25	17	66
	Total	95	96	93	**284**
Arm 3	Regular	45	58	51	154
	Smooth Menthol	27	15	21	63
	Fresh Menthol	22	23	20	65
	Total	94	96	92	**282**
Arm 2 + 3	Regular	94	107	105	306
	Smooth Menthol	49	37	43	129
	Fresh Menthol	46	48	37	131
	Total	189	192	185	**566**

Outcome Measures included in this analysis

1. **Intent to Use THS**
2. **Risk Perception for THS**
3. **Change in Intention to Quit (ITQ) a. smoking and b. all tobacco**

Statistical Methods

The analyses use a descriptive approach, following that used in the study reports. Study arms 2 and 3 were combined due to the limited sample size at the *HeatSticks* pack variant, by subject group by study arm level (see Table 9), and the similarity of the *HeatSticks* packs presented to subjects in arms 2 and 3. Note, as this was an unplanned analysis, the sample sizes are still limited, even after collapsing across arms and therefore the precision of the estimates are limited.

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Results

The full set of results can be found in SRP1_Q18-A1_PMTA-05-NOC-US-AnalysisTables. The key results are presented below.

Intent to Use THS

There were no clear differences in Intent to Use THS comparing the Regular *HeatSticks* pack type with the two menthol *HeatSticks* pack types, for any of the three subject groups. The data are given in Table 10 below.

Table 10 Positive Intent to Use THS (Very likely / Definitely), by Subject Group and *HeatSticks* Pack type for Study Arms 2 and 3 combined

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ		**(N=94)**	**(N=49)**	**(N=46)**
Try THS	n (%)	29 (30.9)	16 (32.7)	18 (39.1)
	LCL	21.7	19.9	25.1
	UCL	41.2	47.5	54.6
Use THS	n (%)	21 (22.3)	12 (24.5)	12 (26.1)
	LCL	14.4	13.3	14.3
	UCL	32.1	38.9	41.1
S-IQ		**(N=107)**	**(N=37)**	**(N=48)**
Try THS	n (%)	42 (39.3)	17 (45.9)	15 (31.3)
	LCL	30.0	29.5	18.7
	UCL	49.2	63.1	46.3
Use THS	n (%)	30 (28.0)	14 (37.8)	15 (31.3)
	LCL	19.8	22.5	18.7
	UCL	37.5	55.2	46.3

(table continues)

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		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
FS		**(N=105)**	**(N=43)**	**(N=37)**
Try THS	n (%)	5 (4.8)	3 (7.0)	3 (8.1)
	LCL	1.6	1.5	1.7
	UCL	10.8	19.1	21.9
Use THS	n (%)	3 (2.9)	0	2 (5.4)
	LCL	0.6	0.0	0.7
	UCL	8.1	8.2	18.2

n = number of subjects with a positive intention to use or try THS.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.1.1a

Perceived Health Risk

There were no clear differences in Perceived Health Risk of THS comparing the Regular *HeatSticks* pack type with the two menthol *HeatSticks* pack types, within S-NIQ and S-IQ. The data are given in Table 11 below.

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Table 11 Mean Perceived Health Risk of THS, by Subject Group and *HeatSticks* Pack type for Study Arms 2 and 3 combined

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ	N	94	49	46
	mean	48.3	45.1	47.0
	LCL	44.0	39.1	40.5
	UCL	52.7	51.2	53.4
S-IQ	N	107	37	48
	mean	48.1	44.7	47.8
	LCL	43.3	36.9	41.5
	UCL	52.9	52.6	54.0
FS	N	105	43	37
	mean	60.7	51.9	57.6
	LCL	55.7	43.7	48.0
	UCL	65.7	60.0	67.1

n = number of subjects with an evaluable Perceived Health Risk score.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.3.1a

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Perceived Addiction Risk

There were no clear differences in Perceived Addiction Risk of THS comparing the Regular *HeatSticks* pack type with the two menthol *HeatSticks* pack types, within S-NIQ and S-IQ. The data provide provisional evidence that Perceived Addiction Risk of THS was higher for Regular than for Smooth Menthol *HeatSticks* pack within FS (see Table 12 below). These results are consistent with those for Perceived Health Risk of THS in Table 11.

Table 12 Mean Perceived Addiction Risk of THS, by Subject Group and *HeatSticks* Pack type for Arms 2 and 3 combined

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ	N	94	49	46
	mean	49.0	43.0	49.8
	LCL	43.5	35.0	41.4
	UCL	54.5	50.9	58.1
S-IQ	N	107	37	48
	mean	52.9	44.6	47.7
	LCL	47.5	33.9	37.9
	UCL	58.2	55.4	57.5
FS	N	105	43	37
	mean	64.7	47.2	57.3
	LCL	59.2	37.7	46.2
	UCL	70.2	56.7	68.4

n = the number of subjects with an evaluable Perceived Addiction Risk score.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.3.2a

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Change in Intention to Quit Smoking and all Tobacco Use THS

There were no differences in the Intention to Quit (either smoking or all tobacco) by pack type, as shown in Table 13 below.

Table 13 Change in Intention to Quit smoking and All Tobacco (% Post-Exposure - % Pre-Exposure), within S-IQ, for Study Arms 2 and 3 combined

	HEATSTICKS PACK TYPE		
	Regular	**Smooth Menthol**	**Fresh Menthol**
	(N=107)	**(N=37)**	**(N=48)**
Smoking	**-3.7%**	**-5.4%**	**-6.3%**
All Tobacco	**0.0%**	**0.0%**	**0.0%**

N = number of subjects within each *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Tables 15.2.2.4.3a and 15.2.2.4.4a
Note: negative signs indicate a decrease in the post-exposure intention to quit relative to pre-exposure values (i.e. baseline)

PART 2

The second part of Question 18 was as follows:

"Never smokers and legal age to 25-year-old never smokers who were randomized to Arm 2 or Arm 3 were presented with the Regular package of Heatsticks. You have not submitted information on perceptions of IQOS and intention to use or try IQOS among never smokers presented with "Smooth Menthol" or "Fresh Menthol" Heatsticks packages. This information would assist FDA in evaluating the likelihood of IQOS use for each product. Submit any information that describes perceptions of IQOS or intention to try or use IQOS among never smokers and legal age to 25-year-old never smokers."

Response

NS and LA-25 NS who were randomized to Arm 2 or Arm 3 were *only* presented with the Regular pack of *HeatSticks*, i.e. they were not presented with "Smooth Menthol" or "Fresh Menthol" *HeatSticks* packs. The rationale for this aspect of the study design was that the Regular pack of *HeatSticks* would be the type NS would be most likely to see in a real world situation. This assumption is based on the fact that regular (non-menthol) cigarettes comprise approximately a third of the cigarette market in the United States (NSDUH Report, Recent Trends in Menthol Use, 2011).

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PART 3

The third part of Question 18 was as follows:

"Also, submit any bridging information from Regular to the Menthol packages or from one smoker group to never smokers."

Response

The above analyses indicate that there were no clear differences between exposure to the Regular *HeatSticks* pack compared to the Smooth Menthol or Fresh Menthol *HeatSticks* packs in terms of Intent to Use and Change in Intention to Quit. However, our data provides provisional evidence that Perceived Addiction Risk was higher for the *HeatSticks* Regular pack compared to the *HeatSticks* Smooth menthol pack within FS. A similar effect might be expected within never smokers. However, given the small NS in these analyses, this is speculative. To aid the FDA's consideration of this issue, below we provide tables (Table 14, Table 15, and Table 16) which present the data comparing Regular, Smooth Menthol and Fresh Menthol packs for all study groups.

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Table 14 **Intent to Use (Very likely / Definitely), by Subject Group and *HeatSticks* Pack type for Arms 2 and 3 combined**

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ		**(N=94)**	**(N=49)**	**(N=46)**
Try THS	n (%)	29 (30.9)	16 (32.7)	18 (39.1)
	LCL	21.7	19.9	25.1
	UCL	41.2	47.5	54.6
Use THS	n (%)	21 (22.3)	12 (24.5)	12 (26.1)
	LCL	14.4	13.3	14.3
	UCL	32.1	38.9	41.1
S-IQ		**(N=107)**	**(N=37)**	**(N=48)**
Try THS	n (%)	42 (39.3)	17 (45.9)	15 (31.3)
	LCL	30.0	29.5	18.7
	UCL	49.2	63.1	46.3
Use THS	n (%)	30 (28.0)	14 (37.8)	15 (31.3)
	LCL	19.8	22.5	18.7
	UCL	37.5	55.2	46.3
FS		**(N=105)**	**(N=43)**	**(N=37)**
Try THS	n (%)	5 (4.8)	3 (7.0)	3 (8.1)
	LCL	1.6	1.5	1.7
	UCL	10.8	19.1	21.9
Use THS	n (%)	3 (2.9)	0	2 (5.4)
	LCL	0.6	0.0	0.7
	UCL	8.1	8.2	18.2

(table continues)

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		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
NS		**(N=192)**	**n/a**	**n/a**
Try THS	n (%)	1 (0.5)	n/a	n/a
	LCL	0.0	n/a	n/a
	UCL	2.9	n/a	n/a
Use THS	n (%)	2 (1.0)	n/a	n/a
	LCL	0.1	n/a	n/a
	UCL	3.7	n/a	n/a
LA-25 NS		**(N=195)**	**n/a**	**n/a**
Try THS	n (%)	1 (0.5)	n/a	n/a
	LCL	0.0	n/a	n/a
	UCL	2.8	n/a	n/a
Use THS	n (%)	2 (1.0)	n/a	n/a
	LCL	0.1	n/a	n/a
	UCL	3.7	n/a	n/a

n = number of subjects with a positive Intention to Use or Try THS.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.1.1a

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Table 15 Perceived Health Risk for THS, by Subject Group and Pack type for Study Arms 2 and 3 combined

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ		**(N=94)**	**(N=49)**	**(N=46)**
	n	82	46	40
	mean	48.3	45.1	47.0
	LCL	44.0	39.1	40.5
	UCL	52.7	51.2	53.4
S-IQ		**(N=107)**	**(N=37)**	**(N=48)**
	n	93	34	40
	mean	48.1	44.7	47.8
	LCL	43.3	36.9	41.5
	UCL	52.9	52.6	54.0
FS		**(N=105)**	**(N=43)**	**(N=37)**
	n	85	40	29
	mean	60.7	51.9	57.6
	LCL	55.7	43.7	48.0
	UCL	65.7	60.0	67.1
NS		**(N=192)**	n/a	n/a
	n	168	n/a	n/a
	mean	61.7	n/a	n/a
	LCL	58.3	n/a	n/a
	UCL	65.1	n/a	n/a
LA-25 NS		**(N=195)**	n/a	n/a
	n	190	n/a	n/a
	mean	60.2	n/a	n/a
	LCL	57.4	n/a	n/a
	UCL	62.9	n/a	n/a

n = number of subjects with an evaluable perceived health risk score.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.3.1a

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Table 16 Perceived Addiction Risk for THS, by Subject Group and Pack type for Arms 2 and 3 combined

		HEATSTICKS PACK TYPE		
SUBJECT GROUP		**Regular**	**Smooth Menthol**	**Fresh Menthol**
S-NIQ		**(N=94)**	**(N=49)**	**(N=46)**
	n	84	41	42
	mean	49.0	43.0	49.8
	LCL	43.5	35.0	41.4
	UCL	54.5	50.9	58.1
S-IQ		**(N=107)**	**(N=37)**	**(N=48)**
	n	94	34	40
	mean	52.9	44.6	47.7
	LCL	47.5	33.9	37.9
	UCL	58.2	55.4	57.5
FS		**(N=105)**	**(N=43)**	**(N=37)**
	n	95	41	33
	mean	64.7	47.2	57.3
	LCL	59.2	37.7	46.2
	UCL	70.2	56.7	68.4
NS		**(N=192)**	n/a	n/a
	n	171	n/a	n/a
	mean	66.2	n/a	n/a
	LCL	62.0	n/a	n/a
	UCL	70.3	n/a	n/a
LA-25 NS		**(N=195)**	n/a	n/a
	n	188	n/a	n/a
	mean	63.7	n/a	n/a
	LCL	59.7	n/a	n/a
	UCL	67.7	n/a	n/a

n = number of subjects with an evaluable perceived addiction risk score.
N = number of subjects within each subject group by *HeatSticks* pack type.
Source: THS-PMTA-05-NOC-US Table 15.2.2.3.2a

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FDA QUESTION 19:

In the PMTA05-NOC study, you submitted information about legal age to 25-year old never smokers as well as current and former smokers over age 18. You did not provide any information about perceptions and intention to try or use IQOS among youth under age 18. Information about the expected intention to try and use IQOS and perceptions of IQOS among youth under age 18 would help FDA understand the likelihood of youth initiated use of IQOS. Submit any available information that bridges the information on these groups to youth under age 18.

PMP S.A. RESPONSE:

In the meeting between the Center for Tobacco Products and representatives of Philip Morris International held on September 5, 2013, SNT: TC000737, questions concerning studies among youth under age 18 were addressed. More specifically, the following questions were asked as part of its meeting request dated June 11, 2013.

*"**PBA Program Studies among Minors***

The Draft Guidance suggests assessing the likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product[2]. PMI internal policy prohibits conducting any study of tobacco products in minors[3]. However, PMI believes that postmarket studies conducted by qualified third parties could provide the contemplated information on initiation potential among minors. If FDA considers that premarket studies involving minors are necessary and directs MRTP applicants to undertake such studies, PMI will agree to adapt the design of the relevant PBA studies and seek appropriate third-parties for governance and execution.

1. *Does CTP consider that data from premarket studies involving minors are necessary to support an MRTP application?*
2. *If so, does CTP consider it appropriate for PMI to utilize independent third party research organizations to implement such studies?*
3. *Can CTP provide any further specific direction on the design and conduct of such studies in addition to what PMI has proposed for adult populations?"*

[2] *See* Draft Guidance at page 20.

[3] Although PMI has an appropriate basis to comment on public data regarding youth smoking

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In the official Meeting Minutes, issued on November 8, 2013, the following summary of the discussion is reported.

Question 1

Does CTP consider that data from premarket studies involving minors are necessary to support an MRTP application?

FDA Response:

FDA does not believe that it is necessary for applicants to conduct research with non-adult populations. However, FDA recommends that applicants provide information about the likely impact that marketing a product as modified risk may have on non-adults and their tobacco use behavior. This information may be inferred from studies with other similar populations, such as young adults.

Meeting Discussion:

PMI accepted the topic as presented by FDA in the preliminary comments. No additional discussion occurred.

Question 1(a)

If so, does CTP consider it appropriate for PMI to utilize independent third party research organizations to implement such studies?

FDA Response:

At this time, FDA makes no recommendations regarding the use of independent third party research organizations in the conduct of tobacco-related research. FDA recommends that you request a meeting with FDA to discuss plans prior to the conduct of any study involving youth or young adults, whether conducted by PMI or through an independent third party.

Meeting Discussion:

PMI accepted the topic as presented by FDA in the preliminary comments. No additional discussion occurred.

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Question 1(b)

Can CTP provide any further specific direction on the design and conduct of such studies in addition to what PMI has proposed for adult populations?

FDA Response:

FDA makes no specific recommendations regarding the design and conduct of such studies. As mentioned above, FDA recommends that you request a meeting with FDA to discuss plans prior to conduct any study involving youth or young adults.

Meeting Discussion:

PMI accepted the topic as presented by FDA in the preliminary comments. No additional discussion occurred.

In view of the above, PMI did not conducted any study including youth under age 18 for its submitted MRTPAs. However, as recommended by the FDA, PMI included groups of legal age to 25-year old never smokers, the closest age cohort.

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FDA QUESTION 20:

In the PBA-07 study, total tobacco consumption was assessed over the study period and included Heatsticks and conventional cigarettes. Provide information you possess about how an estimate of total tobacco consumption that includes Heatsticks, conventional cigarettes, e-cigarettes, as well as cigars, cigarillos, and smokeless tobacco changed over the 6 week study period. This information would help FDA evaluate the likelihood that use of IQOS reduces total consumption of all tobacco products.

PMP S.A. RESPONSE:

In THS-PBA-07-US study, participants self-reported stick-by-stick consumption of *HeatSticks* and cigarettes over the study period. Participants also self-reported the usage of e-cigarettes, nicotine replacement therapies (NRTs) as well as cigars, cigarillos, and smokeless tobacco on a daily basis over the study period. Participants were requested to self-report on a daily basis whether they use e-cigarettes, NRTs as well as cigars, cigarillos, and smokeless tobacco using a [Yes/No] answer. They were, however, not requested to enter any quantity related to the use of those products. In view of those differences, PMI does not think it is appropriate to combine *HeatSticks* and cigarettes data with e-cigarettes, NRTs as well as cigars, cigarillos, and smokeless tobacco data to estimate the total consumption of all tobacco products. Information on the daily consumption of those products can be found in Section 7.3.2 of the original MRTP applications, more specifically in Table 20 (page 101 of 274) of the THS-PBA-07-US Study Report.

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FDA QUESTION 21:

On page 28 of the document title "PHIM Simulation Sensitivity Report", Section 7.4, you state that Version 4.0 of the Population Health Impact Model (PHIM) was used to run a set of simulation and sensitivity analysis. Appendixes 1 to 19 of Section 7.4 include computer outputs of Version 9.4 of the Statistical Analysis System (SAS) based on version 4.0 of the PHIM. The SAS code or any other computer implementation associated with version 4.0 of the PHIM was not submitted. Provide the SAS code/software or any other software application used to generate the results from the PHIM, including any relevant documentation describing how to execute (run) the code/software.

PMP S.A. RESPONSE:

As the SAS code/software application and related documentation cannot be transmitted as individual files via the FDA electronic Submission Gateway, they have been sent by separate courier on a virus-checked CD and are expected to be delivered to CTP today December 22, 2017.

Version 4.0 of the Population Health Impact Model (PHIM) was used for all of the simulations and results. The simulations & sensitivity analysis was run on SAS version 9.4 (PN Lee Statistics and Computing, Ltd.), while the simulations presented in Module 6.5 and 2.7 were run on SAS version 9.2 (PM Products S.A.). General instructions on how to access and run the Population Health Impact Model (PHIM) are described in Table 17.

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Table 17 General instructions on how to access and run the PHIM

SAS Code/ Software	The model is run in SAS therefore we are providing the entire infrastructure (folder structure and files) for the PHIM, which includes: • Model documentation and testing files • SAS Code (including the configuration file) • Fixed data files • Control file templates • Assumption file templates
Other Software Application	Microsoft Word and Microsoft Excel were the only other software that were used in running the PHIM as these were used for output reporting. The f-factor modeling was separate projects that was not integrated into the model, but was used to inform the selection of the effective dose (*f*-value).
Additional Information/Instructions	Below are the general instructions on how to access and run the Population Health Impact Model (PHIM) – executing the SAS programs using the provided fixed data. As well we provide the required folder structure for the model to correctly run and test files that can be executed in a new infrastructure to ensure that the PHIM was installed correctly. Please note that instructions are specific to running the PHIM in SAS 9.2 in the SAS Enterprise platform.

INSTALLATION OF THE PHIM

1. Copy the entire folder structure (including sub-folders and files) into the SAS server.
2. Locate the model documentation and instructions for use in the "**PHIM\Documentation**" Folder.
   a. Users Guide
   b. Operators Manual
   c. Training Manuel
   d. Functional Specifications
3. Important file locations
   a. Configuration file → "**PHIM**" Folder
   b. SAS executable files → "**PHIM\PHIM_SAS\PHIM_SAS_4_0**" (main program: **PHIM_Main.sas**)
   c. Fixed data files → "**PHIM\Fixed**"
   d. Control files → "**PHIM\Control_Files**"
   e. Assumptions file → "**PHIM\Assumptions**"

(table continues)

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RUNNING THE SYSTEM INTERACTIVELY

When running the system from a server, (e.g., SAS Enterprise Guide) SAS must be run in Interactive mode using a user specific configuration file (named: **PHIMConfig.SAS**).

This configuration file defines in the system:

1. To run in Interactive mode
2. The location of the Top Directory ("**PHIM**" folder)
3. The location of the Source file directory ("**PHIM\PHIM_SAS**" folder)
4. The name of the options control file
5. The names of the two STP assumption files
6. The name of the output choices file.

THE CONFIGURATION FILE AND TEST RUN

The default Configuration file "**PHIMConfig.SAS**" is provided with the model. The user must update this file to reflect the details of the location and names of the file included in the specific simulation that they are running.

The default Configuration file was created as a template, where the file locations and file names are specific for running the initial TEST RUN simulation. The TEST RUN is used to ensure that the system is operational. The user executes the TEST RUN and verifies that it ran successfully by checking the output that was generated from the TEST RUN "**PHIM\MAIN_RESULTS\Test_CF1.rtf**" (which is the default name in the control file) against the verification file provided "**PHIM\MAIN RESULTS\Test Verification file Test CF1 rtf**" to ensure that the model was installed correctly with the SAS environment.

(table continues)

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FOUR CONTROL FILES NECESSARY FOR SIMULATION RUN

Within the "**PHIMConfig.SAS**"file the user specifies the name and location of the four control files necessary for each run:

Two Control Files for the system

- Options Control file (**OPT.CSV**),
- Output Choices file (**OUTC.CSV**), and

Two Assumption Files for the system

- Smoking transition probabilities for the Null Component (**STP_NULL.CSV**),
- Smoking transition probabilities for the MRTP Component (**STP_MRTP.CSV**),

For the TEST RUN (above) the control files used are:

- **OPT** = CF-TEST1.csv
- **OUTC** = OUTC_BASIC.csv.

Additionally the assumption files used in the TEST RUN are:

- **STP_NULL** = STP_NULL_WP.csv
- **STP_MRTP** = STP_MRTP_WP.csv.

In running simulations, the user has to define the control files and assumption files according to the scenario of interest. The system will check the existence of the file as well as copying the files to the correct place. If any of these files do not exist an error report will appear and the system will stop.

ERRORS IN SAS CODE

If problems are discovered during the running of the SAS a file is created in the "**PHIM\Check_RESULTS**" Folder with the name: ERRORLEVEL_<n> html, where <n> has the values:

50	if a syntax error has been found in the SAS code
41	where required files have errors or are missing
42	where errors have been found in the control files

The command file will inform the user of the error and then stop. Otherwise the user will be informed that the run has been successful and given the details of the results files.

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FDA QUESTION 22:

On pages 29, 180, 181, 185 of the document title "Simulation and Sensitivity Analysis Report", Section 7.4, you state that all input parameters for the simulation and sensitivity analyses are described more fully in "Notes on data files for PHIM project". We have not located this information. Provide the information, or location of the information, described in the document "Notes on data files for PHIM project" from Section 7.4.

PMP S.A. RESPONSE:

The "Notes on data files for the PHIM project" file (as referred to in Section 7.4) was inadvertently not included in the original MRTP applications. With this response we are providing the requested file as attachment SRP1_Q22-A1_Notes-PHIM-V4-project.

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FDA QUESTION 23:

The applications contain no technical details describing the mathematical/statistical methods used to generate the tobacco use histories via the P-Component of the PHIM. The Weitkunat et al. (2015) manuscript (primary reference provided for the development of the PHIM) states that the P-Component involves a Markov Chain Transition Model to generate individual tobacco histories. However, technical details explaining the implementation of the simulation methods associated with the P-Component of the PHIM are not included in the publication and were not submitted with the applications. For example, the mathematical formulation driving the dynamic of the population via the Markov Chain Transitional Model, incorporating the transitional probabilities, is not discussed in Weitkunat et al. or the submission. Provide information on the mathematical and computational structure of the P-Component of the PHIM. This could be documentation describing how the P-Component generates the tobacco use histories - under the "NULL" and "MRTP" scenarios - via the Markov Chain Transitional Model over the simulation period including description of any mathematical equations (deterministic or stochastic) for incorporating the tobacco transitional probabilities and other input parameters into the Markov structure.

This information will help FDA understand verification and validation in relation to the PHIM including assumptions associated with input parameters, validity of outputs generated from the model; and mathematical, statistical, and computational structure of the model.

PMP S.A. RESPONSE:

Please find below the technical details and process for implementing the simulation methods associated with P-component:

No formulae are used in the P-Component. Rather an identical process is used for each individual in the simulated population to:

(a) allocate initial age and smoking status,

(b) determine smoking histories in the Null Scenario and

(c) determine smoking histories in the MRTP Scenario.

At each step of the process, the probability, p_i, of an individual being allocated to one of multiple categories ($i = 1, \ldots n$) is known, and the category that the individual is allocated to is determined by a random number in the range (0, 1). Thus, for example, given probabilities p_1, p_2, p_3, ...p_n, where the probabilities sum to 1, a random number selected which is less than p_1 will allocate the individual to the first category, one which is p_1 or greater but is less than $p_1 + p_2$ will allocate the

individual to the second category, one which is $p_1 + p_2$ or greater but is less than $p_1 + p_2 + p_3$ will allocate the individual to the third category, and so on.

For example, if, for the given country, year, sex and age group, the current smoking prevalence is 0.23, the former smoking prevalence is 0.32, so that the never smoking prevalence is therefore 1 – 0.32 – 0.23 = 0.45, choosing a random number less than 0.23 will define the individual's initial status to be a current smoker, one in the range 0.23 to less than 0.23 + 0.32 = 0.55 will define a former smoker, and one of 0.55 or greater will define a never smoker.

Similarly if, in the MRTP Scenario, an individual at a given time point during follow-up is a current CC smoker, and has assumed probabilities of switching to MRTP, switching to dual use or quitting in the defined period of, respectively, 0.002, 0.005 or 0.003, the individual's probability of remaining a current CC smoker is estimated by subtraction as 0.990. The individual's smoking status at the next time point during follow-up will then be determined by whether the selected random number is less than 0.002 (becomes a current MRTP user), is in the range 0.002 to less than 0.007 (becomes a current dual user), in the range 0.007 to less than 0.010 (becomes a former user), or is 0.010 or greater (stays a current CC smoker).

Initial age and smoking status

This step requires access to files holding data by five year age group (10-14 up to 75-79) for the given baseline year on population, prevalence of current and of former CC smokers, and time quit for former smokers. For each individual in the simulated populations, which are identical for the Null and MRTP Scenarios, random numbers are used to allocate in turn five year age group, age within age group (assuming a uniform distribution), CC smoking status (never, current, former) and, for former smokers, grouped time of quit, and years quit within group (again, assuming a uniform distribution).

Note that the process described, when applied to determining smoking histories, is a modified version of a Markov chain, as the transition probabilities may depend on the individual's past history, and not just on the individual's current smoking status. See Table 18 for further clarification.

Determining individual smoking histories in the Null Scenario

There are three smoking groups in the Null Scenario; never (N), current (C) and former (F) smoker, and the user must define a set of monthly smoking transition probabilities (STPs), which may vary by age group and period of follow-up, to determine whether the individual stays in the same group or transitions to another. There are three STPs; initiation (P_{NC}), quitting (P_{CF}) and re-initiation (P_{FC}), the first subscript being the smoking group switched from, and the second the group switched to, Double changes in an interval are not allowed. PHIM also allows the user to define a factor (F_2) by which P_{CF} may be multiplied for someone who has previously quit, and another factor (F_3), by which P_{CF} may be multiplied for a short-term quitter, the user being able to define short-term.

Where the follow-up interval is a month, these STPs, together with random numbers, are used directly to determine whether the individual remains in the same smoking group or transitions to another. Thus, for example, initiation will occur in a never smoker if the selected random number (in the range 0 to 1) is less than or equal to the value of P_{NC} that is relevant to the given age group and follow-up period.

Where the follow-up interval is longer than a month, a revised set of STPs suitable for the extended period is created from the initial set, taking into account that a double change of smoking status is not allowed in the extended period, and the possibility that the monthly STPs may change within that period. This revised set of STPs is then used as in the previous paragraph to determine changes in smoking group over the interval.

Determining individual smoking histories in the MRTP Scenario

Here, there are five smoking groups; never (N), current CC (C), current MRTP (M), current dual use (D), and former (F). Again, the user must define a set of monthly STPs which may vary by period of follow-up. Here, there are 15 STPs; initiation (P_{NC}, P_{NM}, P_{ND}), quitting (P_{CF}, P_{MF}, P_{DF}), re-initiation (P_{FC}, P_{FM}, P_{FD}), and switching (P_{CM}, P_{CD}, P_{MC}, P_{MD}, P_{DC}, P_{DF}), with double changes in an interval again not allowed. Here, four factors may multiply STPs, F_2 and F_3 being similar to those that apply in the Null Scenario. F_1 multiplies P_{MC} for a CC smoker who was previously a CC smoker, F_2 multiplies P_{CF}, P_{MF} and P_{DF} for a smoker who has previously quit, F_3 multiplies P_{FC}, P_{FM} and P_{FD} for quitters defined as short-term, and F_4 multiplies P_{MC} and P_{MD} after a smoker has been using MRTP for a user-defined number of years. F_1, F_2 and F_3 are typically taken to be greater than 1 and F_4 as less than 1.

As for the Null Scenario, the STPs together with random numbers are used to determine whether the individual remains in the same smoking group or transitions to one of the other three groups that are allowable (e.g. P_{CM}, P_{CD} and P_{CF} for a current CC smoker).

Further details of how the revised set of STPs is estimated in this more complex case are provided below:

Where the time interval specified is longer than a month, the set of STPs required for that interval has to be created from the relevant set of monthly STPs, assuming that a double change of smoking status is not allowed within the interval, taking into account the possibility that monthly STPs may change within the interval. The most complex case is considered below, where:

1) the time interval is of length Z months,

2) the set of STPs is relevant to the MRTP Scenario, where an individual in a particular smoking group may change to one of three alternative groups A, B and C (e.g. CC only to MRTP only, Dual, or Former), and

3) one set of monthly STPs applies in the first U months, and a second set applies in the final Z-U months.

In simpler cases (e.g. when considering the Null Scenario where an individual may switch to only one alternative smoking group), the simpler formulae can readily be derived from this most complex case.

In this most complex case, it is assumed that the monthly probabilities for the three alternatives are P1A, P1B and P1C in the first U months, and P2A, P2B and P2C in the second U−2 months. The compounded probability for the first alternative at the end of the Z months, PA* is then given by:

$$PA^* = P1A\ (1 - (1 - P1A - P1B - P1C)^U) / (P1A + P1B + P1C) + P2A\ (1 - P1A - P1B - P1C)^U\ (1 - (1 - P2A - P2B - P2C)^{Z-U}) / (P2A + P2B + P2C)$$

Similarly, we have

$$PB^* = P1B\ (1 - (1 - P1A - P1B - P1C)^U) / (P1A + P1B + P1C) + P2B\ (1 - P1A - P1B - P1C)^U\ (1 - (1 - P2A - P2B - P2C)^{Z-U}) / (P2A + P2B + P2C)$$ and

$$PC^* = P1A\ (1 - (1 - P1A - P1B - P1C)^U) / (P1A + P1B + P1C) + P2C\ (1 - P1A - P1B - P1C)^U\ (1 - (1 - P2A - P2B - P2C)^{Z-U}) / (P2A + P2B + P2C)$$

Where the STPs are invariant within the time interval, so that U = Z, only the first line of each of the formulae is relevant.

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Table 18 Modified version of Markov chain-explanation

In a standard Discrete Time Markov Chain the process at a given time (t) can only be in one of k discrete states. The probability of being in state j at time t+1 should only depend on the state at time t and a set of transition probabilities, p_{ij}, giving the probability of transitioning from state i at time t to state j at time t+1. The p_{ij} are independent of t.

Thus if X_t is a random variable holding the state at time t, the transition probabilities can be written as:

$$p_{ij} = \Pr\{X_{t+1} = j \mid X_t = i\}$$

In PHIM the possibility that there may not always be independence of these transition probabilities over time has to be considered. Thus, someone who has quit smoking recently may be more likely to re-initiate smoking than someone who quit many years before.

To deal with this the concept of extra factors that apply to some particular transition probabilities for a limited time period has been added.

Thus a quitter at time t can transition to a smoker of current cigarettes (with probability P_{FC}), a smoker of a new product (with probability P_{FM}), a dual smoker of both products (with probability P_{FD}) or stay as a quitter (with probability P_{FF}). As one of these states must occur the probabilities must sum to 1:

$$P_{FC} + P_{FM} + P_{FD} + P_{FF} = 1$$

However one may believe that the probability of returning to smoking current cigarettes is higher in the first 2 years after quitting, say by a factor F.

It is assumed that the probability of staying in the same state is much larger than that of switching to a new state. The transition probabilities in the first 2 years after smoking are therefore set at:

$F.P_{FC}$	Transition probability from former to current cigarettes
P_{FM}	Transition probability from former to new product
P_{FD}	Transition probability from former to both products
$1 - F.P_{FC} - P_{FM} - P_{FD}$	Transition probability for staying as former smoker

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FDA QUESTION 24:

We have identified issues in Labstat International ULC Tobacco Product Master File (TPMF) MF0000243 for which additional information or clarification will be needed by FDA to perform a complete review. These issues are being conveyed separately to the TPMF owner. If you have questions related to the TPMF, we encourage you to contact the TPMF owner. Please respond with a statement acknowledging that you understand that the TPMF owner's complete and timely response or lack thereof may impact FDA's review of your submissions.

PMP S.A. RESPONSE:

We hereby confirm that we understand that the TPMF owner's complete and timely response or lack thereof may impact FDA's review of our submissions.

At the same time we would like to inform that Labstat International ULC, the owner of the TPMF (MF0000243), confirmed that responses to the FDA's request for additional information or clarification relating to the TPMF were submitted December 15th, 2017 (via FedEx) and delivered to FDA December 18th, 2017.

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Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (November 18, 2011). The NSDUH Report: Recent Trends in Menthol Cigarette Use. Rockville, MD

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APPENDICES

- The files listed below are provided as appendices to this response:

Filename	Title / Description
SRP1_Q01-A1_PLA-RTD-Regular.pdf	Poly Lactic Acid - Resistance to Draw
SRP1_Q01-A2_PLA-RTD-M1-Batch-1.pdf	Poly Lactic Acid - Resistance to Draw – Menthol 1 – Batch 1
SRP1_Q01-A3_PLA-RTD-M1-Batch-2.pdf	Poly Lactic Acid - Resistance to Draw – Menthol 1 – Batch 2
SRP1_Q01-A4_PLA-RTD-M2.pdf	Poly Lactic Acid - Resistance to Draw – Menthol 2
SRP1_Q01-A5_MPF-RTD-Batch-1.pdf	Mouth piece filter - Resistance to Draw – Batch 1
SRP1_Q01-A6_MPF-RTD-Batch 2.pdf	Mouth piece filter - Resistance to Draw – Batch 2
SRP1_Q01-A7_MPF-RTD-Batch 3.pdf	Mouth piece filter - Resistance to Draw – Batch 3
SRP1_Q03-A1_15006-XReference-list.xlsx	Un-blinded cross-reference table for study 15006
SRP1_Q03-A2_15025-XReference-list.xlsx	Un-blinded cross-reference table for study 15025
SRP1_Q03-A3_15020-XReference-list.xlsx	Un-blinded cross-reference table for study 15020
SRP1_Q03-A4_15015-XReference-list.pdf	Un-blinded cross-reference table for study 15015
SRP1_Q05-A1_15006-HbCO-data.pdf	Carboxyhemoglobin data from health check animals exposed to high levels of CO
SRP1_Q05-A2_15006-HealthCheckAnimals.pdf	Health reports for the health check animals exposed to high levels of CO
SRP1_Q07-A1_DescStatsBW.csv	Descriptive statistics related to body weight

(table continues)

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Filename	Title / Description
SRP1_Q07-A2_DescStats.csv	Descriptive statistics related to Carboxyhemoglobin, clinical chemistry, hematology, lung functions and volume, plaque size, biomarkers of exposure in urine and plasma, various cell counts in BALF, MMP activity in BALF, biomarkers in BALF and serum, oxysterols
SRP1_Q07-A3_DescStats_Atherotech.csv	Descriptive statistics related to lipoproteins
SRP1_Q07-A4_DescStats_Histo.csv	Descriptive statistics related to morphometry and histopathology
SRP1_Q07-A5_DescStats_NictMetSG.csv	Descriptive statistics related to urine nicotine metabolites and urine volume
SRP1_Q08-A1_Oxysterols_P15015.xlsx	Un-blinded data table for oxysterols in plasma
SRP1_Q10-A1_PMI_Report_Combustion.pdf	Analysis of the EHTP Features with respect to Biomass/Tobacco Combustion" by Prof. Dr. Valerio Cozzani
SRP1_Q11-A1_MarketResearch-JP_StudyDesign.pdf	Market Research Panel of Adult IQOS Owners: Japan - Study Design – December 2017
SRP1_Q11-A2_MarketResearch-JP_StudyReport.pdf	Market Research Panel of Adult IQOS Owners: Japan - Study Report – August 2016
SRP1_Q14-A1_WOT-Studies.pdf	Additional analysis on the WOT studies: a) average number of cigarettes per day for each study week, overall and by the IQOS usage categories at week 4 and; b) "Exclusive HeatStick use" category and the mean number of cigarettes per day and total tobacco use per day (i.e., cigarettes plus HeatSticks) stratified by average number of cigarettes per day smoked at baseline and then further stratified by main IQOS use category at week 4 for each country
SRP1_Q15-A1_PMI-PBA07-FAS-ExclHS-W6.pdf	Average number of cigarettes per day and total tobacco per day at baseline and week 6 for participants who were "Exclusive Heatstick users" at week 6

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Filename	Title / Description
SRP1_Q15-A2_PMI-PBA07-FAS-ByUsageW6.pdf	Changes in average number of cigarettes and total tobacco per day (provide baseline and week 6 data) by average cigarettes smoked at baseline (1-4, 5-10, 11-20, 20-30, and ≥30) and then further stratified by main usage category of IQOS at week 6
SRP1_Q18-A1_PMTA-05-NOC-US-AnalysisTables.pdf	Additional analysis on the THS-PMTA-05-NOC-US study data
SRP1_Q22-A1_Notes-PHIM-V4-project.pdf	Description of the input parameters for the simulation and sensitivity analyses