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RESPONSE TO AUGUST 4, 2017 INFORMATION REQUEST for MR0000059-MR0000061 and AMENDMENT to MR0000059-MR0000061

September 8, 2017

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FDA QUESTION 1

All of your MRTPAs provided general descriptions and diagrams of the components and materials used in the Holder and Charger devices of the IQOS system. However, the descriptions and diagrams do not provide sufficient detail and specifications regarding the assembly, components and materials that comprise the Holder and Charger devices. In order for FDA to adequately characterize the IQOS system and perform a full and complete assessment of the design, assembly and operation of the products, provide detailed schematics and engineering drawings and diagrams of the Holder and Charger devices, including sub-assemblies and components, with dimensional and material specifications. If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

PMP S.A. RESPONSE:

Further details of the assembly processes described in section 3.2.3.1 of the applications are provided in the following figures:

- Figure 1 represents the sub-assembly processes done for the Holder prior to top level assembly. Each block represents a separate process: (b) (4) are assembled (b) (4) by (b) (4) (b) (4) are assembled by (b) (4) on a specific pre-assembly (b) (4)
- F 2 represents the top level assembly of the Holder done in parallel on multiple cells at (b) (4) for the (b) (4). Final quality check is done separately of the manufacturing cells and the codentify engraving is done with laser machine setup.
- Figure 3 represents the (b) (4) done (b) (4) (b) (4), before shipping the sub-assemblies to (b) (4)
- Figure 4 represents the top level assembly of the Charger done in parallel on multiple cells at (b) (4) for the (b) (4). Final quality check is done separately of the manufacturing cells and the codentify engraving is done with laser machine setup.

Abbreviations in Figure 1 - Figure 4:

PCB:	Printed Circuit Board
PCBA:	Printed Circuit Board Assembly
SMT:	Surface Mount Technology
MT1:	Manufacturing Testing on PCB panel
MT4:	Manufacturing Testing on sub-assembly and calibration
MT5:	Manufacturing Testing on final assembly device

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(b) (4)

Figure 1 Sub-assembly process for the Holder

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(b) (4)

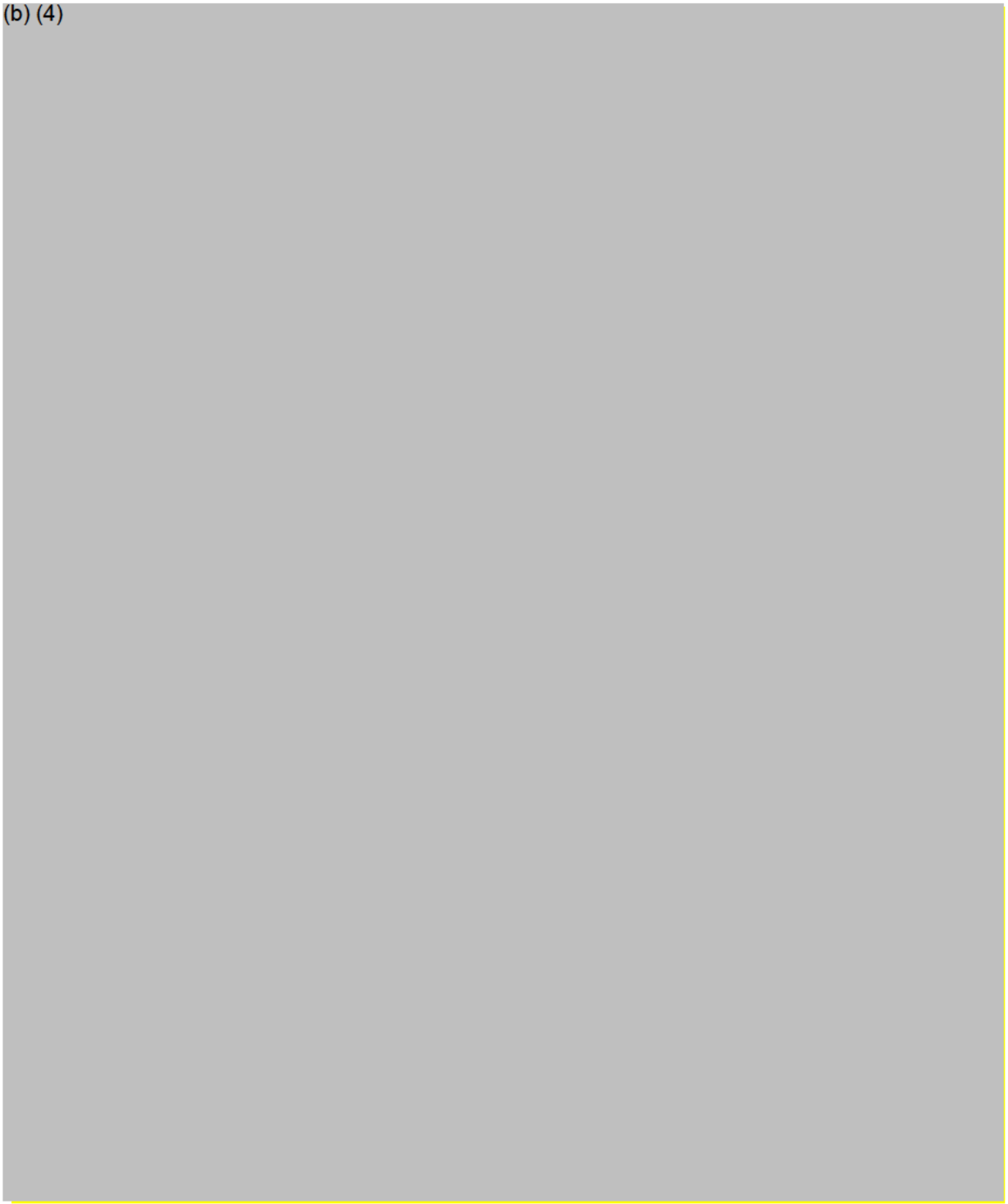

Figure 2 Top level assembly process for the Holder

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(b) (4)

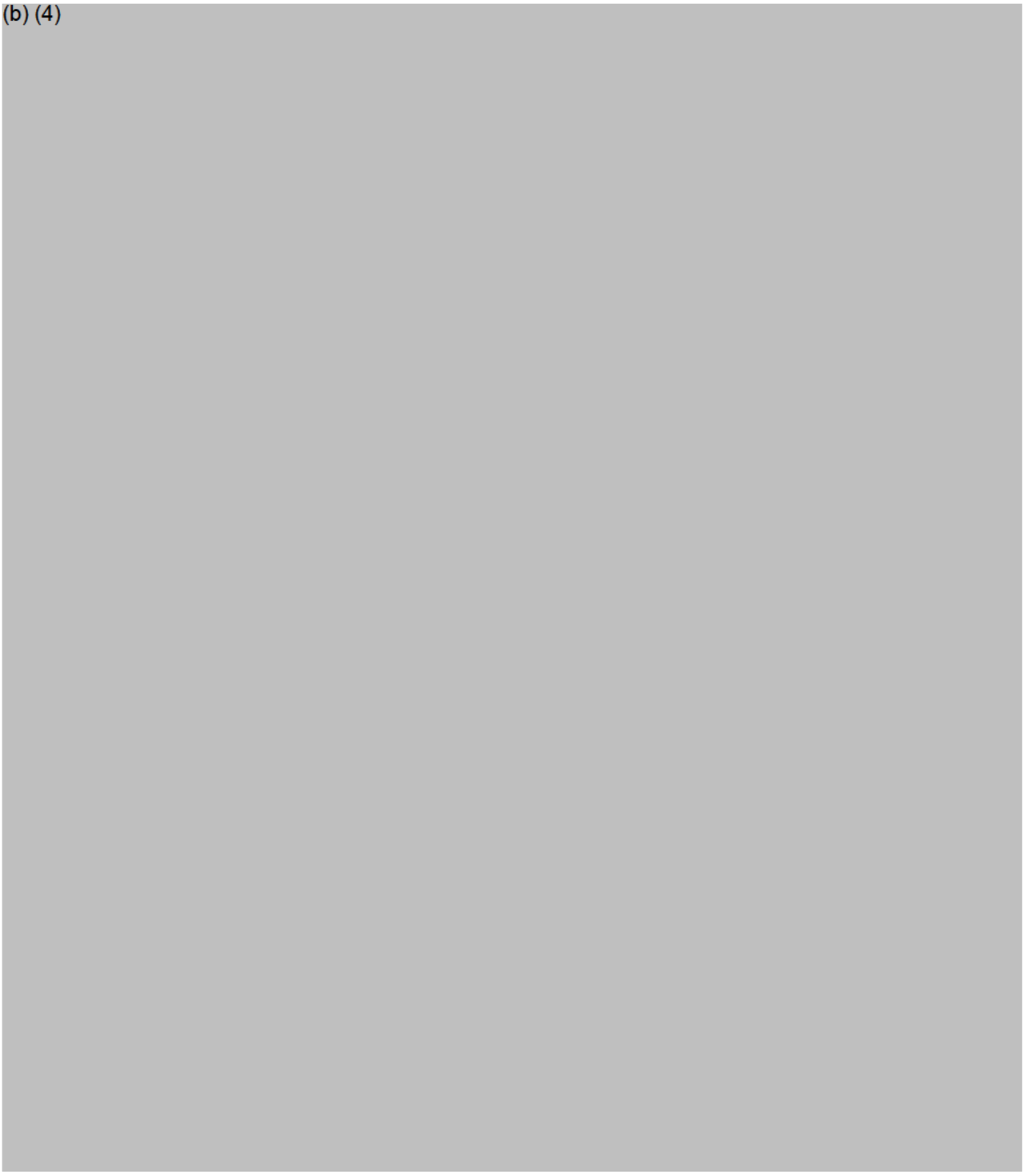

Figure 3 Sub-assembly process for the Charger

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(b) (4)

Figure 4 Top level assembly process for the Charger

Part by part and sub-assembly details are provided in the appendices listed below, submitted herein in amendment (additional) to Module 3 of the applications:

- A3.2.3-5 Contact PCB Assembly Schematics and Layout
- A3.2.3-6 Heater Control PCB Assembly Schematics and Layout
- A3.2.3-7 Charger PCB Assembly Schematics and Layout
- A3.2.3-8 Holder Mechanical Drawings (including sub-assemblies)
- A3.2.3-9 Charger Mechanical Drawings (including sub-assemblies)
- A3.2.3-10 Heating Blade Specification

These schematics, layouts, drawings and specifications are for components used in manufacture, as described in Appendix A3.2.3-2 (v2) Device Bill of Materials provided in attachment.

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FDA QUESTION 2

All of your MRTPAs, in Appendix A3.2.3-2, include a Device Bill of Materials, which lists the structural materials of the Charger and Holder of the IQOS device. However, your applications lack detailed information on the structural materials, such as the name, function, quantity, and CAS number for all of the device materials. Additional information is needed to identify the device materials and help FDA to review your applications, thus provide the name, function, quantity, and CAS number for all of the device materials. If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

PMP S.A. RESPONSE:

Detailed bills of materials are maintained in our product lifecycle management system from which extracts have been performed on August 8th, 2017. The Device Bills of Materials are provided in Appendix A3.2.3-2 (v2) for the following references, including the quantity used for each component:

- Dark Slate Holder: DV.000174
- White Holder: DV.000180
- Dark Slate Charger: DAC.000027
- White Charger: DAC.000028

The name, function and CAS numbers of device materials for the Holder and Charger are detailed in Table 1 and Table 2, respectively.

Table 1 IQOS Holder material

Material Description	Material Type	Used for / Function	CAS numbers / Remarks
(b) (4)	Plastic	Rear Housing	No hazardous ingredients subject to reporting under the Toxic Chemical Release Inventory (SARA 313) are known at this time.
	Plastic	Front Housing	No hazardous ingredients subject to reporting under the Toxic Chemical Release Inventory (SARA 313) are known at this time.

(table continues)

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Material Description	Material Type	Used for / Function	CAS numbers / Remarks
(b) (4)	Plastic	Extractor	31694-16-3 or 29658-26-2 for the polymer 1333-86-4 for the carbon black powder
	Plastic	Power Button Body, Plastic Ring	9003-56-9 for Acrylonitrile-Butadiene - Styrene copolymer 9010-96-2 for α-methylstyrene copolymer 31621-07-5 for N-Phenylmaleimide copolymer
	Plastic	Frame Flex B	25776-72-1 for polyphthalamide 65997-17-3 for fiberglass "proprietary" for block polymer 1333-86-4 for carbon black
	Plastic	Overmolded heater	31694-16-3
	Plastic	Light Guide	9011-14-7 for Poly methyl methacrylate 25852-37-3 for Methyl methacrylate-n-butyl acrylate copolymer 80-62-6 for Residual methyl methacrylate monomer
	Potting material	Potting around the Heater	For hazardous chemical (covering 2.1% to 21% of the composition): 2768-02-7 for Trimethoxyvinylsilane 6175-45-7 for 2,2-Diethoxyacetophenone 999-97-3 for 1,1,1,3,3,3-Hexamethyldisilazane
	Glue	Glue Light Guide to Power Button Body	For hazardous chemical (covering 60% to 100% of the composition): 7085-85-0 for Ethyl cyanoacrylate

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Table 2 IQOS Charger material

Material Description	Material Type	Used for / Function	CAS numbers / Remarks
(b) (4)	Plastic	Top Cover, Bottom Cover, Lid P1M24 Plus	1332-58-7 for Aluminum silicate (kaolin clay) representing 0.1% to 1% No information for the rest of the composition
	Plastic	Chassis, Latch, Button MU, Lid Band	103598-77-2 for Polycarbonate 181028-79-5 for BPADP (Flame retardant) 9003-56-9 for Acrylonitrile-Butadiene-Styrene Terpolymer
	Plastic	Window	No CAS reference available
	Plastic	Fascia	24969-26-4 for base resin
	Plastic	Sleeve, Mount Bottom, Mount Top	24969-26-4 for base resin 50-00-0 for Formaldehyde (less than 0.1%)
	Plastic	Lightpipe body	25213-88-1 for Methyl methacrylate 9003-55-8 for Acrylonitrile-Butadiene-Styrene
	Plastic	Lightpipe window	24936-68-3 for Polycarbonate

The Appendix A3.2.3-2 (v2) Device Bill of Materials submitted herein in amendment to the applications has been updated to include changes linked to the extension of the manufacturing capacity and continuous improvement of the device reliability, more specifically these changes can be grouped in the following categories:

- Improvement of the robustness of the devices
- Extension of the suppliers or production capacity
- Correction of specifications (tolerances, technical drawings and MPNs)

These changes are listed in the revised Appendix A3.2.1-21 (v2) Changes which has been updated to include changes that have been introduced after submission of the applications.

All the changes followed our change management processes and evidences were collected according to our Quality Management System requirements.

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FDA QUESTION 3:

All of your MRTPAs, in Section 2.7 Executive Summary, *Figure 9: THS temperature profiles*, provide heating blade temperatures at 0.0 mm and 0.2 mm from the heating blade over a 360 second period averaged from five replicates. However, the temperature profiles graphs do not contain sufficient detail to allow FDA to fully assess the design and performance characteristics of the heating blade. Provide the following:

- The detailed test protocol used to assess the temperature profile, including test equipment, sample preparation, test conditions, acceptance criteria, and results, including the data from the individual replicates.
- The design specifications for the heating blade operation, including electrical and mechanical specifications such as but not limited to: heating blade resistance (including upper and lower limit tolerances); input current and voltage (including maximum values and durations); power consumption during use (nominal and maximum levels and durations); heating blade compressive, tensile and shear requirements and tolerances, and; thermal characteristics of the heating blade and its component materials. Provide any testing that was performed to verify these design specifications.
- Describe and explain how hot spots, if any, on the heating blade are prevented or minimized, and how this was assessed during testing.
- Provide any available temperature profile information and data beyond the 360 second heating period during the power-off period.

If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

PMP S.A. RESPONSE:

The THS heating blade specifications are provided in Appendix A3.2.3-10.

The individual data points requested in relation to the *Figure 9: THS temperature profiles* (section 2.7 Executive Summary) are provided in attachment:

- SR1_Q03-A1_THS-TempProfile-00mm.xls
- SR1_Q03-A2_THS-TempProfile-02mm.xls

The temperature profiles shown in *Figure 9* 2.7 Executive Summary are the average of 5 replicates.

The testing performed to characterize the temperature profile is described below.

The dissipation of the heating blade temperature was measured in several locations from within the tobacco plug at specified distances from the heating blade over a 360 second period, while puffing using a programmable dual syringe pump (air intake by a pump, drawing 55 mL during 2 seconds).

In order to do so, an IQOS device was slightly modified by drilling a hole of 0.5mm in order to receive a 0.25mm diameter thermocouple (type K). After drilling, these holes were covered with Polyimide tape that would then be perforated by the sole thermocouple in order to minimize any modification of the airflow within the device.

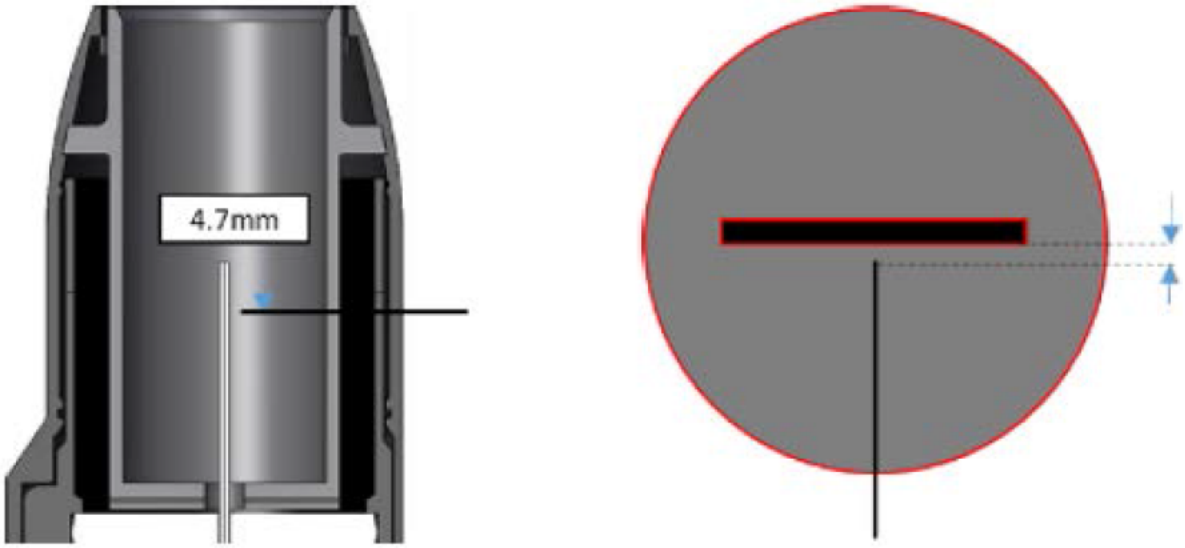

Figure 5 **Schematic representation of the thermocouple insertion in the IQOS Holder.** The black line represents the thermocouple.

The thermocouple was positioned in the center of the heating blade, 4.7 mm from the tip, corresponding to the warmest location on the heating blade. The thermocouple was mounted on a micrometer that allowed the thermocouple to be positioned in the tobacco plug at different distances relative to the surface of the heating blade. To allow a smooth insertion of the thermocouple into the tobacco substrate, a pointed needle was used to pierce the wrapping paper of the HeatStick already in the Holder prior to the insertion of the thermocouple.

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In order to set the reference position of the thermocouple, it was placed in direct contact with the heating blade surface. This position was denoted 0.0 mm on the micrometer. The temperature distribution profile in the tobacco plug during heating was measured by positioning the thermocouple 0.2 mm, 0.5 mm, 1.7 mm and 3.4 mm radially, respectively, from the heating blade surface. After positioning the thermocouple in the Holder, the Holder was turned on and air was drawn through the device according to the HCI regimen [puff volume of 55 mL, puff duration of 2 s, puff frequency 30 s] using a calibrated piston pump.

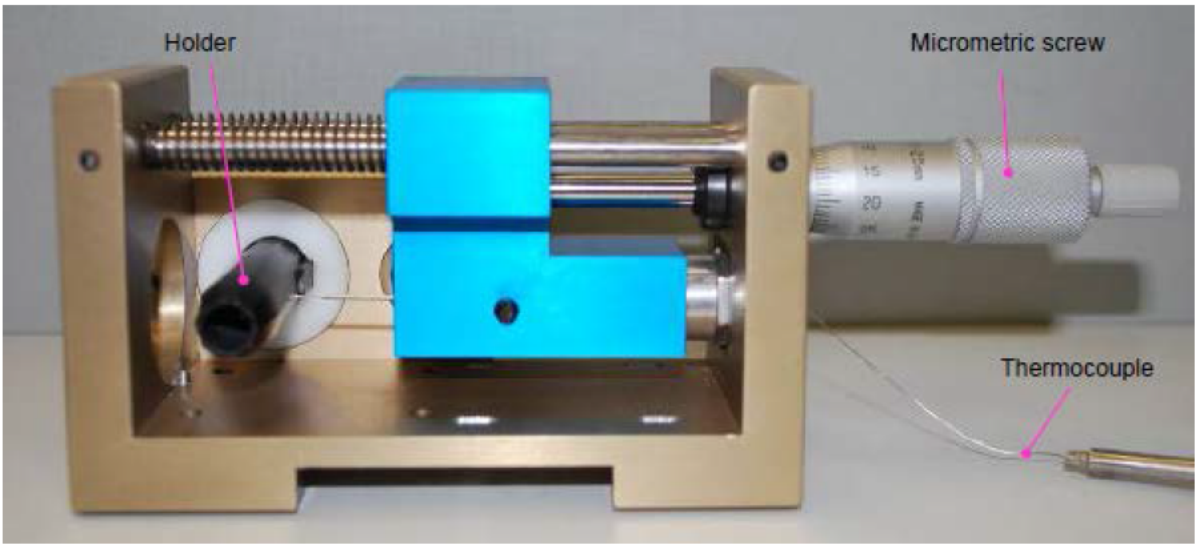

Figure 6 Temperature test bench

To further investigate the temperature of the tobacco substrate in the HeatStick under simulated puffing, the data acquisition was continued approximately 15 seconds after the heater was turned off and the temperature of the tobacco substrate was measured. Power to the heater was turned off after 365 s (maximum duration of the heating profile).

Since the heater was turned off, there is no recovery in the temperature of the system and, as time passed, the temperature of the tobacco substrate continued to decrease significantly. Data acquisition was stopped after a total time of approximately 380 s. The temperature profiles shown are the individual recordings of 5 replicates.

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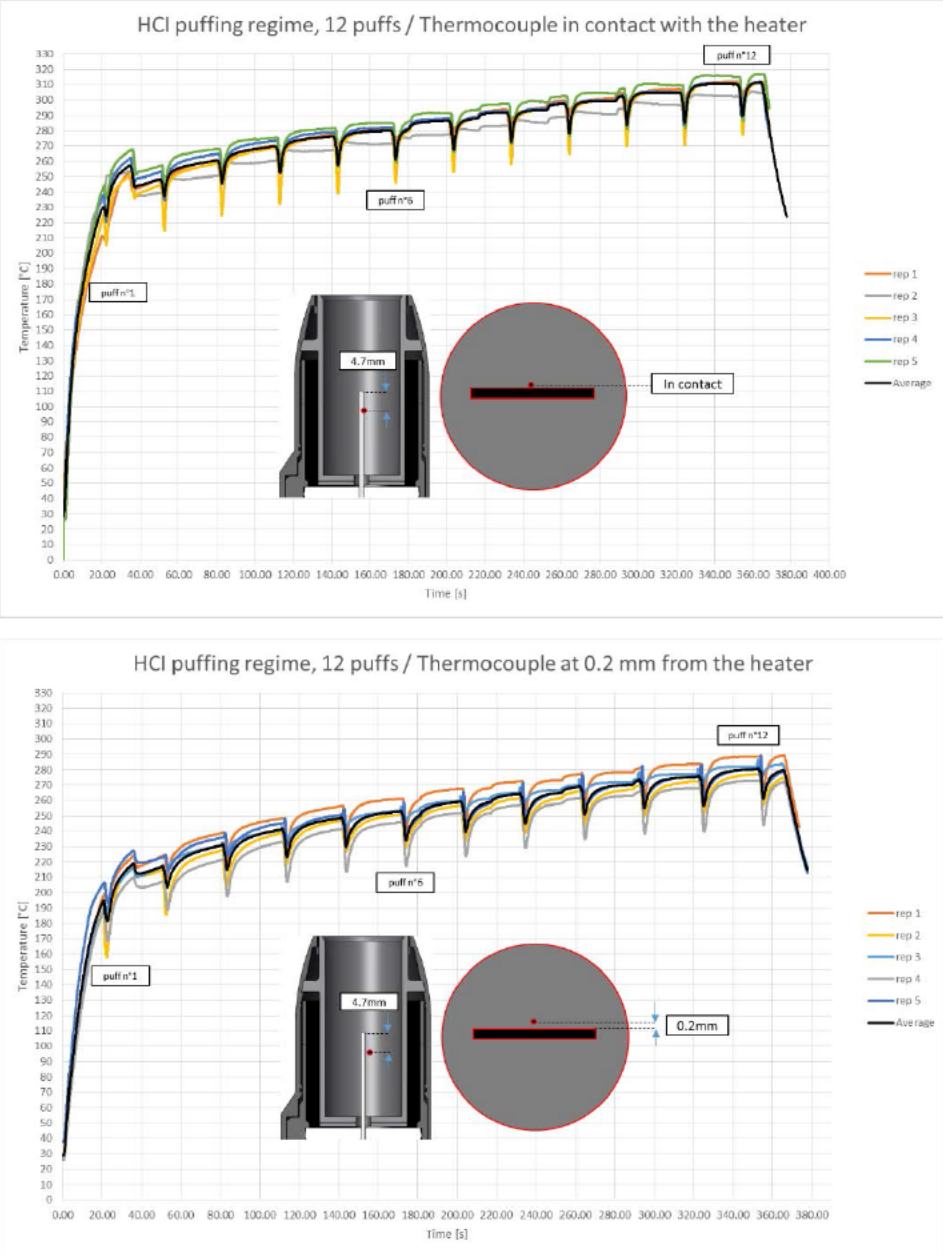

Figure 7 **Tobacco substrate temperature profile (measured at 0.0 mm and 0.2 mm from the heater's surface). The HCI regimen was used to draw air through the Holder and HeatStick. Heating was stopped after 365 s and data acquisition was stopped after approximately 380 s.**

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(b) (4)

as illustrated in Figure 8.

(b) (4)

Figure 8 Blade temperature ceramic side for the selected temperature level

(b) (4)

(b) (4) the heater temperature specification and tolerances have been studied and reported with the following outcomes:

- The aerosol deliveries follow a predictable tendency to increase with temperature.
- (b) (4), the deliveries are within performance specifications for all studied aerosol constituents.
- The aerosol deliveries obtained with heater temperatures at the upper and lower limits (b) (4) as defined in the Design Input Requirements, confirm that the tolerances were set properly in order to stay within performance criteria in all cases.

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- (b) (4)
- (b) (4)

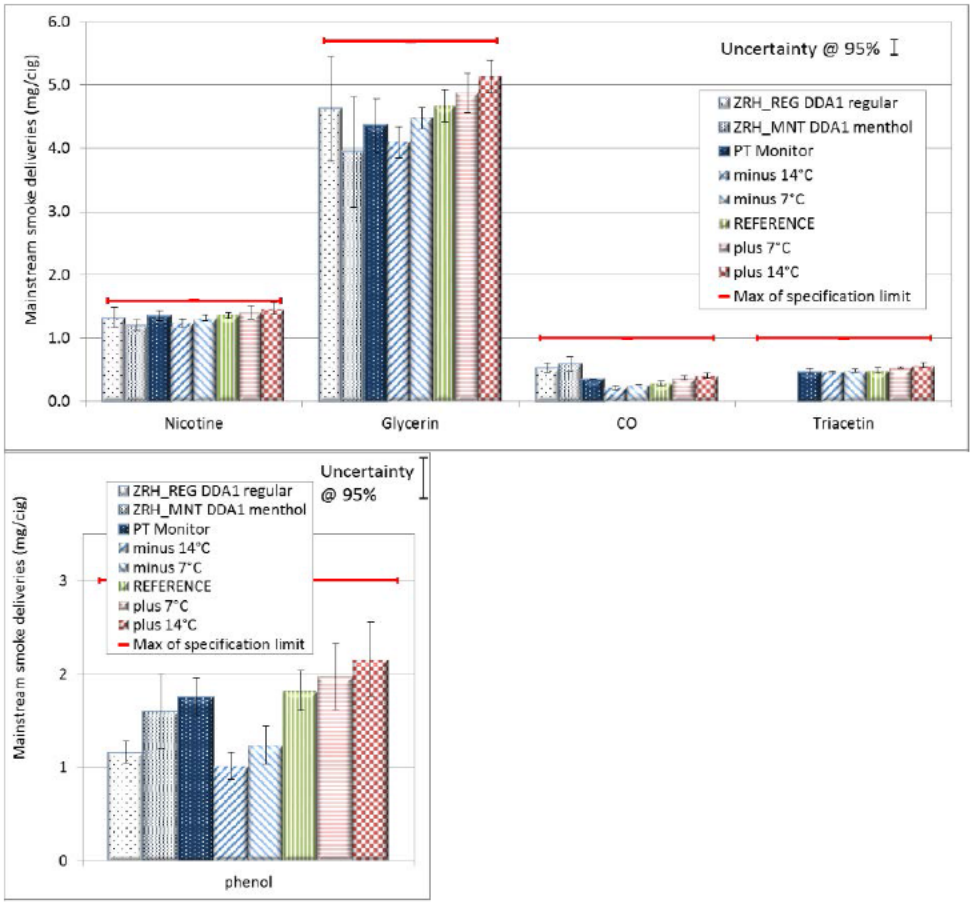

Figure 9 Aerosol deliveries under Health Canada smoking regime, 12 puffs

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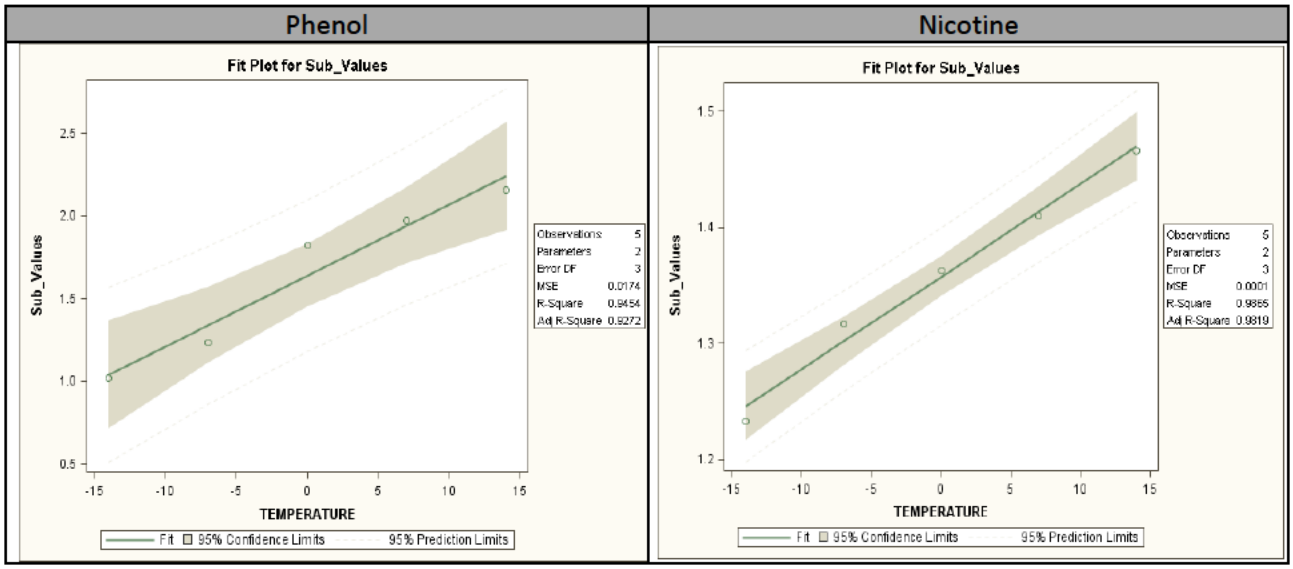

Figure 10 Linear regression between the substances and the temperature increasing, with the confidence interval at 95%

In conclusion, the results of this assessment demonstrate that the heater temperature profile was designed properly in order to meet the acceptance criteria and that the tolerance could even be extended to (b) (4) without generating an aerosol out of performance specifications.

In order to minimize hotspots, (b) (4)

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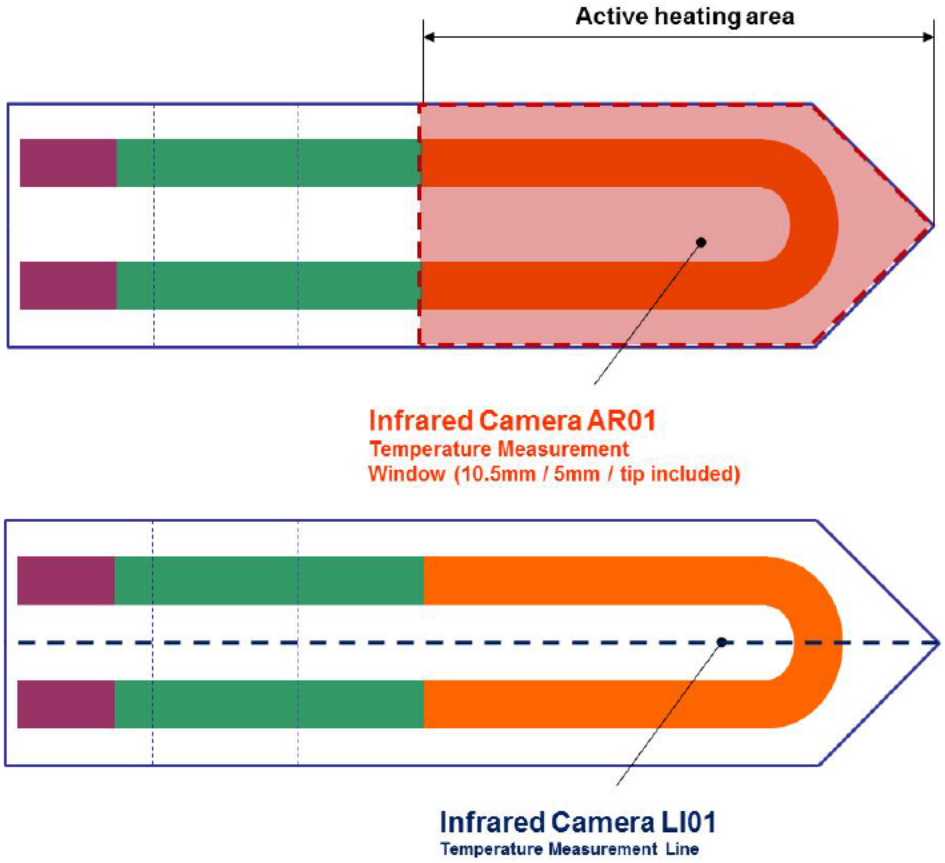

Figure 11 **Schematic of the heater active area (the part of the heater that is inserted into the tobacco plug) with infrared measurement areas (AR01 for heater average and maximum temperature, LI01 for longitudinal distribution of the temperature at certain time points)**

The thermal evaluation considered the delta between the curves average and maximum temperature at a constant heating profile of 375°C. To avoid hotspots, the difference between the mean and the maximum temperature recorded has been minimized by design (and selection of heating blade) in order to (b) (4) . This difference is indicating the temperature homogeneity of the active surface of the heater, and by design, hotspots were eliminated.

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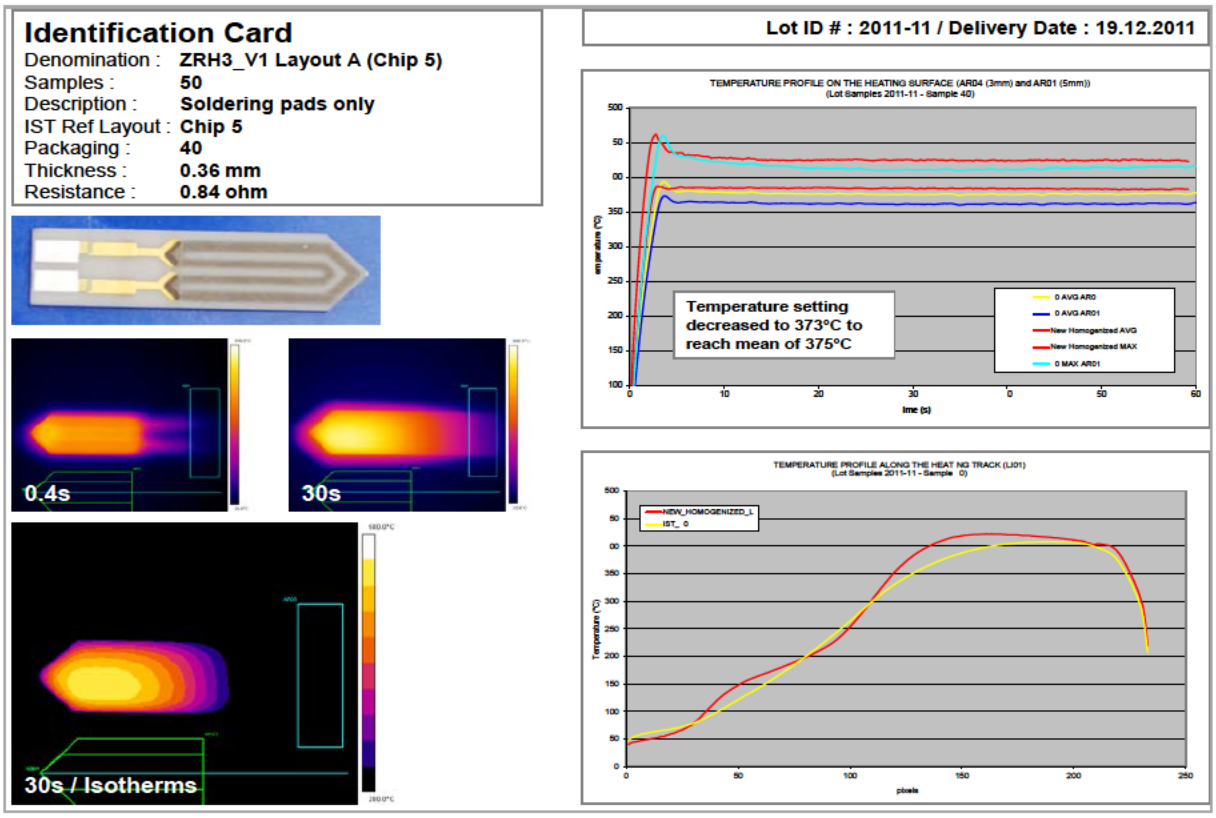

Figure 12 **ID card for the selected heating track layout in IQOS.** This card contains thermal images taken after 0.4 and 30 s after the beginning of the heating profile on the left. In the graphs on the right side of the figure, one can see the comparison between the first homogenized heaters (red curves) that were taken as reference for comparison with new heater candidates (blue and yellow curves). The top graph shows the maximum and average temperatures recorded during 60 seconds. The bottom graph shows the thermal distribution along the central line of the heater (Li01). Similar cards were established for other heater candidates during development phase

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FDA QUESTION 4:

All of your MRTPAs, in Section 3.1 Product Description and Formulation, state that the Holder and Charger contain microcontrollers and firmware to control the following:

- Holder:
  - The heating process (both during inhalation and the blade cleaning process);
  - The safety mechanisms (*e.g.*, overheating prevention, electronic hardware integrity by self-test, puff limitation); and
  - The user interface.
- Charger:
  - The Holder charging process;
  - The Charger recharging process;
  - The user interface; and
  - The blade cleaning process.

However, insufficient detail has been provided regarding these functions to adequately characterize the performance and behavior of the devices. Provide the following:

a. A detailed description of all feedback control mechanisms in the Holder and Charger and how they were validated.
b. A detailed description of how heating blade resistance and heating blade temperature are correlated for temperature measurement and how the measurement was validated with specifications for accuracy and tolerance.
c. A detailed description of the blade cleaning process and associated blade temperature profiles and electrical usage (voltage and current) during this operation.
d. A detailed description of the inhalation detection function and operation, including a diagram of air flow in the holder and air flow design specifications (including the quantity of pressure differential needed to activate detection; the quantity of air flow; and the draw resistance), including how specifications were verified.
e. A detailed description of any battery management functions in the Holder and Charger, along with their associated design and performance specifications, including how they were verified.

If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

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PMP S.A. RESPONSE:

The Holder and Charger contain microcontrollers and firmware to control the following:

- Holder:
  - The heating process (both during inhalation and the blade cleaning process);
  - The safety mechanisms (*e.g.*, overheating prevention, electronic hardware integrity by self-test, puff limitation); and
  - The user interface.
- Charger:
  - The Holder charging process;
  - The Charger recharging process;
  - The user interface; and
  - The blade cleaning process.

Additional descriptions and evidence can be found below to provide details to characterize the performance and behavior of the device.

Holder charge regulation is performed using 3 feedback analog signals converted in digital using ADC periodical measurements:

- Holder battery voltage measured near the battery pads
- Charger output voltage
- Charging current

Given that there is a direct correlation between blade temperature and measured resistance, holder heating regulation is performed by adjusting the heating blade power duty cycle based on ADC measurement feedback of heating blade voltage and heating blade current. The detailed design is provided in the (b) (4) .

Correct correlation between blade temperature and resistance is calibrated during production.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

The test report is provided in A3.2.1-5 Design Verification Report – Device (Design Input ID #FR-02-024 and #FR-02-037) in the applications.

During the heating process, the heating blade resistance is measured periodically using digital conversion (ADC) of voltage and current analog signal going through the heating blade. Temperature regulation is then performed using this resistance measurement. Resistance and temperature are correlated using platinum material physical specification. As described in Chapters 3.1/3.2/3.3/4.1 of the attached Specification ZRH CH Factory Heater Calibration, SR1_Q04-A2, (b) (4)

Chapters 3.1/3.2/3.3/4.1 of SR1_Q04-A2 explain how the relation between temperature and resistance is done and the historic of the method to find the best approach.

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Description of the factory heater calibration is described in the following appendices:

- Process used for clinical devices: SR1_Q04-A2
- Process used for commercial devices: SR1_Q04-A3, section 2.2.4.3, of Manufacturing Test Sequence Design Description Report, SFT.000079_R1 P1 Holder 2.4 MT4 (Calibration)
- Equivalence study between both methods: SR1_Q04-A1

Cleaning uses a standard heating regulation with different target temperature (b) (4) and duration (b) (4). The inhalation detection feature is disabled during cleaning.

Details of the heating profile (called C28) are described in appendix SR1_Q04-A4, Requirements Specifications, C28 Energy Profile for Platform Model 2.X Devices. Details of the selection of the heating profile is described in the answer of question 3 above.

The test report is provided in A3.2.1-5 Design Verification Report – Device (Design Input ID #FR-02-014 and #FR-02-015) in the applications.

Puff detection (see Software Design Specification: Holder in A3.2.1-10, chapter 2.11, in the applications).

(b) (4)

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The test report is provided in A3.2.1-5 Design Verification Report – Device (Design Input ID #FR-02-058) in the applications.

Holder: no battery management is performed by the Holder. Only usage prevention in low battery condition:

- Need of (b) (4) to start heating
- Need of (b) (4) during heating

Charger (see Software Design Specification: Charger in A3.2.1-10, chapter 3.5.1, in the applications):

- (b) (4)

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- (b) (4)
- (b) (4)
- (b) (4)

Charger (see Software Design Specification: Charger in A3.2.1-10, chapter 3.4.1, in the applications):

- (b) (4)
- (b) (4)

Charger usage prevention in low battery condition

- Need of (b) (4) to start Holder charge

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FDA QUESTION 5:

All of your MRTPAs describe the Heatsticks as single-use only. However, not all individuals may use the product as intended. Provide information on likely or foreseeable misuse, such as what happens if a user tries to re-use a used Heatstick or tries to use a conventional tobacco product with the Holder, such as a cigar or cigarette. If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

PMP S.A. RESPONSE:

We have tested the potential re-use of HeatSticks. The results are provided in the attached report: "Determination of Aerosol Deliveries of THS 2.2 Sticks when Re-used", SR1_Q05-A1.

The conclusions can be summarized as follows:

- Re-used HeatSticks hardly deliver any aerosol. Comparing to new HeatSticks, re-used HeatSticks deliver 17 % of nicotine and 12 % of the Total Particulate Matter.
- To test whether re-used HeatSticks would result in higher tobacco temperature, and therefore higher levels of HPHCs, we have measured the level of phenol (phenol being the most sensitive HPHC vs temperature variation) and have found that its level was not increased when re-using HeatSticks.

The conclusion is that re-use of HeatSticks delivers low levels of aerosol and will not increase HPHCs levels.

Regarding potential misuse, such as, use of conventional tobacco products (like cigars or cigarettes) with the Holder, we have not generated data. The reason is that heating tobacco can only generate an aerosol if the tobacco contains enough aerosol former (Nordlund and Kuczaj 2016), such as glycerin. Although glycerin is used in tobacco as a humectant, its level in conventional products is far below the level required to generate a nicotine containing aerosol. Instead, only low levels of vapors of the most volatile portion of tobacco would be emitted. From a chemistry standpoint, the tobacco of the conventional product would be heated at only a maximum of 350 °C (which is, by design, the maximum temperature of the heating blade), lower than the original intended use, and lower than the combustion threshold of tobacco (>400 °C) (Barontini et al. 2013; Senneca O. et al. 2007). Therefore, the levels of HPHCs would be significantly lower compared to those obtained under intended use (when lighting the cigarette or cigar).

Furthermore, only products with a circumference of 22.9 mm or less would be potentially usable with IQOS, which would exclude most conventional US cigarettes (Agnew-Heard et.al. 2016).

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FDA QUESTION 6:

All of your MRTPAs, in Appendix A3.2.3-4 THS 2 Device Compliance Certificates, provide testing certificates for the Holder (model 10370) and Charger (model 18650) batteries. Three manufacturers each are listed for the test certifications for the model 10370 and model 18650 batteries. Clarify if the different manufacturers' batteries are considered interchangeable for use in the IQOS system for each battery model. Provide the minimum battery specifications for use in the Holder and Charger, including minimum, nominal and maximum voltage, and current draw and duration. Compare and contrast these battery specifications against the voltage and current specifications of the Holder and Charger, including maximum voltage and current draw and duration. If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

PMP S.A. RESPONSE:

A generic specification covering the different suppliers was issued, as it is a requirement to have interchangeable batteries. Every supplier issued their own manufacturing specifications aligned with our specifications, as outlined in Table 3 (Holder) and Table 4 (Charger) below.

Table 3 Main specification comparison for Holder battery

	PMI Specs	(b) (4)		(b)		(b) (4)	Aucopo*
Nominal voltage	(b) (4)						
Nominal capacity							
Internal resistance							
Maximum charging voltage							
Maximum charging current							
End of charge current							
Maximum discharging current							
Minimum voltage							

*Company name changed

(b) (4)

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Table 4 Main specification comparison for Charger battery

	PMI Specs	(b) (4)	(b)	(b) (4)
Nominal voltage	(b) (4)			
Nominal capacity				
Internal resistance				
Maximum charging voltage				
Maximum charging current				
End of charge current				
Maximum discharging current				
Minimum voltage				

The voltage range specified by PMI is the minimal working range of the battery. The actual supplier range of the batteries can be wider.

(b) (4)

(b) (4)

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FDA QUESTION 7:

All of your MRTPAs, in Section 3.2.3 Device Manufacturing, describe three facilities engaged in the design, manufacture or assembly of the Holder and Charger devices:

- Philip Morris Products S.A. (PMP S.A.) (Switzerland): (b) (4) (b) (4)
- Philip Morris International Research Laboratories Pte Ltd (PMIRL) (Singapore): (b) (4)
- (b) (4)

However, there is insufficient information provided to allow FDA to assess the design/manufacturing processes and quality assurance activities at these sites. In order for FDA to assess these activities, address the following questions:

Philip Morris Products S.A. (Switzerland)

a. Describe and discuss the activities associated with (b) (4) performed at this facility. Describe how these activities relate to the manufacture of device subcomponents and final device assembly.
b. Describe and discuss how (b) (4) are determined for subcomponents and final assembly.
c. Describe how (b) (4) are determined and authorized. Provide examples of these changes. Describe what level or type of change does not require authorization and provide some examples.
d. Describe how (b) (4) (b) (4) are determined. Identify the subcomponents for the Holder and Charger and their associated manufacturing sites.
e. Describe how supplier products or components are (b) (4) (b) (4) Describe how certifications to performance standards are assessed.
f. Discuss if methods and processes (b) (4) (b) (4) are determined by this facility. If these methods and processes are not determined by this facility, discuss how manufacturing quality assurance processes are determined and at what facility. Describe how these quality processes are confirmed at the associated manufacturing sites. Describe any statistical information/data or metrics that are collected at the manufacturing sites regarding quality processes. Describe how the final manufactured product is assessed for conformance to product requirements.

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g. Describe the activities that are associated with (b) (4) (b) (4) performed at this facility. Describe how these activities relate to the manufacture of device subcomponents and final device assembly.
h. Describe how (b) (4) are determined for subcomponents and final assembly. Discuss how changes to these criteria are determined and authorized and provide examples of these changes. Discuss what level of change does not require authorization and provide some examples.
i. Describe how (b) (4) for subcomponents and their suppliers are determined. Identify the subcomponents for the Holder and Charger and their associated manufacturing sites.
j. Describe how supplier products or components (b) (4) (b) (4) Describe how certifications to performance standards are assessed.
k. Discuss if methods and processes (b) (4) (b) (4) are determined by this facility. If these methods and processes are not determined by this facility, discuss how manufacturing quality assurance processes are determined and at what facility. Describe how these quality processes are confirmed at the associated manufacturing sites. Describe any statistical information/data or metrics that are collected at the manufacturing sites regarding quality processes. Describe how the final manufactured product is assessed for conformance to product requirements.

(b) (4)

l. Describe the (b) (4)
Describe the (b) (4)
m. Describe the (b) (4)
(b) (4) Describe the (b) (4)
(b) (4)
n. Describe the (b) (4)
(b) (4) Describe (b) (4)
(b) (4)
o. Describe (b) (4)
(b) (4) Discuss if (b) (4)
(b) (4)

If this has already been provided, include a reference for the exact location of the information contained within your MRTPAs.

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PMP S.A. RESPONSE:

Responsibilities of PMP S.A., PMIRL, (b) (4) (b) (4) have been clarified in section 3.2.3 (v2) Device Manufacturing provided in attachment.

Information regarding site-specific activities related to design, manufacture, testing and quality assurance is provided in Table 5 below. Additional information related to Question 7.a. to 7.o. is also provided.

Philip Morris Products S.A. (PMP S.A.) (Switzerland) has the accountability for (b) (4) (b) (4) PMP S.A. and (b)(4) R&D are responsible to (b) (4) (b) (4) (b) (4)

PMI project managers are stationed at (b) (4) to (b) (4) (b) (4) PMI project management staff at (b) (4) ensure that (b) (4) (b) (4) .

(b) (4) .

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Table 5 Roles and responsibilities in relation to Tobacco Heating Devices described in MR0000059 – MR00000061

Company	Development and Design Activities	Manufacturing Activities	Quality Assurance Activities	Applicable QMS	CMC Reference Section
PMP S.A.	(b) (4)			PMI QMS	3.2.3
PMIRL				PMI QMS	3.2.3

(table continues)

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Company	Development and Design Activities	Manufacturing Activities	Quality Assurance Activities	Applicable QMS	CMC Reference Section
(b) (4)					3.2.3
					3.2.3

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Philip Morris Products S.A. (Switzerland) (PMP S.A.)

a) The (b) (4) at PMP S.A. (b) (4)
(b) (4)

b) PMP S.A. are (b) (4)
(b) (4)
(b) (4) .
(b) (4)
(b)(4)
(b) (4)

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c) (b) (4)

d) (b) (4)

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(b) (4)

Table 6 DAC.000027 – Dark Slate Charger

Level	Description	Product Code / Code	Product Type / Type	Supplier(s) Site
0	Main Unit Platform 1 - ZRH/FPD 4.2 National Launch / Dark Slate beta	DAC.000027	Accessories	(b) (4)
.1	Assembly MU 4.2 Dark Slate-EAC+ANZ	ASM.000677	Assembly	
..2	Assembly 066_1005 Main Unit PCBA	ASM.000279.RD	Assembly	
..2	Assembly 18650 Battery with foam	ASM.000333	Assembly	
…3	Battery LiCoO2 3.7V 2600mAh 18650 with side PCM Cylindrical	BAT.000064.RD	Battery	
..2	Assembly 066_1026 Lid & Chassis Assembly Dark Slate	ASM.000667	Assembly	
..2	Assembly 066_1010 Sleeve & Foam Dark Slate	ASM.000391	Assembly	
..2	066_0001 Top Cover (Pantone 7547C, Soft Touch)	MHP.000334.RD	Machined Part	
..2	066_0002 Bottom Cover (Pantone 7547C, Soft Touch)	MHP.000335.RD	Machined Part	
.1	Secure bootstrap loader - 1.1.3 Platform ID:0x0014 Secure bootstrap loader (SBL) for ASM.000165.RD (P1 charger 4.1 PCB)	SFT.000052.RD	Software	
.1	ZRH charger firmware - 1.1.2 Platform ID:0x0014/0x001a Charger firmware for ASM.000165 and ASM.000279 hardware	SFT.000084	Software	

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Table 7 DAC.000028 – White Matte Charger

Level	Description	Product Code / Code	Product Type / Type	Supplier(s)
0	Main Unit Platform 1 - ZRH/FPD 4.2 National Launch / White Matte - beta	DAC.000028	Accessories	(b) (4)
.1	Assembly MU 4.2 White Matte-EAC+ANZ	ASM.000688	Assembly	
..2	Assembly 066_1005 Main Unit PCBA	ASM.000279.RD	Assembly	
..2	Assembly 18650 Battery with foam	ASM.000333	Assembly	
….3	Battery LiCoO2 3.7V 2600mAh 18650 with side PCM Cylindrical	BAT.000064.RD	Battery	
..2	Assembly 066_1026 Lid & Chassis Assembly White Matte	ASM.000671	Assembly	
..2	Assembly 066_1010 Sleeve & Foam White Matte	ASM.000392	Assembly	
..2	066_0001 Top Cover (White, Matte)	MHP.000431	Machined Part	
..2	066_0002 Bottom Cover (White, Matte)	MHP.000432	Machined Part	
.1	Secure bootstrap loader - 1.1.3 Platform ID:0x0014 Secure bootstrap loader (SBL) for ASM.000165.RD (P1 charger 4.1 PCB)	SFT.000052.RD	Software	
.1	ZRH charger firmware - 1.1.2 Platform ID:0x0014/0x001a Charger firmware for ASM.000165 and ASM.000279 hardware	SFT.000084	Software	

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Table 8 DV.000174 – Dark Slate Holder

Level	Description	Product Code / Code	Product Type / Type	Supplier(s)
0	Platform 1 - ZRH/THD 2.4/ZRH holder firmware - 1.1.2 (v2.4)/C28/P1 THD V2.4 Holder - Dark Slate	DV.000174	NGP Device	(b) (4)
.1	Assembly P1 THD V2.4 Holder Dark Slate IQOS	ASM.000689	Assembly	
..2	Assembly 064_1005 Heater Frame Assy	ASM.000281.RD	Assembly	
…3	Assembly F43H1 Heater control PCB	ASM.000123.RD	Assembly	
…3	Assembly 064_1206 Overmolded Heater	ASM.000718	Assembly	
…3	Battery LiFeP04 3.2V 120mAh 064_0013 Battery TSH Cylindrical	BAT.000040.RD	Battery	
..2	064_0002 Extractor (Black, -)	MHP.000351.RD	Machined Part	
..2	064_0005 Middle part (Black, Anodized)	MHP.000354.RD	Machined Part	
.1	Secure bootstrap loader - 1.0.1 Platform ID:0x0011/0x0018 Secure bootstrap loader (SBL) for ZRH FPD holder 4.1 & 4.2s	SFT.000042.RD	Software	
.1	ZRH charger firmware - 1.1.2 Platform ID:0x0018 ZRH FPD 4.2s Holder temperature control without clean overdue, deployment version	SFT.000075	Software	

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Table 9 DV.000180 – White Matte Holder

Level	Description	Product Code / Code	Product Type / Type	Supplier(s)
0	Platform 1 - ZRH/THD 2.4/ZRH holder firmware - 1.1.2 (v2.4)/C28/P1 THD V2.4 Holder - White Matte	DV.000180	NGP Device	(b) (4)
.1	Assembly P1 THD V2.4 Holder White Matte IQOS	ASM.000690	Assembly	
..2	Assembly 064_1005 Heater Frame Assy	ASM.000281.RD	Assembly	
…3	Assembly F43H1 Heater control PCB	ASM.000123.RD	Assembly	
…3	Assembly 064_1206 Overmolded Heater	ASM.000718	Assembly	
…3	Battery LiFePO4 3.2V 120mAh 064_0013 Battery TSH Cylindrical	BAT.000040.RD	Battery	
..2	064_0002 Extractor (Black, -)	MHP.000351.RD	Machined Part	
..2	064_0005 Middle part (Black, Anodized)	MHP.000354.RD	Machined Part	
.1	Secure bootstrap loader - 1.0.1 Platform ID:0x0011/0x0018 Secure bootstrap loader (SBL) for ZRH FPD holder 4.1 & 4.2s	SFT.000042.RD	Software	
.1	ZRH charger firmware - 1.1.2 Platform ID:0x0018 ZRH FPD 4.2s Holder temperature control without clean overdue, deployment version	SFT.000075	Software	

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e) (b) (4)

f) (b) (4)

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(b) (4)

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(b) (4)

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(b) (4)

Figure 14 Holder batteries packaging from (b) (4)

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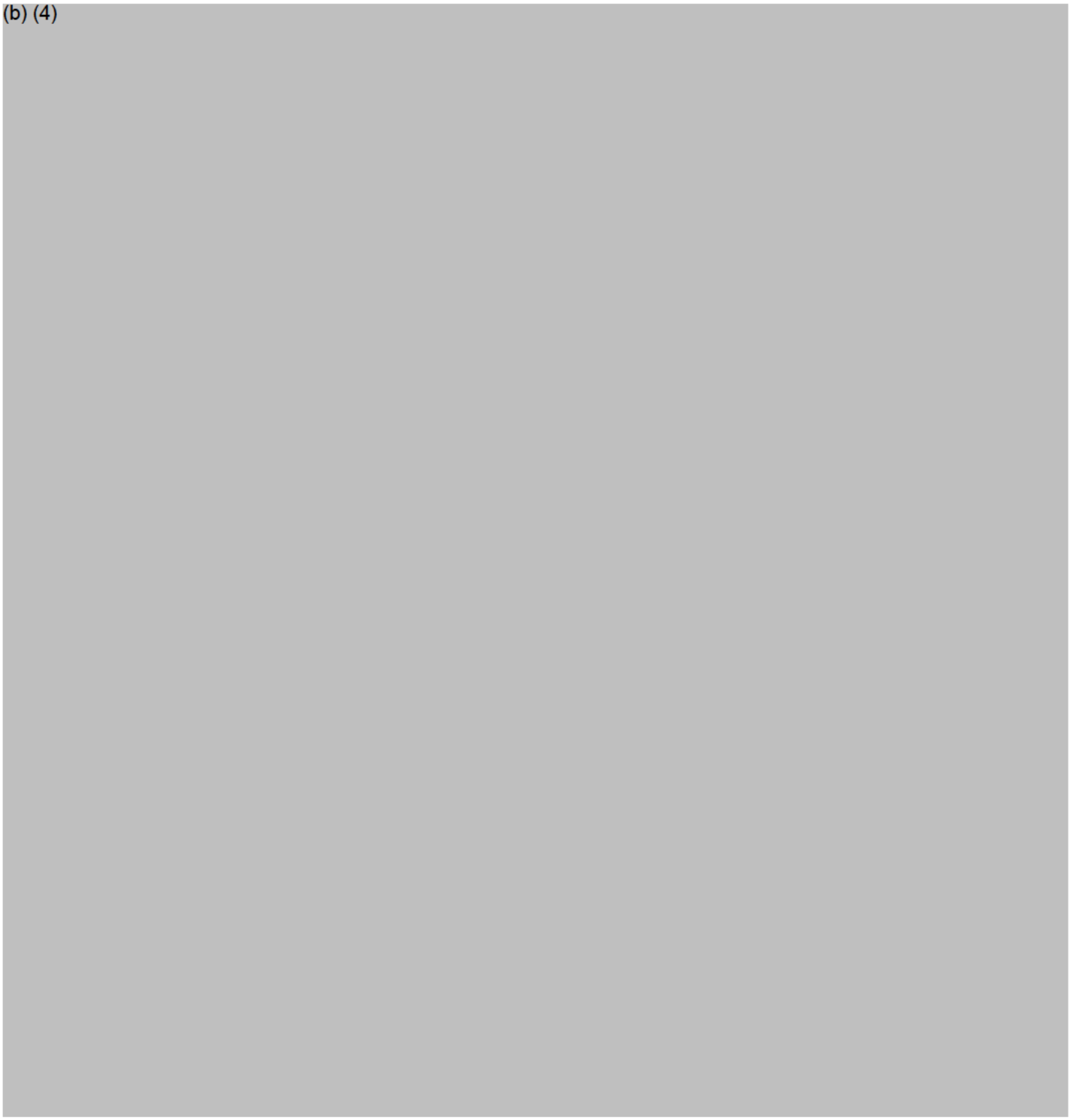
(b) (4)



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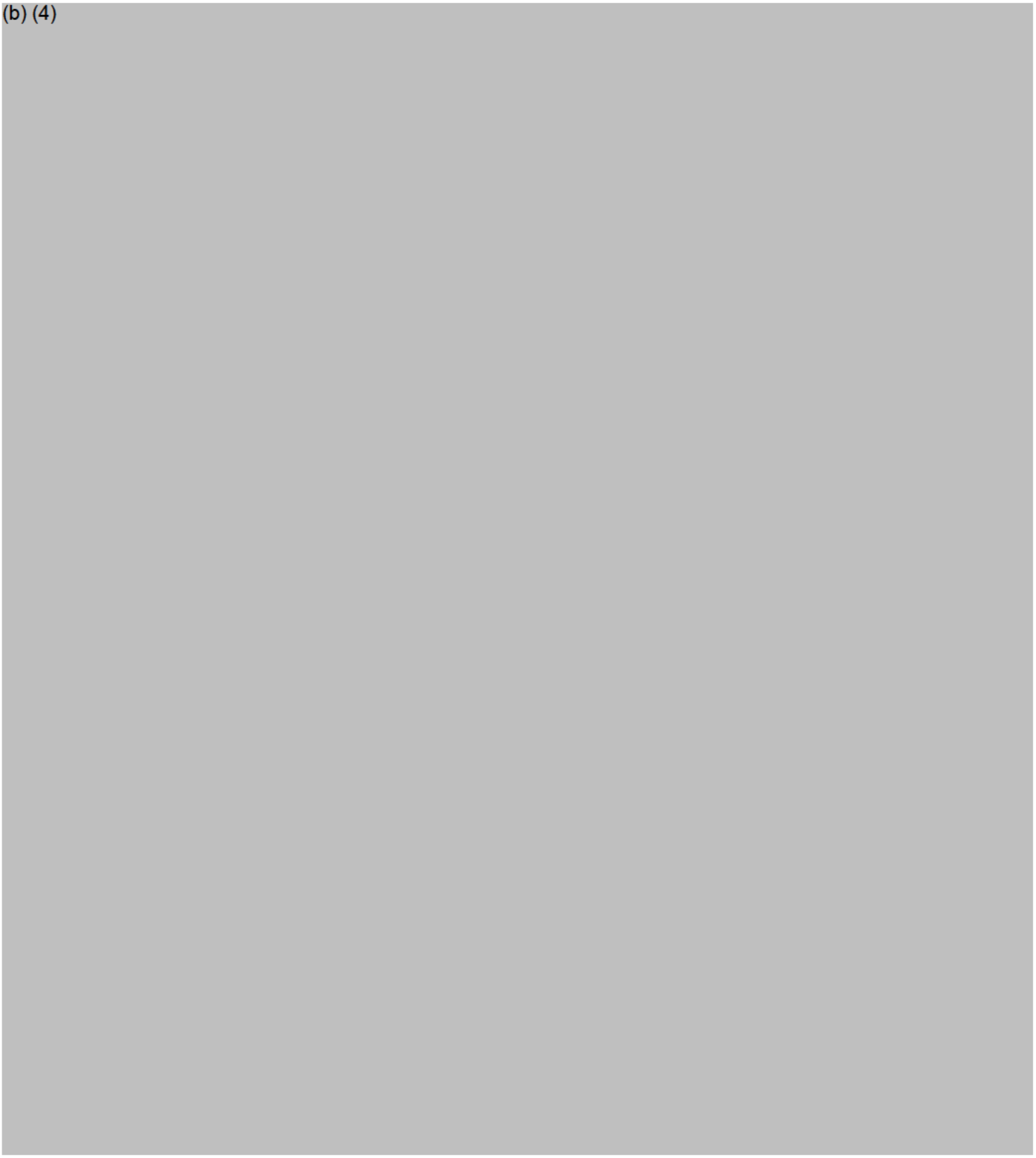
(b) (4)



PHILIP MORRIS
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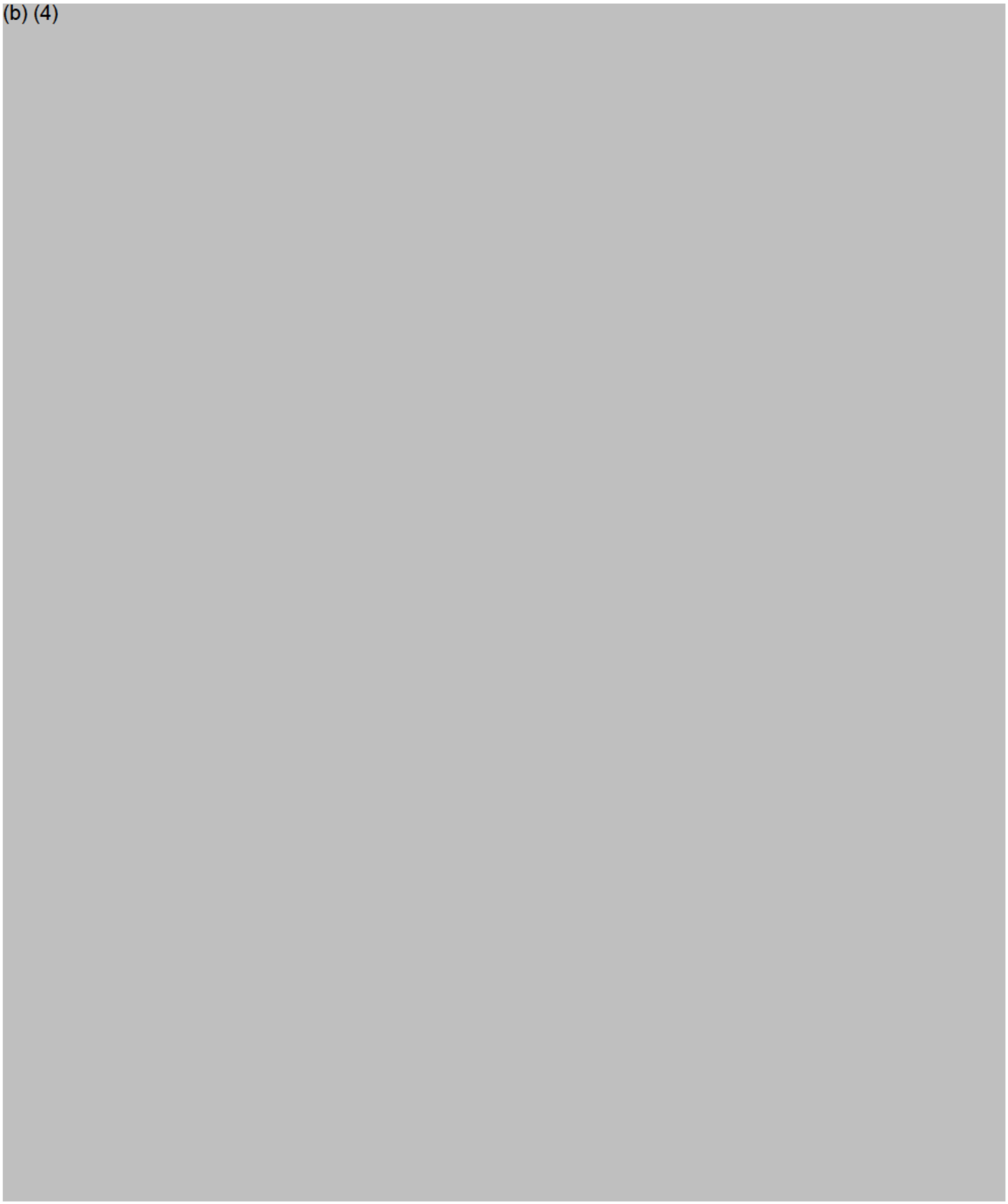
(b) (4)



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(b) (4)

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Table 10 Device Traceability

(b) (4)

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Table 11 Packaging Traceability

(b) (4)

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FDA QUESTION 8:

All of your MRTPAs, in section 6.1.1.3.4, pages 36 and 37, state that you "compare the FDA 18 HPHCs levels in the THS 2.2 aerosol to the median levels measured in smoke from cigarette brands commercially available in the U.S." and "…the median of the mean yields of each of the 31 cigarette brands was calculated on stick basis (referred to as "US market map Median (stick basis)." However, we cannot locate the underlying datasets in your applications with individual-level results from the analyses of the 31 commercial US cigarette brands. The full datasets along with the details of the analytical methodology are necessary for a comprehensive scientific review of your applications. Provide complete datasets and the analytical methodology for the US market map analysis. If this has already been provided, include a reference for the exact location of the information contained within your applications.

PMP S.A. RESPONSE:

As indicated in section 6.1.1.3.4 (page 36) of the applications, the HPHC levels in THS 2.2 aerosol were compared to median levels measured in smoke for cigarette brands commercially available in the U.S. The data from smoke chemistry analyses of 31 Philip Morris USA (PM USA) conventional cigarette brands for the FDA Abbreviated Harmful and Potentially Harmful Constituents (HPHCs) was provided by Altria Client Services. The 31 products were chosen to be representative of the PM USA portfolio and had been used for modeling HPHCs of the entire PM USA portfolio. This modeling work was presented at the Tobacco Science Research Conference in 2013 (Morton M. and Wang J. 2013).

The full datasets are provided in attachment:

- SR1_Q08-A1_HPHC-MarketMap-Results.xls

The analytical methods are described in the following document:

- SR1_Q08-A2_MarketMap-Test-Mtds.pdf

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FDA QUESTION 9:

All of your MRTPAs, in Appendix A3.3.-4 and Appendix A3.3.-8, include intermediate stability results (up to 6 months) for the Regular (Marlboro) and Menthol 1 (Marlboro Smooth Menthol) Heatsticks. However, you did not include intermediate stability results for the Menthol 2 (Marlboro Fresh Menthol) Heatstick. You state in stability study protocols located in Appendix A3.3.-3, page 8, table 9 for Regular Heatstick; Appendix A3.3.-7, page 8, table 9 for Menthol 1 Heatstick; and Appendix A3.3.-10, page 8, table 9 for Menthol 2 Heatsticks that 12 month stability studies will be performed. If you have completed the 12 month stability study for the Regular, Menthol 1, and Menthol 2 Heatsticks, and have completed the analysis of the intermediate stability results (up to 6 months) for the Menthol 2 Heatsticks, submit the full reports, including a detailed description of the TNCO and HPHC analyses, total particulate matter and physical parameters measured. If you have not yet completed your stability studies and analyses, provide a timetable with the current status of the study, when the study will be complete, and when you anticipate submitting the final report, dataset, and other associated study materials.

PMP S.A. RESPONSE:

The 12-month stability studies on Regular (Marlboro HeatSticks) and Menthol 1 (Marlboro Smooth Menthol HeatSticks) have been completed. The final stability reports are provided attached:

- Appendix A3.3-4 (v2) Stability Final Results (12 months) – Regular
- Appendix A3.3-8 (v2) Stability Final Results (12 months) – Menthol 1

These appendices replace the 6-month interim reports A3.3-4 and A3.3-8, respectively, included in Module 3 of the applications.

For Menthol 2 (Marlboro Fresh Menthol HeatSticks), the stability study is on-going. The 12-month time point began end August 2017. All analytical results will be available by end September 2017. The final report will be completed by end of October 2017 and will be submitted in amendment to the applications.

No intermediate report was written for the Menthol 2 stability study, as the relevance of an intermediate report is not demonstrated with only a few time points, which does not allow to perform appropriate statistical analyses. However, the results obtained to present did not show any particular trends or differences versus the observations made for the Menthol 1 variant.

The analytical methods are described in the applications in the following Module 3 Appendices:

A3.2.2-5 Carbon Monoxide (page 19)
A3.2.2-6 TPM, Nicotine, Triacetin
A3.2.2-7 Glycerin, Menthol
A3.2.2-8 Phenol
A3.2.2-9 Acrylamide, Acetamide
A3.2.2-10 Pyridine*
A3.2.2-11 Acetaldehyde, Butyraldehyde
A3.2.2-12 Ammonia
A3.2.2-13 Physical

*same method as Isoprene and Acrylonitrile

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FDA QUESTION 10:

All of your MRTPAs, in section 6.1.3.3, include an overview of the bioanalytical methods. Additionally, you state that the full validation reports are archived at Celerion and are available upon request. The full validation reports are necessary for FDA's review of the accuracy and precision of the data submitted. Provide the following full validation reports:

- Celerion 2013. Validation of an LC-MS/MS Method for the Determination of S-Benzyl Mercapturic Acid and S-Phenyl Mercapturic Acid in Human Urine. 22-Oct-2013. Celerion Study VAA98876-01. Zurich, Switzerland.
- Celerion 2014a. Validation of a LC-MS/MS Method for the Determination of Nicotine and Cotinine in Human Plasma (EDTA). 08-Aug-2014. Celerion Study AA33664-07. Lincoln, NE.
- Celerion 2014b. Validation of a LC-MS/MS Method for the Determination of Nicotine and Cotinine in Human Plasma (EDTA). 08-Aug-2014. Celerion Study AA33664-08. Lincoln, NE.
- Celerion 2014c. Validation of an LC-MS/MS Method for the Determination of 4 Aminobiphenyl, o-Toluidine, 2-Aminonaphthalene, and 1-Aminonaphthalene in Human Urine. 06-Nov-2014. Celerion Study ZZ37540-01. Lincoln, NE.
- Celerion 2014d. Validation of an LC-MS/MS Method for the Determination of Caffeine and Paraxanthine in Human Plasma (Heparin). 06-Oct-2014. Celerion Study ZZ25187-02. Lincoln, NE.
- Celerion 2014e. Validation of an LC-MS/MS Method for the Determination of HEMA in Human Urine. 30-Oct-2014. Celerion Study ZZ38073-01. Lincoln, NE.
- Celerion 2014f. Validation of an LC-MS/MS Method for the Determination of Nicotine, Cotinine, trans-3´-Hydroxycotinine, Nicotine-N-Glucuronide, Cotinine-N-Glucuronide, trans-3´-Hydroxycotinine-O-Glucuronide in Human Urine. 30-Oct-2014. Celerion Study ZZ33881-04. Lincoln, NE.
- Celerion 2015a. Validation of a LC-MS/MS Method for the Determination of 3- HPMA, HBMA, and CEMA in Human Urine. 22-Oct-2015. Celerion Study ZZ36536-01. Lincoln, NE.
- Celerion 2015b. Validation of an LC-MS/MS Method for the Determination of Total NNAL and Total NNN in Human Urine. 21-Dec-2015. Celerion Study ZZ34313-03. Lincoln, NE.
- Celerion 2016a. Validation of a LC-MS/MS Method for the Determination of Nicotine and Cotinine in Human Plasma (EDTA). 18-Mar-2016. Celerion Study AA33664-06, Lincoln, NE.
- Celerion 2016b. Validation of a LC-MS/MS Method for the Determination of Nicotine, Cotinine, and trans-3´-Hydroxycotinine in Human Plasma (EDTA). 18-Feb-2016. Celerion Study AA33664-01. Lincoln, NE

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- Celerion 2016c. Validation of an LC-MS/MS Method for the Determination of Monohydroxy-3-butenyl-mercapturic Acid in Human Urine. 03-Feb-2016. Celerion Study VAA98876-02. Zurich, Switzerland.
- Celerion 2016d. Validation of an LC-MS/MS Method for the Determination of Nicotine, Cotinine, trans-3′-Hydroxycotinine, Nicotine-N-Glucuronide, Cotinine-N-Glucuronide, trans-3′-Hydroxycotinine-O-Glucuronide in Human Urine. 08-Mar-2016. Celerion Study ZZ33881-03. Lincoln, NE.
- Celerion 2016e. Validation of an LC-MS/MS Method for the Determination of Total 1-Hydroxypyrene in Human Urine. 02-Feb-2016. Celerion Study VAA98876-03. Zurich, Switzerland.
- Celerion 2016f. Validation of an LC-MS/MS Method for the Determination of Total 3-Hydroxybenzo[a]pyrine in Human Urine. 02-Mar-2016. Celerion Study ZZ42666-01. Lincoln, NE.

PMP S.A. RESPONSE:

Given that the full validation reports are the property of Celerion, the reports have been submitted by Celerion to the FDA as a Tobacco Product Master file on August 23, 2017.

Once the Tobacco Product Master File number will be issued to Celerion by FDA, Celerion will send PMP S.A. a letter of authorization to incorporate information contained in their master file by reference. We will, in turn, submit the letter of authorization to FDA in an amendment to the applications.

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FDA QUESTION 11:

All of your MRTPAs state, in Section 3.3 (pp. 25, 46 and 47), that based on the 6 month stability data submitted for Regular (Appendix A3.3-4) and Menthol 1 (Appendix A3.3-8) Tobacco Heatsticks and the anticipated availability of acceptable 12 month data during the review process for all proposed Tobacco Heatstick products, a shelf life of 12 months is proposed for the Heatstick products included in MR0000059-61. Additionally, you state (Section 3.3, p. 4) that stability data is provided to support the proposed shelf life of the products. However, the stability data provided does not include any water activity (a_w) measurements for the products tested and measurement of a_w is also not included as a testing parameter in the stability protocol of the Heatstick products (Section 3.3, pp. 25, 46 and 48) included in MR0000059-61. Water and humectants have the potential to affect the moisture content of the product which, in turn, has the potential to affect microbial growth and product stability. Your MRTPAs provide a tabular list of ingredients (Section 3.1, p.10) that constitute the tobacco plug component of the Regular (Marlboro), Menthol 1 (Marlboro Smooth Menthol) and Menthol 2 (Marlboro Fresh Menthol) Tobacco Heatsticks, which includes water (used as a processing aid), glycerol and propylene glycol (used as a humectants). Additionally, you report (Section 3.1, Table 3, p.10) the amount of water added to the tobacco plug component of each Heatstick product in MR0000059-61. However, the amount of water added to a tobacco product is not a good indication of the amount of water available to support microbial growth. The water requirements for microbial growth are described in terms of the a_w of the substrate, which also takes into account humectants that modify the a_w[1,2]. Humectants are intended to keep a product moist. Because the presence of humectants can impact the moisture content of the product, humectants can affect the a_w of the product, which in turn may impact the product stability. Research has indicated that a_w limit varies with various solutes and humectants. Consequently, products with a high a_w tend to support microbial growth.[3]

To the extent that you possess such information, provide a_w measurements for the finished Heatstick products proposed to be marketed as modified risk tobacco products in MR0000059-61. In addition, to the extent that you possess such information, provide stability testing data for a_w measured over the proposed shelf life of 12 months for each Heatstick product in MR0000059-61. If available, provide full test data (including test protocols, quantitative acceptance criteria (if any), data sets, and a summary of the results) for all testing performed.

[1] Rockland, L.B.; Beuchat, L.R. 1987. Water activity: theory and applications to food (2nd ed.). New York: Marcel Dekker.

[2] Buchanan, R.L. and L.K. Bagi. 1997. Effect of water activity and humectant identity on the growth kinetics of *Escherichia coli* O157:H7. Food Microbiol. 14:413-423.

[3] Evaluation and Definition of Potentially Hazardous Foods - Chapter 3. Factors that Influence Microbial Growth http://www.fda.gov/Food/FoodScienceResearch/ucm094145 htm

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The accuracy, sensitivity, specificity and reproducibility of the test methods should be determined and documented. Providing the requested information will facilitate FDA's review and evaluation of the product stability of the proposed MRTPAs. If you do not possess such information, provide a statement to that effect.

PMP S.A. RESPONSE:

We did not directly monitor water activity (a_w) during our stability studies.

The direct measure of a_w (water activity) is the best way to estimate the risk of mold development in terms of moisture. The presence of humectants, namely glycerin, impacts the moisture content of the product mainly in reducing the a_w, for a same absolute water content. Based on the literature, the risk of mold development in tobacco products was found to be negligible when a_w does not exceed 0.7 (Mutasa et al. 1990). In the tobacco portion of the finished product, the moisture content is approximately 11%, and the humectant concentration exceeds 20%. Under these conditions, water activity is not expected to exceed 0.5.

A 15-month product monitoring study whereby HeatSticks were shipped by air from the manufacturing center in Bologna, Italy to several warehouses in Japan, and stored under standard warehouse conditions during 15 months, showed no meaningful alterations or systematic trends in the moisture content of the HeatSticks during the whole storage period. The results are shown in the Figure 16 below. Therefore, water activity under standard transportation and storage conditions would not be expected to exceed 0.5.

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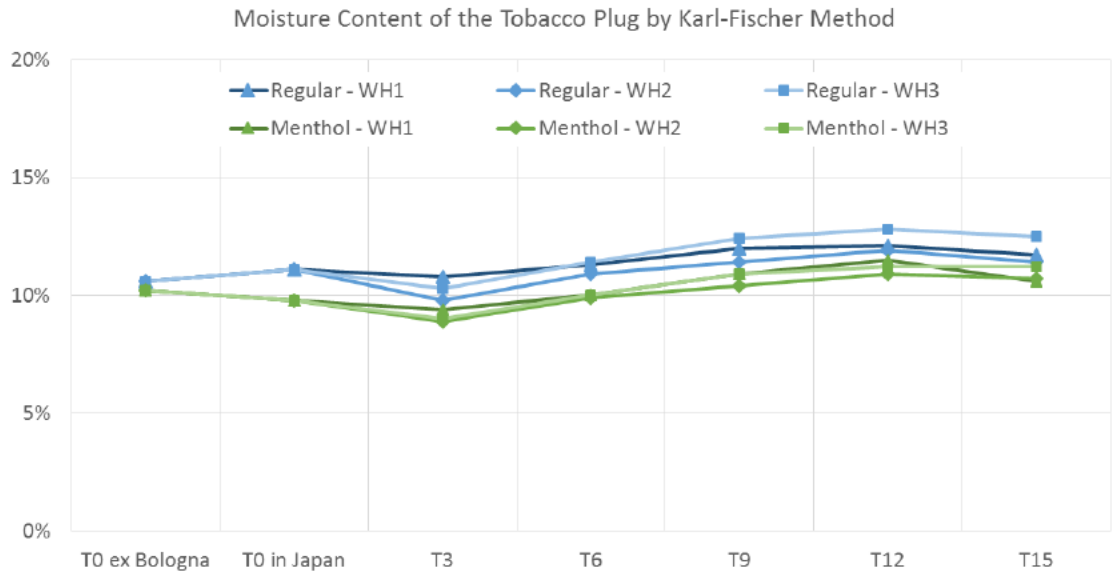

Figure 16 **Moisture content of the tobacco plug of a THS2.2 regular (CONS.01991.RD which corresponds to (b) (4) regular) and a THS2.2 menthol (CONS.02000.RD which corresponds to (b) (4) Menthol 2) as measured with the Karl-Fischer method (ISO 6488) at three different warehouses in Japan (WH1, WH2, WH3) and prior shipment (T0 ex Bologna) over a period of 15 months show no systematic trends in the moisture content up to T15.**

As a direct measurement of a_w in stability studies will provide analytical confirmation of the absence of water available which could potentially support microbial growth, this measurement will be added as an endpoint of our stability studies, with clearly defined acceptance criteria.

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FDA QUESTION 12:

All of your MRTPAs include the IQOS system with three types of tobacco Heatsticks: Marlboro Heatsticks, Marlboro Fresh Menthol Heatsticks, and Marlboro Smooth Menthol Heatsticks. You indicate that the following products were tested in the studies you provided in your MRTPAs:

Section	Study	Tobacco Stick	Holder
7.2	RLS_ZRH_201 5-250 NRU - Regular	ZRH/C3/DORADO II/CL/Flavor Ron(b))/9A222D SI/C3 white	ZRH THD 2.4 FPD 4.4
7.2	RLS_ZRH_201 5-249 NRU - Menthol	ZRH/C3.1/DORADO I/CL/Menthol/Flavor AC Mint Vinny	ZRH THD 2.4 FPD 4.4
7.2	RLS_ZRH_201 5-252 MLA - Regular	ZRH/C3/DORADO II/CL/Flavor Ron(b)) 9A222D SI/C3 white	ZRH THD 2.4 FPD 4.4
7.2	RLS_ZRH_201 5-251 MLA - Menthol	ZRH/C3.1/DORADO I/CL/Menthol/Flavor AC Mint Vinny	ZRH THD 2.4 FPD 4.4
7.2	RLS_ZRH_201 5-253 Ames Assay – Regular	ZRH/C3/DORADO II/CL/Flavor Ron(b)) 9A222D SI/C3 white	ZRH THD 2.4 FPD 4.4
7.2	RLS_ZRH_201 5-254 Ames Assay – Menthol	ZRH/C3.1/DORADO I/CL/Menthol/Flavor AC Mint Vinny Version 3.1	ZRH THD 2.4 FPD 4.4
7.2	15006 90 day OECD Inhalation - Regular	ZRH/DDA1/C3/F Reform 1/CAST LEAF-CL/Flavor/Reynaldo	ZRH-CH/4.2/3.1.3/C28
7.2	15025 90 day OECD Inhalation - Menthol	ZRH /(b) / C3 / F Reform1 / CAST LEAF - CL / Menthol / Flavor / Mint Veronica	THS2.2
7.2	15020 Lung Cancer Tumorigenesis in A/J Mice	RRP THS2.2 CONS.01937.RD	ZRH/FPD4.2/3.2.2/C28/
7.3	04 REXC04JP	THS 2.2 Menthol THS Tobacco Sticks	
7.3	05 PK05JP	THS 2.2 Menthol THS Tobacco Sticks	
7.3	06 PK06US	THS 2.2 Menthol THS Tobacco Sticks	
7.3	07 REXA07JP	THS 2.2 Menthol THS Tobacco Sticks	
7.3	08 REXA08US	THS 2.2 Menthol THS Tobacco Sticks	
7.5	S 170900 Organotypic Acute Human Bronchial Tissue Study	THS2.2/DDA1/C3/ F Reform1 /CAST LEAF – CL /Flavor /Reynaldo	CH FDP4.2
7.5	S 172200 Organotypic Acute Human Nasal Tissue Study	ZRH/DDA1/C3/ F Reform1 / CAST LEAF – CL /Flavor / Reynaldo	CH FDP4.2

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Section	Study	Tobacco Stick	Holder
7.5	S 174300 Organotypic Acute Human Buccal Tissue Study	ZRH/DDA1/C3/ F Reform1 / CAST LEAF – CL /Flavor / Reynaldo	CH FDP4.2
7.5, MR0000066	S 179800 Organotypic Acute Human Gingival Tissue Study	ZRH/DDA1/C3/CAST LEAF– CL/Flavor/Reynaldo	DC.000067.RD(1)/Z RH/FPD4.2/3.2.2/C2 8/FDP 4.2
7.5, MR0000074	S 160400 Organotypic Acute Human Coronary Arterial Tissue Study – Adhesion Assay	THS 2.2 (no Heatstick indicated)	None indicated
7.5, MR0000074	S 173900 Organotypic Acute Human Coronary Arterial Tissue Study – Migration Assay	ZRH/DDA1/C3/CAST LEAF– CL/Flavor/Reynaldo	DC.000067.RD(1)/Z RH/FPD4.2/3.2.2/C2 8/FDP 4.2 Cigarette Holder/3.2.2 software upgrade/Configuration without forced-cleaning feature
7.5	15015 ApoE-/- Mouse Study	Del/C3/FR1/Rdo	FPD 4.2

Knowledge of the characteristics (*e.g.*, ingredients, additives, and components) for the products used in your studies will enable FDA to compare the products tested in your submitted studies with the products in your MRTPAs. Clarify if any of the products tested in the studies listed above are the same products as products in MR0000059 – MR0000061. If so, identify which of the specific study products corresponds to each of the proposed MRTPs and which do not. If the study products listed above are different than those in MR0000059 – MR0000061, provide information on the characteristics (*e.g.*, levels and identities of ingredients, additives, and components) of the test articles in each study and a description of how the test articles from the above studies compare to the proposed MRTPs in MR0000059 – MR0000061 under review. Provide a scientific justification for bridging from the study products to the proposed MRTPs under review in MR0000059 – MR0000061, including, for the clinical studies, any information on potential differences in product use behavior.

PMP S.A. RESPONSE:

All products tested in the above-mentioned studies correspond to the Tobacco Heating System with Regular, Menthol 1 and Menthol 2 variants. The product codes for the device and Tobacco Sticks subject of the applications (THS 2.2, THD 2.4) are listed in Section 3.2.1.2 Table 1 (page 6) of the MRTPAs. In Section 3.2.1.4.3 Table 3 (pgs 14-16) of the MRTPAs, 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.

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Changes to product are captured by assignment of new product codes to ensure the traceability of changes within our product lifecycle management system.

In Table 12 below, the codes for the products (Tobacco Stick and Holder) tested during the above-mentioned studies are indicated. Although the quantitative composition of all ingredients/additives/components are not identical, they are comparable to the proposed MRTPs 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 applications.

As described in Section 3.2.1.4 of the applications, PMI applies a Change Management process to ensure that all proposed changes are assessed with regards to the product performance, safety, and quality prior to implementation.

Product performance comparability provides a set of acceptance criteria for HPHC levels in the aerosol of THS2.2 and for its *in vitro* biological activity. These criteria ensure that the performance of THS2.2 remains unchanged, i.e. remains within the variability of analytical methods, of the tobacco crop over time and, most importantly, and has aerosol deliveries comparable to the products assessed during studies.

The following three points were considered in assessing the tested products and their comparability with the products subject of the applications:

1. The identification of codes for products (Tobacco Sticks and Holders) used in each study and a comparison of the characteristics of the test products with those MR0000059-MR0000061 subject of the applications.

2. Additional analytical data, as provided in the applications, which was generated to demonstrate comparability of the products by assessing the chemical composition of the aerosol and/or its biological activity *in vitro*, as well as sensory evaluation.

3. Available data to date from the clinical studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US with FR-1 blend; and THS-PBA-07-US using Dorado blends) regarding the total number of tobacco products consumed on a daily basis (the sum of Tobacco Sticks and cigarettes) in smokers using THS.

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PRODUCT IDENTIFICATION

The test article references (for Tobacco Stick and Holder) listed for the studies mentioned in Question 12 above consist of various internal descriptive references. The identifying product codes, corresponding to the individual parts (Tobacco Stick and Holder) of THS 2.2, with their respective batch numbers, are listed for the requested studies in Table 12. These codes reference a full design description of the product, which includes the appropriate drawings, composition, product and component specifications, electronic schematics, layouts and PCB design. It also includes information on vendors and manufacturers.

Table 12 Batches and Codes of Tobacco Sticks and Holders used per the listed studies

Section	Study	Tobacco Stick		Holder	
		Batch	CONS Code	Batch	DV Code
7.2	RLS_ZRH_2015-250 NRU - Regular	B-21526	CONS.02402.RD	B-21520	DV.000174
7.2	RLS_ZRH_2015-249 NRU - Menthol	B-21025	CONS.02728.RD	B-21520	DV.000174
7.2	RLS_ZRH_2015-252 MLA - Regular	B-21526	CONS.02402.RD	B-21520	DV.000174
7.2	RLS_ZRH_2015-251 MLA - Menthol	B-21025	CONS.02728.RD	B-21520	DV.000174
7.2	RLS_ZRH_2015-253 Ames Assay - Regular	B-21526	CONS.02402.RD	B-21520	DV.000174
7.2	RLS_ZRH_2015-254 Ames Assay - Menthol	B-21025	CONS.02728.RD	B-21520	DV.000174

(table continues)

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Section	Study	Tobacco Stick		Holder	
		Batch	CONS Code	Batch	DV Code
7.2	15006 90 day OECD Inhalation - Regular	B-00829	CONS.00007.RD	B-00989 B-02351 B-03564 B-04542	DV.000010.RD
7.2	15025 90 day Inhalation - Menthol	B-11129	CONS.01785.RD	B-11452	DV.000067.RD
7.2	15020 Lung Cancer Tumorigenesis in A/J Mice	B-12832 B-17880 B-22622	CONS.01937.RD CONS.02444.RD CONS.02444.RD	B-06050	DV.000067.RD
7.3	04 REXC04JP	B-05772	CONS.00860.RD	B-05252	DV.000047.RD
7.3	05 PK05JP	B-05775	CONS.00863.RD	B-05252	DV.000047.RD
7.3	06 PK06US	B-06238	CONS.00863.RD	B-06690	DV.000047.RD
7.3	07REXA07JP	B-08544 B-05775	CONS.00863.RD	B-05252 B-07113	DV.000047.RD
7.3	08 REXA08US	B-06239 B-08545	CONS.00863.RD	B-07113 B-06690	DV.000047.RD
7.5	S 170900 Organotypic Acute Human Bronchial Tissue Study	B-05771 B-08163 B-13055	CONS.00860.RD CONS.01496.RD CONS.01938.RD	B-06050 B-18731	DV.000067.RD

(table continues)

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Section	Study	Tobacco Stick		Holder	
		Batch	CONS Code	Batch	DV Code
7.5	S 172200 Organotypic Acute Human Nasal Tissue Study	B-08163 B-11433 B-13055	CONS.01496.RD CONS.01719.RD CONS.01938.RD	B-06050 B-18731	DV.000067.RD
7.5	S 174300 Organotypic Acute Human Buccal Tissue Study	B-13055	CONS.01938.RD	B-18731	DV.000067.RD
7.5, MR0000066	S 179800 Organotypic Acute Human Gingival Tissue Study	B-23862	CONS.02444.RD	B-18731	DV.000067.RD
7.5, MR0000074	S 160400 Organotypic Acute Human Coronary Arterial Tissue Study – Adhesion Assay	B-08164	CONS.01496.RD	B-06050	DV.000067.RD
7.5, MR0000074	S 173900 Organotypic Acute Human Coronary Arterial Tissue Study – Migration Assay	B-08164	CONS.01496.RD	B-06050 B-11420	DV.000067.RD
7.5	15015 ApoE-/- Mouse Study	B-05879 B-06132 B-08164	CONS.00860.RD CONS.00115.RD CONS.01496.RD	B-06143 B-07250 B-09492	DV.000067.RD

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As described in Appendix A3.2.1-21 of the applications, all changes are categorized as major or minor through risk and impact assessment. Tests are performed, according to established criteria, to determine product performance, and therefore comparability.

Table 13 and Table 14, respectively, list the Holder and Tobacco Stick codes in chronological order, per variant, that were used in the above-mentioned studies, alongside the corresponding sections of the MRTPAs providing data to support the changes and the comparability decision of the changes. A brief description of the changes are summarized thereafter.

Device

Table 13 Identification of the Holders and supporting data

Device Code	Color	Reference in MRTPA
DV.000010.RD	Black	A3.2.1-20, Section 7.2
DV.000047.RD	Black	Section 3.2.1.4.3, A3.2.1-20, Section 7.3.1
DV.000067.RD	Black	A3.2.1-20, Section 7.2, Section 7.5
DV.000174	Dark Slate	Section 3.2.1.4.3, A3.2.1-19, A3.2.1-20, Section 3.3, Section 7.1, Section 7.2, Section 7.3.2
DV.000180	White	A3.2.1-20

As described in Appendix A3.2.1-20 Development Report included in the applications, (b) (4)
(b) (4)

Holder DV.000047.RD was (b) (4)
(b) (4)
.

DV.000174 and DV.000180 are (b) (4)
(b) (4) The comparability study for the change in manufacturing site can be found in Appendix A3.2.1-18 of the applications, whilst the comparability study for (b) (4)
(b) (4) can be found in Appendix A3.2.1-19 of the applications.

All Holders described in Table 13 were deemed comparable.

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Since the MRTPAs were submitted in December 2016, some minor changes have been made to the Device; these are listed in Appendix A3.2.1-21 (v2) provided in attachment. These changes have been made t (b) (4) . None of these changes were deemed to have impact on the product performance and were part of a continuous improvement plan to address product quality. The changes were all managed according to the internal PMI processes for change management.

Tobacco Stick

Table 14 Identification of the Tobacco Sticks and Supporting Data

Consumable Code	Variant Type	Referenced in MRTPA
CONS.00007.RD	Regular	Section 3.2.1.4.3, A3.2.1-20, Section 7.2
CONS.00115.RD	Regular	Section 3.2.1.4.3, A3.2.1-14, A3.2.1-20, Section 7.5, Section 7.3.1
CONS.00860.RD	Regular	Section 3.2.1.4.3, A3.2.1-20, Section 7.3.1
CONS.01496.RD	Regular	Section 7.5
CONS.01719.RD	Regular	Section 3.2.1.4.3, A3.2.1-15, A3.2.1-20, Section 7.5
CONS.01937.RD	Regular	Section 7.2
CONS.01938.RD	Regular	Section 3.2.1.4.3, A3.2.1-16, A3.2.1-20, Section 7.5
CONS.02402.RD	Regular	Section 3.2.1.4.3, A3.2.1-20, Section 7.2
CONS.02444.RD	Regular	Section 7.2. Section 7.5
CONS.02873.RD	Regular	Section 3.2.1.4.3, A3.2.1-17, A3.2.1-20, Section 3.3, Section 7.1
CONS.02728.RD	Menthol 1	Section 3.2.1.4.3, A3.2.1-16, A3.2.1-20, Section 7.2, Section 7.3.2
CONS.02807.RD	Menthol 1	Section 3.2.1.4.3, A3.2.1-20, Section 3.3, Section 7.1
CONS.00863.RD	Menthol 2	Section 3.2.1.4.3, A3.2.1-14, A3.2.1-20, Section 7.3.1
CONS.01785.RD	Menthol 2	Section 3.2.1.4.3,A3.2.1-15, A3.2.1-20, Section 7.2
CONS.02806.RD	Menthol 2	Section 3.2.1.4.3, A3.2.1-20, Section 3.3, Section 7.1

- Regular Variant

As documented in Appendix A3.2.1-20 and Section 3.2.1.4 Table 3 of the applications, CONS.00007.RD was (b) (4)

CONS.00115.RD was (b) (4)

(b) (4)

CONS.00860.RD was (b) (4)

(b) (4)

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CONS.01719.RD was (b) (4)
(b) (4)
(b) (4)

CONS.01938.RD (b) (4)

CONS.02873.RD, submitted as the proposed MRTP Regular (MR0000059), is produced in (b) (4) The comparability study and data supporting the conclusion that the Regular variant subject of the application and the prior versions of the same product (with different consumable codes) are comparable as described in Appendix A3.2.1-17 of the applications.

In addition to the above information, appendix SR1_Q12-A1 Compositions - Regular, submitted herewith provides a comparison of the ingredients, additives and components for each of the described Regular Tobacco Stick consumable codes used in the above-mentioned studies and the proposed MRTP Regular, MR0000059.

The variations in composition summarized below correspond to changes made during the change of manufacturing site and are primarily due to (b) (4)

Outer Paper

The lower quantities observed in the CONS.02873.RD in the Outer paper and Outer paper adhesive can be explained by (b) (4)
(b) (4) .

Hollow Acetate Tube (HAT)

The varying quantities that can be observed for CONS.02873.RD in the HAT are due to the (b) (4)

Glue

(b) (4)

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Tipping Paper

(b) (4)

All Regular Tobacco Sticks listed above are considered comparable (data found in Appendices A3.2.1-14, A3.2.1-15, A3.2.1-16, A3.2.1-17 of the applications).

Since the submission of the applications end-2016, some minor changes have been made to the Regular Tobacco stick. These are listed in Appendix A3.2.1-21 (v2) provided in attachment, and are reflected in the updated Tobacco Stick bill of materials (BOM) provided in Appendix A3.2.2-2 (v2). These changes have been made to (b) (4) (b) (4) and are deemed to have no impact on product performance.

- Menthol 1 Variant

CONS.02728.RD was (b) (4) (b) (4) (b) (4)

CONS.02807.RD, submitted as the proposed MRTP Menthol 1 (MR0000060), is produced in (b) (4) The comparability study and data supporting the conclusion that this and the above consumable code is comparable.(b) (4) can be found in Appendix A3.2.1-17 of the applications.

Appendix SR1_Q12-A2, Compositions - Menthol 1, submitted herewith provides a comparison of the ingredients, additives and components for the described Menthol 1 Tobacco Stick consumable code used in the above-mentioned studies and the proposed MRTP Menthol 1, MR0000060.

The variations in composition summarized below correspond to changes made during the change of manufacturing site and are primarily due to (b) (4) (b) (4)

Outer Paper

The lower quantities observed in the CONS.02807.RD in the Outer paper and Outer paper adhesive can be explained by (b) (4) (b) (4)

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HAT

The varying quantities that can be observed for CONS.02807.RD in the HAT are due to (b) (4)

Menthol Thread

(b) (4) .

Glue

(b) (4)

The Menthol 1 Tobacco Sticks listed above are considered comparable (data found in Appendix, A3.2.1-17 of the applications).

Since the submission of the applications end-2016, some minor changes have been made to the Menthol 1 Tobacco Stick. These are listed in Appendix A3.2.1-21 (v2) provided in attachment, and reflected in the updated Tobacco Stick bill of materials (BOM) provided in Appendix A3.2.2-3 (v2). These changes have been made to address (b) (4) and are deemed to have no impact on product performance.

- Menthol 2 Variant

CONS.0863.RD, (b) (4) CONS.01785.RD was (b) (4)

CONS.02806.RD, submitted as the proposed MRTP Menthol 2 (MR0000061), is produced in (b) (4) The comparability study and data supporting the conclusion that this and the above consumable codes are comparable, (b) (4) can be found in Appendix A3.2.1-17 of the applications.

Appendix SR1_Q12-A3, Compositions - Menthol 2, submitted herewith provides a comparison of the ingredients, additives and components for the described Menthol 2 Tobacco Stick consumable codes used in the above-mentioned studies and the proposed MRTP Menthol 2, MR0000061.

The variations in composition summarized below correspond to changes made during the change of manufacturing site and are primarily due to (b) (4)

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Outer Paper

The lower quantities observed in the CONS.02806.RD in the Outer paper and Outer paper adhesive can be explained by (b) (4) (b) (4) .

HAT

The varying quantities that can be observed for CONS.02806.RD in the HAT are due to the (b) (4) (b) (4)

Menthol Thread

(b) (4) .

Glue

(b) (4)

All Menthol 2 Tobacco Sticks listed above are considered comparable (data found in Appendix, A3.2.1-17 of the applications).

Since the submission of the applications end-2016, some minor changes have been made to the Menthol 2 Tobacco Stick. These are listed in Appendix A3.2.1-21 (v2) provided in attachment, and reflected in the updated Tobacco Stick bill of materials (BOM) provided in Appendix A3.2.2-3 (v2). These changes have been made to (b) (4) (b) (4) and are deemed to have no impact on product performance.

In addition to the comparison of product composition, presented above, all product changes after performance lock are evaluated as part of the change management process, described in Section 3.2.1.4 of the applications, and major product changes may be assessed by means of product performance comparability as described in Section 3.2.1.4.2. All major changes between the product at performance lock, the products tested in studies listed in Question 12, and the three variants subject of the applications are provided in Section 3.2.1.4.3, Table 3 of the applications, including where applicable references to any additional testing performed at the time to demonstrate comparability of the post-change products to the product at performance lock.

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Briefly the major changes during development were,

1. In terms of the composition of the tobacco mixture, the most notable change was the (b) (4) This change (b) (4) has been assessed (Acceptance Criteria: Appendix A3.2.1-13 in the applications) by means of aerosol chemistry studies whereby it was demonstrated that the levels of HPHCs in the aerosol of the products with the (b) (4) (b) (4) are within the ranges of the levels of emissions of the product with the (b) (4) considering crop variability and method variability over time (Appendix A3.2.1-16).

   In addition, two comparative sensory evaluations of the blends, (b) (4) (b) (4), performed by a quantitative descriptive panel, showed comparable sensory characteristics between (b) (4) (b, as illustrated in Figure 17. The reports are provided in attachment:

   - SR1_Q12-A4 Sensory Evaluation Report – Dorado Dry Blends TO-04796
   - SR1_Q12-A5 Sensory Evaluation Report – QDP Consumer Test Platform 1 ZRH

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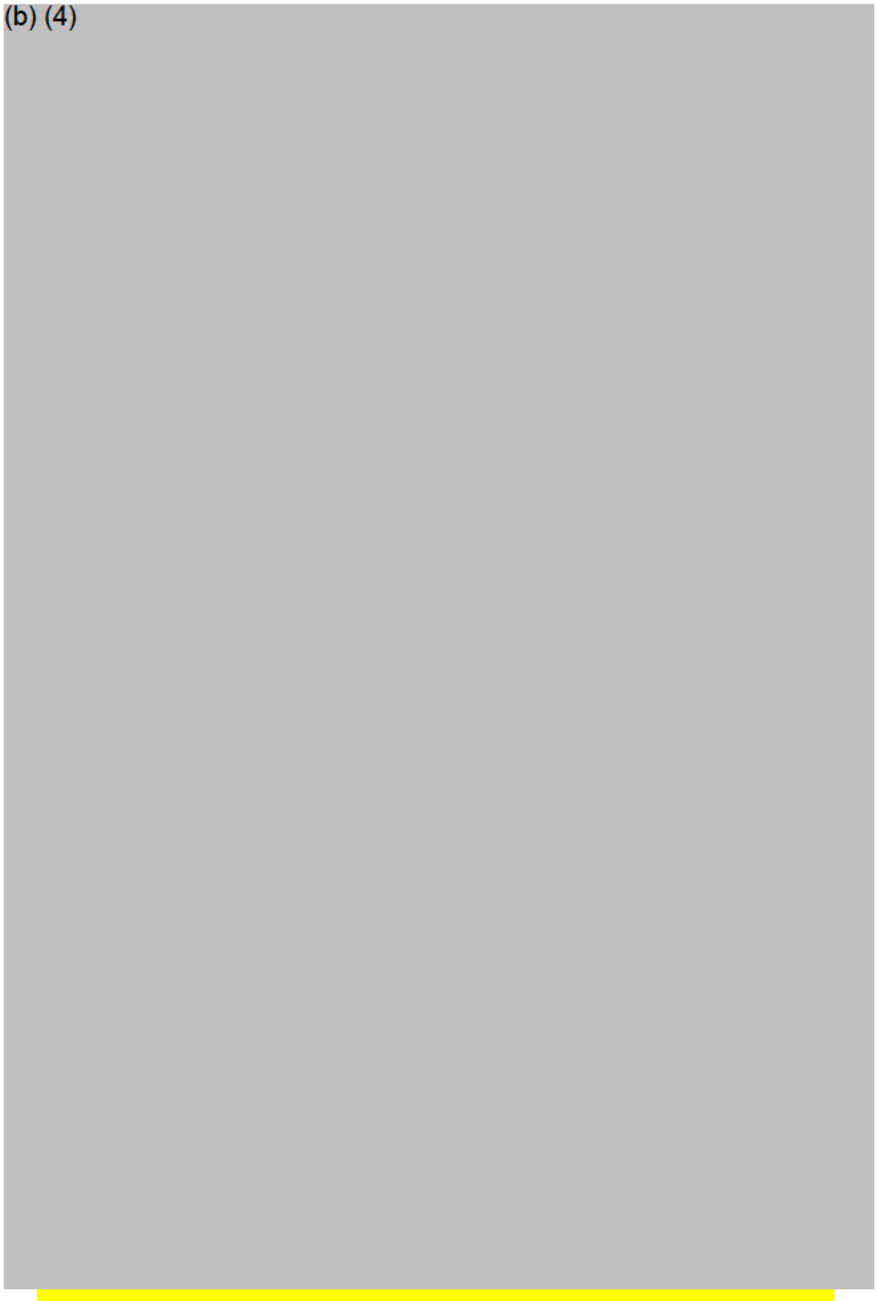

Figure 17 **Graphical Representations of the Sensory Profiles of** (b) (4)
(b) (4)

2. In order to support the need to scale-up the manufacturing process manufacturing site, changes have been made. Changes in process (to optimize efficiency), facilities and personnel required a large degree of qualification testing to ensure the product performance and quality were not impacted by the changes. In addition to the qualification of the facilities and equipment, comparability testing was performed to ensure the product produced is representative of that used to obtain the assessment data.

   The conclusion for all site changes was that the HPHCs derived from the two products from the different manufacturing sites could be considered equivalent across all measured HPHCs. The reports supporting these conclusions can be found in Appendix A3.2.1-14, A3.2.1-17 and A3.2.1-18 in the applications.

3. Change of the device from the developmental version THD2.2 to the commercial soft touch version THD2.4 (Appendix A3.2.1-19 in the applications).

In summary, 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 application 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. Furthermore, sensory evaluation profiles were similar for blends tested which indicates that no differences in product use would be expected.

Product Use in Clinical Studies and Observational Study

Product consumption was monitored during the ambulatory periods of both ZRHM-REXA-07-JP and ZRHM-REXA-08 clinical studies (FR-1 blend; CONS.00863.RD) and the THS-PBA-07-US observational study (Dorado blends; CONS.02728.RD) and measured as the number of cigarettes and THS Tobacco Sticks used per day as self-reported on a stick by stick by the study participants on an electronic diary. Regardless of the product blend used, product consumption in smokers of cigarettes in the THS group was comparable during the observational period to the cigarette consumption reported at baseline by smokers in the studies conducted. Results are presented below for the group of smokers in the THS group (from the full analysis set population).

The ZRHM-REXA-07-JP and ZRHM-REXA-08-US were randomized, open-label, parallel group reduced exposure studies included THS (*ad libitum* use), cigarette (*ad libitum* use), and smoking abstinence (SA) arms and had two distinct periods: a five day confinement investigational exposure period to investigational product in confinement followed by an eighty-five-day ambulatory investigational exposure period. These studies enrolled healthy subjects smoking at least 10 menthol cigarettes per day. The full analysis set population (FAS) in the THS group consisted of 78 subjects, and 80 subjects in ZRHM-REXA-07-JP and ZRHM-REXA-08-US respectively.

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The THS-PBA-07-US study was a single group, prospective observational study from 8 limited geographic areas of the United States evaluating subject-reported stick by stick consumption of THS Tobacco Sticks and cigarettes in participants receiving THS Tobacco Sticks free of charge. This actual use study of 8 weeks (1-week Baseline period+ 6 week observational period+ 1 week close out period) enrolled participants 18+ years old adult daily smokers of cigarettes with positive intention to use THS. The FAS population consisted of 1106 participants who recorded their consumption of at least one cigarette in the electronic diary during.

The full clinical study reports and associated tables of both studies are provided in the Section 7.3.1 of the applications; whereas the full study report and associated tables of the THS-PBA-07-US study are provided in the Section 7.3.2.

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Table 15 Summary of Average Reported Daily Product Use (Tobacco Sticks and cigarettes) in THS users (FAS population) from ZRHM-REXA-08-US, ZRHM-REXA-07-JP, and THS-PBA-07-US at the End of the Observational Period

	FR- 1 Blend		Dorado Blends
	ZRHM-REXA-08-US Over 90 days	**ZRHM- REXA-07-JP Over 90 days**	**THS-PBA-07-US (week 6)**
Baseline Tobacco consumption	n=79	n=78	n=1106
CC	12.1 (3.62)	13.0 (3.83)	10.2 (7.22)
Ambulatory tobacco consumption	n=76	n=76	n=1106*
THS +CC	13.7 (7.17)	12.1 (6.16)	9.3 (6.56)

Abbreviations: THS: Tobacco Heating System Tobacco Sticks; CC: cigarette; FAS: Full analysis set.
Means (standard deviations) are provided in the table
Sources: Table 15.2.2.1.1 and Table 15.2.2.5.1 from ZRHM-REXA-08-US and ZRHM-REXA-07-JP clinical study reports.
*Results of 3 participants, who were in the category "no CC or HeatSticks use" at Week 6, of 137 participants who dropped out before Week 6 and 1 participant who did not document CC use or HeatSticks use at Week 6 but was not deemed a drop-out because use of other tobacco products was documented at Week 6 are not presented in the table.
Table 15.2.3.11, Table 15.2.4.1, Table 15.2.4.2, Table 15.2.4.3, FAS ByUsageW6, Table 15.2.3.11, Table 15.2.4.1, Table 15.2.4.2, Table 15.2.4.3 from THS-PBA-07-US study report.

In the clinical studies ZRHM-REXA-08-US and ZRHM-REXA-07-JP studies (FR-1 blend) and the observational THS-PBA-07-US study (b) (4)), overall the daily average tobacco product consumption (THS Tobacco Sticks and cigarettes) in participants using THS was comparable during the observational period to the cigarette consumption reported at baseline when they were smoking their cigarettes. The different tobacco blends had no apparent impact on product use behavior in terms of total daily tobacco consumption.

Discussion:

All continuous improvement and sustainability measures are assessed within the context of product safety, performance and quality through our change management process.

Although there are slight differences in quantitative composition between articles tested and the products subject of the applications, comparability has been demonstrated. Variations in components, such as glue, paper, etc., have no impact on the final product attributes of aerosol deliveries. Comparability of aerosol deliveries of (b) (4) tobacco blends has been confirmed. The results of sensory testing performed to evaluate these changes in tobacco blends in-use showed similar profiles. Therefore, there is no indication that use behavior would differ.

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Conclusion:

The products subject of the applications:

- MR0000059 Marlboro HeatSticks (Regular)
- MR0000060 Marlboro Smooth Menthol HeatSticks (Menthol 1)
- MR0000061 Marlboro Fresh Menthol HeatSticks (Menthol 2)

are deemed comparable to the study products. We consider that the study results provided in the applications are fully applicable and representative for the assessment of MR0000059-61.

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FDA QUESTION 13:

All of your MRTPAs describe several studies you are conducting that were ongoing at the time that you submitted your applications. For each ongoing study of the products that are the subject of these applications, provide a timetable with the current status of the study, when the study will be complete, and when you anticipate submitting the final report, dataset, and other associated study materials. For all studies that have been completed, provide all information including final study reports, datasets, and other associated study materials, in response to this request.

As an example of what is needed for FDA review of these studies, you submitted an 18-month inhalation chronic toxicity/carcinogenicity study in A/J mice which was completed in June 2016. However, you state that data analysis is still ongoing (refer to page 25 of section 6.1.2 Pre-clinical Safety Testing or 6.1.2.3.2.1) and have only submitted interim data after 1, 5, and 10 months of exposure to THS2.2 and 3R4F cigarettes. In addition, page 64 of the study plan and page 8 of study report Part 1 indicate that a no observed effect concentration (NOEC)/benchmark concentration (BMC) will be derived and quantitative risk assessment (QRA) performed using the study data. However, these analyses were not included with your MRTPAs. A complete dataset and analysis of the long-term carcinogenic studies is necessary to adequately assess the carcinogenic potential of these products from these studies. Provide a timetable for when you anticipate submitting the final report, data, standard for exchange of nonclinical data (SEND) files, BMC analysis, and QRA to FDA.

PMP S.A. RESPONSE:

Status: Completed studies and analyses on THS

The following studies and analyses have been completed after the submission of the applications:

- Study Report Addendum - THS-PBA-07-US - Actual Use Study of THS 2.2 - 30-Day Follow-Up Interview, Version 1.0, 01 December 2016

  In the letter dated July 16, 2015 (FDA Submission Tracking Number (STN): IU0000145 and IU0000198), the Agency suggested *"adding a 30-day follow-up for all enrolled study participants to document ongoing tobacco and nicotine use (including e-cigs)"* for the THS-PBA-07-US study. Following this recommendation, and in addition to the main PBA-07 study, a "30-day follow-up interview" was conducted between 30 days and 60 days after the start of the close-out period of the main study. At the time of submission of the MRTP applications, the final report and dataset for this "30-day follow-up interview" were not yet finalized.

  We hereby submit* the final report, associated documents and datasets as a complement to the PBA-07 study included in Module 7.3.2 of the MRTPAs.

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Note that these PBA-07 datasets (ADaM, SDTM) include the full study data and are provided in replacement of the datasets included in the original applications in Module 7.3.2.

- Study Report Addendum - THS-PBA-07-US - Actual Use Study of THS 2.2 - Posthoc Analysis by *HeatSticks* Order Type, Version 1.0, 28 April 2017
  We hereby submit* the final report and associated documents, based on the PBA-07 dataset, in complement to the PBA-07 study included in Module 7.3.2 of the MRTPAs.
- Safety Update Report - Tobacco Heating System / *IQOS*
  THS 2.2 and 2.4 Products with HeatSticks / *IQOS,* 01-Jan-2016 to 31-Dec-2016
  v1.0, 27-Mar-2017
  We hereby submit* the final report and associated documents in complement to Module 7.3.1 of the applications.

* As these study reports, associated documents and data cannot be transmitted as individual files via the FDA Electronic Submission Gateway, they have been sent to CTP by separate courier on September 8, 2017.

Status: On-going studies on THS

To extend and foster the evidence base that THS is a product appropriate for the promotion of public health, PMI is conducting further long-term assessment and various studies. These include human studies in countries where the product is already marketed. The studies are listed in Table 16 below.

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Table 16 Ongoing Studies on THS

Area of Investigation	Study Number	Study Design	Objectives	Product tested	Completion dates (estimated)
Product Characterization	ZRH_2016_76 LC-HRAM-MS ZRH_2016_75_ GC×GC-TOFMS RLS-ZRH-2016-403_404 LC-HRAM-MS RLS-ZRH-2016-401_GC×GC-TOFMS	Non-targeted differential screening (NTDS) of THS products compared with the conventional reference cigarette 3R4F	To identify chemical constituents present in THS aerosols which are either unique, or present at higher concentration compared to the smoke of the reference cigarette 3R4F	THS 2.2 Regular THS 2.2 Menthol 1 THS 2.2 Menthol 2	Analytical reports for NTDS activities available end Sept 2017 Report for the toxicological evaluation of identified constituents end Oct 2017
Product Characterization	RLS-ZRH-2016-119 RLS-ZRH-2016-120 RLS-ZRH-2016-126 RLS-ZRH-2016-215 RLS-ZRH-2016-218	'P1 Characterization': Full chemical characterization of particulate and gas-vapor phases of THS regular aerosol using non-targeted analytical methods (LC-HRAM-MS, GC-HR-MS, GCxGC-TOFMS)	To identify and semi-quantify all chemical constituents present in the aerosol of THS 2.2 regular with an estimated abundance above 100 ng/stick	THS 2.2 Regular	Final report end March 2018
Non-Clinical	15020	Concentration-response of THS 2.2 according to OECD TG 453 Study Title: Lung Cancer Tumorigenesis in A/J Mice in Response to 18 Months of Chronic Exposure to Mainstream Aerosol From THS 2.2 and Conventional Cigarettes	Assess the lung tumor incidence and multiplicity, chronic toxicity lung inflammation and emphysematous changes in A/J mice exposed to THS2.2 and 3R4F	THS 2.2 Regular	End Q2 2018 (final report including SEND files, BMC analysis and QRA)*

(table continues)

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Area of Investigation	Study Number	Study Design	Objectives	Product tested	Completion dates (estimated)
Systems Toxicology	180200	Color, surface roughness and gloss assessment of dental composite resins and human premolar teeth exposed to THS2.2 aerosol or 3R4F smoke for 3 weeks. Chemical characterization of depositions on dental composite resins after 1 week exposure	Test and compare the effects of 3R4F smoke and THS2.2 aerosol on surface properties and color stability of dental composite resins in vitro. Characterize smoke or aerosol deposits associated with chromogenic activities on dental composite resins	THS 2.2 Regular	End Q4 2017, final report
Systems Toxicology	161710	In vitro study with a 12 week exposure study of lung cells with particulate matter of from the aerosol of a candidate modified-risk tobacco product THS2.2	Assess functional and molecular changes in human bronchial epithelial BEAS-2B cells following a 12-week exposure to total particulate matter (TPM) from the aerosol of a candidate modified-risk tobacco product THS2.2 in comparison to TPM from the 3R4F reference cigarette	THS 2.2 Regular	Q4 2017
Systems Toxicology	S175910	ZRH-REXA-08-US blood transcriptomics investigations	Blood was collected from subjects enrolled in REXA-08-US clinical study to investigate if the previously established gene signature for smoking exposure response separates the THS 2.2M switchers from subjects who continue the consumption on conventional products.	THS 2.2 Menthol	Q4 2017

(table continues)

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Area of Investigation	Study Number	Study Design	Objectives	Product tested	Completion dates (estimated)
Systems Toxicology	181020	Organotypic small airway in-vitro study with Parallel-group air, reference cigarettes 3R4F, and THS2.2 aerosols	Assessing an in vitro human small airway epithelium model, the biological impact of an aerosol from THS2.2, compared with the impact from 3R4F cigarette smoke, at similar nicotine concentrations.	THS 2.2 Regular	Q4 2017
Systems Toxicology	182100	Mucociliary transport and cilia motility; dose & time-course analysis. In-vitro study on Nasal Mucilair™ with parallel group reference cigarettes 3R4F and THS2.2 aerosols.	Characterizing exposure effects on cilia motility and cellular integrity (cytotoxity) following exposure toTHS2.2 in comparison to 3R4F reference cigarette	THS 2.2 Regular	Q4 2017
Systems Toxicology	179500	In-vivo rat inhalation to characterization of the pharmacokinetic profile of THS2.2 after nose-only inhalation exposure of Sprague Dawley at 23 and 50 µg/L nicotine.	Characterization of the pharmacokinetic profile of THS2.2 after nose-only inhalation exposure of Sprague Dawley rats to smoke from a new smoking device	THS 2.2 Regular	Q4 2017
Clinical	ZRHR-ERS-09-US	A randomized, controlled, open-label, 2-arm, parallel group, study of 6 month *ad libitum* exposure	To evaluate favorable biological and functional changes in smokers of cigarettes who switch to THS for 6 months	THS 2.2 Regular	May 2018 (final report including reconciliation of study master file)
Clinical	ZRHR-ERS-09-EXT-US	Extension of the ZRHR-ERS-09-US: a randomized, controlled, open-label, 2-arm, parallel group study of 6 month *ad libitum* exposure	To evaluate favorable biological and functional changes in smokers of cigarettes who switch to THS for 12 months	THS 2.2 Regular	September 2018 (final report including reconciliation of study master file)

(table continues)

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Area of Investigation	Study Number	Study Design	Objectives	Product tested	Completion dates (estimated)
Clinical	SA-SCR-01	A multicenter, multiregion, smoking cessation in healthy smokers who are continuously smoking abstinent for one year	To evaluate favorable biological and functional changes in smokers of cigarettes who stop smoking continuously for one year	Not applicable	End of April 2018 (final report including reconciliation of study master file)
Post-Market	P1-PMC-01-JP	A prospective, observational, open cohort study of adults, legally authorized to purchase tobacco products in Japan.	To assess the patterns of product use and changes in health status associated with the use of HeatSticks with the IQOS tobacco heating system	THS product commercially available in Japan (IQOS)	End of July 2022 (final report including reconciliation of study master file)
Post-Market	P1-PMX-01-JP	An observational, cross-sectional survey conducted for three years in two population samples: (1) a General Population Sample and (2) a Targeted IQOS Users Sample.	To assess Tobacco Use Prevalence and Patterns of Tobacco Product Use in the Japanese Population	THS product commercially marketed in Japan (IQOS)	End of January 2020 (final report including reconciliation of study master file)

*For the 18-month inhalation chronic toxicity/carcinogenicity study in A/J mice for which the animal inhalation exposure was completed in June 2016 (study 15020), histopathology analysis of the respiratory and non-respiratory tract organs (including peer review), as well as systems biology analysis of different organs is ongoing and will be completed end Q1, 2018. During Q2 2018, the report, SEND files and QRA will be prepared and the final report will be available end-Q2 2018. Therefore, we anticipate submitting the final report, dataset and associated materials for this study to FDA in Q3 2018.

During the pre-market phase, all on-going studies will be submitted to FDA within 3 months of completion. For products subject of a market order, studies will be submitted to FDA in accordance with postmarket reporting requirements.

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FDA QUESTION 14:

All of your MRTPAs, in Section 7.2, include a 90-day nose only inhalation study for a mentholated Heatstick, which includes a comparison to two additional mentholated reference cigarettes, DDA3 1XMIS and DDA3 2XMIS. You state that these additional products are similar to the 3R4F Kentucky reference cigarette. While you provided the target mainstream smoke menthol levels for each cigarette (1.2 mg for DDA3 1XMIS and 2.4 mg DDA3 2XMIS), we did not identify any other characterizing information. Provide information on the characteristics (*e.g.*, levels and identities of ingredients, additives, and components) including HPHC levels in the mainstream smoke for each mentholated reference cigarette. If this has already been provided, include a reference for the exact location of the information contained within your applications.

PMP S.A. RESPONSE:

Both mentholated reference cigarettes DDA3 1XMIS and DDA3 2XMIS were designed and manufactured by Philip Morris Products S.A., Neuchatel, Switzerland to match the nicotine, total particulate matter (TPM), and carbon monoxide (CO) levels of the 3R4F reference cigarette (University of Kentucky, Center for Tobacco Reference Products), (Table 17 and Module 7.2 of the applications, on pages 8 to 11 of the document "15025 THS SR Part 1") but with menthol added in order to match as well as possible the menthol levels retrieved in the aerosol from the mentholated THS2.2.

Table 17 Performance of 3R4F, DDA3 1XMIS and DDA3 2XMIS in terms of Tar, nicotine and CO. Menthol levels in the different reference cigarettes were also included.

Reference cigarette	Nicotine (mg/cig)	Tar (mg/cig)	CO (mg/cig)	Menthol (CAS 2216-51-5) (mg/cig)
3R4F	0.7	9.4	12.0	0
DDA3 1XMIS	0.64	9.9	11.4	11.1 mg/cig (9.0 mg/cig in the filter, 2.1 mg/cig pack inner liner)
DDA3 2XMIS	0.64	10.5	11.3	18.4 mg/cig (9.0 mg/cig in the filter, 3.9 mg/cig pack inner liner, 5.5 mg/cig cut filler or tobacco rod)

Detailed information on levels and identities of ingredients, additives, and components of DDA3 1XMIS and DDA3 2XMIS reference cigarettes are provided in Table 18.

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Table 18 Levels and identities of ingredients, additives, and components of DDA3 1XMIS and DDA3 2XMIS reference cigarettes.

Category	Ingredient Name	CIG.15854.D (DDA3 THS2M/2/1XMIS) (mg/Cigarette)	CIG.15855.D (DDA3 THS2M/2/2XMIS) (mg/Cigarette)	Ingredient Function	Registration Number [CAS#]
Tobacco Ingredient	tobacco	718.0	718.0	-	-
Tobacco Ingredient	propylene glycol	4.99	9.08	humectant	57-55-6
Tobacco Ingredient	glycerol	21.4	21.2	humectant	56-81-5
Tobacco Ingredient	sugar: invert sugar	45.5	44.9	casing	8013-17-0
Tobacco Ingredient	carob bean extract	0.203	0.203	flavor	84961-45-5
Tobacco Ingredient	fenugreek extract	0.004	0.004	flavor	68990-15-8
Tobacco Ingredient	menthol	2.1	9.4	flavor	2216-51-5
Cigarette Paper	cellulose	23.5	23.5	fiber	65996-61-4
Cigarette Paper	calcium carbonate	12.5	12.5	filler	471-34-1
Cigarette Paper	sodium citrate	0.190	0.190	combustion modifier	6132-04-3
Cigarette Paper	potassium citrate	0.190	0.190	combustion modifier	6100-05-6
Side Seam Adhesive	ethylene-vinyl acetate copolymer	1.37	1.37	adhesive	24937-78-8
Side Seam Adhesive	hydroxyethylene - vinyl acetate copolymer	0.011	0.011	adhesive	25213-24-5

(table continues)

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Category	Ingredient Name	CIG.15854.D (DDA3 THS2M/2/1XMIS) (mg/Cigarette)	CIG.15855.D (DDA3 THS2M/2/2XMIS) (mg/Cigarette)	Ingredient Function	Registration Number [CAS#]
Tipping Paper and Tipping Paper Ink	cellulose	19.2	19.2	fiber	65996-61-4
Tipping Paper and Tipping Paper Ink	calcium carbonate	8.00	8.00	filler	471-34-1
Tipping Paper and Tipping Paper Ink	kaolin	1.29	1.29	filler	1332-58-7
Tipping Paper and Tipping Paper Ink	titanium dioxide	1.29	1.29	color	13463-67-7
Tipping Paper and Tipping Paper Ink	alkylketene dimer	0.062	0.062	sizing agent	84989-41-3
Tipping Paper and Tipping Paper Ink	guar gum	0.800	0.800	binder	68411-94-9
Tipping Paper and Tipping Paper Ink	epichlorhydrine resin	0.031	0.031	sizing agent	25212-19-5
Tipping Paper and Tipping Paper Ink	collodion	0.766	0.766	binder	9004-70-0
Tipping Paper and Tipping Paper Ink	triacetin	0.064	0.064	plasticizer	102-76-1
Tipping Paper and Tipping Paper Ink	acetyl tributyl citrate	0.319	0.319	plasticizer	77-90-7

(table continues)

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Category	Ingredient Name	CIG.15854.D (DDA3 THS2M/2/1XMIS) (mg/Cigarette)	CIG.15855.D (DDA3 THS2M/2/2XMIS) (mg/Cigarette)	Ingredient Function	Registration Number [CAS#]
Filtration Material	triacetin	1.4	1.4	plasticizer	102-76-1
Filtration Material	titanium dioxide	0.001	0.001	color	13463-67-7
Filtration Material	cellulose acetate	0.150	0.150	filtration material	9004-35-7
Filtration Material	menthol	9.0	9.0	flavor	2216-51-5
Filter Wrap	cellulose	17.6	17.6	fiber	65996-61-4
Filter Wrap	polyvinol	0.929	0.929	adhesive	9002-89-5
Filter and Tipping Adhesive	polyvinyl acetate	0.765	0.765	adhesive	9003-20-7
Filter and Tipping Adhesive	hydroxyethylene - vinyl acetate copolymer	0.298	0.298	adhesive	25213-24-5
Filter and Tipping Adhesive	ethylene-vinyl acetate copolymer	14.0	14.0	adhesive	24937-78-8
Filter and Tipping Adhesive	paraffin	0.269	0.269	other	64742-60-5; 8002-74-2
Filter and Tipping Adhesive	hydrocarbon resin	0.273	0.273	adhesive	68132-00-3
Filter and Tipping Adhesive	polyisobutylene	0.028	0.028	adhesive	9003-29-6

The L-menthol (CAS 2216-51-5) used had a purity >99%.

In terms of the HPHC levels present in the mainstream smoke of the mentholated reference cigarettes, the following smoke constituents were measured in the diluted aerosol, at the inhalation port level of the used nose-only exposure inhalation chambers: TPM, CO, nicotine, formaldehyde, acetaldehyde and acrolein, as well as menthol. No further HPHCs were

determined in the diluted aerosol, and no analytical smoking was performed to measure HPHCs in the undiluted mainstream smoke.

The data on the HPHCs mentioned above can be retrieved in the report of study 15025 "90-day OECD Inhalation-Menthol in section 7.2 of the applications (pages 20 to 25 of the document "15025 THS SR Part 1").

Furthermore, analysis of urinary biomarkers of exposure was conducted in rats exposed to the different reference items 3R4F, DDA3 1XMIS and DDA 2XMIS. The analysis showed similar recovery of CEMA (metabolite of acrylonitrile), HPMA (metabolite of acrolein), total NNAL (biomarker of NNK), and SPMA (metabolite of benzene), indicating similar levels of a further group of HPHCs present in the diluted mainstream smoke to which the rats were exposed (section 7.2 of the applications, pages 67 to 68 of the document "15025 THS SR Part 1").

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FDA QUESTION 15:

All of your MRTPAs, in the Neutral Red Uptake assays (RLS_ZRH_2015-249 and RLS_ZRH_2015-250), Mouse Lymphoma Assays (RLS_ZRH_2015-251 and LS_ZRH_2015-252), and Ames Tests (RLS_ZRH_2015-253 and RLS_ZRH_2015- 254), state that the concentration of TPM and GVP aerosol fractions are expressed as either item/L, µg TPM/mL, µg TPM equivalent/mL, or mg TPM/plate, respectively. Clarify the meaning of the term "item" in the study plan and study report for these assays. It is unclear whether the term "item" in the units or in the study design, results and conclusions sections refers to a single cigarette (3R4F), a Heatstick, or a single Cambridge Filter Pad.

PMP S.A. RESPONSE:

In our studies, the Tobacco Heating System (THS) tobacco sticks (HeatSticks) were regarded as the test item and the 3R4F research cigarettes were regarded as the reference item. Once the aerosol/smoke from both the test and reference item was generated, it was fractionated into two parts, namely TPM (Total Particulate Matter) and GVP (Gas and Vapor Phase), during the same aerosol generation. For the test item and reference item, TPM was collected on Cambridge filter pads (44 mm diameter) and extracted using dimethylsulfoxide (DMSO). GVP, which was not retained by the filter pad(s), was bubbled into a glass impinger containing ice-cold phosphate buffered saline (PBS) to capture the PBS-soluble fraction of the test and reference items.

The term "item" in the units express the concentration of TPM and GVP aerosol fractions obtained by taking into account the number of test and reference item accumulations to produce the aerosol fractions for each test occasion, as well as the volume of DMSO and PBS in which TPM and GVP was collected. As an example: in the study RLS_ZRH_2015-249 (section 7.2 of the applications, page 12 of the document “RLS-ZRH-2015-249 NRU Ment SP”), we used 4 reference items (3R4F) to generate the respective TPM and GVP fractions used in the study. At the end of the smoking run, the smoke trapped on a filter pad from these four 3R4F was extracted with 5 ml of DMSO. This defines the concentration as 0.8 item/ml (4 3R4F/5 ml DMSO) or 800 item/L. The same is true for the GVP. All gasses not retained by the filter pad were bubbled in 36 ml of PBS. This defines the concentration as 0.1 item/ml (4 3R4F/36 ml PBS) or 111.1 item/L. In conclusion, the term “item” in the unit refers to a single cigarette (3R4F) or HeatStick.

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FDA QUESTION 16:

All of your MRTPAs state, in the study report for S160400 involving the adhesion of MM6 monocytes to human coronary arterial endothelial cells (HCAECs), that THS2.2 aerosol was compared to the smoke of the 3R4F cigarette. However, all figures include data for 3R4F and P1. Clarify what P1 represents, as it is unclear if P1is a product in one of your MRTPAs. If P1 is different than the products in your MRTPAs, then provide information on the characteristics (*e.g.*, levels and identities of ingredients, additives, and components) of the test articles for P1 and a description of how P1 compares to the products in your MRTPAs. Provide a scientific justification for bridging from these products to the proposed MRTPs.

PMP S.A. RESPONSE:

The term "P1" is defined in the MRTPAs in the Section 2.6 Glossary (pg. 19) as:

"Platform 1 – Tobacco Heating System (THS)".

Our naming convention of THS has evolved over the duration of the assessment program.

As explained on page 6 of the mentioned study report "ADHESION ASSAY STUDY (SP160400) Systems toxicology assessment of THS 2.2 (BATCH N° B-08164) vs 3R4F sbPBS using an adhesion assay established with monocytic Mono Mac 6 cells and primary human coronary artery endothelial cells" in Table 1, row 2, the tested product referred to in the study documentation as "ZRH", "P1" and "THS2.2" are all referring to the same product THS2.2.

The product used in this study (CONS.01496.RD) corresponds to a Regular Tobacco Stick. The applicability of this test article in support of the proposed MRTPAs is covered in response to Question 12 above. The characteristics of CONS.01496.RD compared to the proposed MRTP MR0000059 are provided in appendix SR1_Q12-A1 Compositions - Regular.

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FDA QUESTION 17:

All of your MRTPAs provide eight published studies that refer to a "prototypic modified risk tobacco product" (pMRTP). Based on the information provided in each of the eight publications, it is unclear how the pMRTP used in each study compared to products in your MRTPAs. Provide a description of how the characteristics (*e.g.*, levels and identities of ingredients, additives, and components) of the pMRTPs used in the studies listed below compare to the proposed MRTPs.

a. Elamin A, et al., Quantitative proteomics analysis using 2D-PAGE to investigate the effects of cigarette smoke and aerosol of a prototypic modified risk tobacco product on the lung proteome in C57BL/6 mice. J Proteomics. 2016 Aug 11:145:237-45
b. Kogel U, et al., Biological impact of cigarette smoke compared to an aerosol produced from a prototypic modified risk tobacco product on normal human bronchial epithelial cells. Toxicol In Vitro. 2015 Dec;29(8):2102-15
c. Phillips B, et al., A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product. Food Chem Toxicol. 2015 Jun;80:328-45
d. van der Toorn M, et al., A prototypic modified risk tobacco product exhibits reduced effects on chemotaxis and transendothelial migration of monocytes compared with a reference cigarette. Food Chem Toxicol. 2015 Jun;80:277-89
e. Kogel U, et al., A 28-day rat inhalation study with an integrated molecular toxicology endpoint demonstrates reduced exposure effects for a prototypic modified risk tobacco product compared with conventional cigarettes. Food Chem Toxicol. 2014 Jun;68:204-17
f. van der Toorn M, et al., Aerosol from a candidate modified risk tobacco product has reduced effects on chemotaxis and transendothelial migration compared to combustion of conventional cigarettes. Food Chem Toxicol. 2015 86:81-87
g. Titz B, et al., Effects of cigarette smoke, cessation, and switching to two heat-not-burn tobacco products on lung lipid metabolism in C57BL/6 and Apoe$^{-/-}$ mice – An integrative systems toxicology analysis. Toxicol Sci 2016 Feb;149(2):441-57
h. Ansari S, et al., Comprehensive systems biology analysis of a 7-month cigarette smoke inhalation study in C57BL/6 mice. Sci Data 2016 Jan 5;3:150077

PMP S.A. RESPONSE:

We would like to provide clarification regarding the test articles used in the studies described in the above-mentioned publications.

The following publication relates to a study on THS:

f. van der Toorn M, et al., Aerosol from a candidate modified risk tobacco product has reduced effects on chemotaxis and transendothelial migration compared to combustion of conventional cigarettes. Food Chem Toxicol. 2015 86:81-87

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The following publication includes data on both THS and the "pMRTP":

g. Titz B, et al., Effects of cigarette smoke, cessation, and switching to two heat-not burn tobacco products on lung lipid metabolism in C57BL/6 and Apoe-/- mice – An integrative systems toxicology analysis. Toxicol Sci 2016 Feb;149(2):441-57

The six other publications (a. Elamin A et al. 2016, b. Kogel U et al. 2015, c. Phillips B et al. 2015, d. van der Toorn et al. 2015a, e. Kogel U et al. 2014, and h. Ansari S et al. 2016), concern studies conducted using the prototypic MRTP (pMRTP).

These six publications were included in the applications, as they were referenced within the scope of the systems toxicology approach we have established to assess potential modified risk tobacco products *in vitro* and *in vivo*. The main purpose of the published studies was to:

1. Develop and test our systems toxicology approach to both *in vitro* and *in vivo* assessments of potential modified risk tobacco products.
2. Serve as *proof of concept* studies to evaluate the potential of the heat-not-burn principle.

The "pMRPT" is a prototype of a different type of heat-not-burn tobacco product (which does not involve the combustion of tobacco) and is described below. Therefore, the studies on pMRTP are not submitted in support of the products that are the subject of the applications *per se*.

Like THS, the "pMRTP" (also referred to as Platform 2 or P2) functions according to a heat-not-burn principle that does not involve combustion. (b) (4)
(b) (4)

Below we provide a brief description of the pMRTP (also called "Smoking Article (SMAR)" in some documents), an early version of Platform 2 (P2), to clarify the similarities and differences between both platforms.

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(b) (4)

(b) (4)

(b) (4)

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(b) (4)

(b) (4)

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Table 19 Yields of selected analytes (per mg nicotine) from cigarette smoke and tobacco-heating product aerosols.

Product tested	Units	pMRTP	Cigarette	pMRTP	cMRTP	Cigarette
Product code		(b) (4)	3R4F	(b) (4)	THS2.2	3R4F
Publication [Reference]			[e]		[f, g]	[a-d, f, g]
Analytes						
ISO parameters						
1. Carbon monoxide	mg/mg nicotine		17.1 ± 0.13		0.437 ± 0.031	14.8 ± 0.715
2. Nicotine	mg/mg nicotine		1.00 ± 0.02		1 ± 0.045	1 ± 0.0542
3. Tar	mg/mg nicotine		13.8 ± 0.29		6.304 ± 1.214	14.3 ± 0.717
4. TPM	mg/mg nicotine		20.0 ± 0.47		34.72 ± 1.396	22.2 ± 1.2
5. Water	mg/mg nicotine		5.11 ± 0.24		27.41 ± 1.937	7.01 ± 0.673
Aliphatic dienes						
6. 1,3-butadiene	µg/mg nicotine		51.8 ± 2.04		0.298 ± 0.053	36.7 ± 3.6
7. Isoprene	µg/mg nicotine		482 ± 19.1		2.483 ± 0.335	427 ± 36.4
Carbonyls						
8. Acetaldehyde	µg/mg nicotine		829 ± 28.3		157.9 ± 15.78	719 ± 50.1
9. Acetone	µg/mg nicotine		N.D.		29.35 ± 3.463	323 ± 11.9
10. Acrolein	µg/mg nicotine		96.8 ± 3.62		8.165 ± 1.189	77 ± 5.51
11. Butyraldehyde	µg/mg nicotine		N.D.		20.32 ± 2.024	41.7 ± 3.64
12. Crotonaldehyde	µg/mg nicotine		N.D.		2.809 ± 0.333	40.5 ± 4.31
13. Formaldehyde	µg/mg nicotine		38.3 ± 2.03		2.623 ± 0.271	28.3 ± 3.48
14. Methyl ethyl ketone	µg/mg nicotine		N.D.		5.986 ± 0.91	91.9 ± 5.79
15. Propionaldehyde	µg/mg nicotine		65.5 ± 2.33		11.75 ± 1.483	58.1 ± 2.68

(table continues)

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Product tested	Units	pMRTP	Cigarette	pMRTP	cMRTP	Cigarette
Product code		(b) (4)	3R4F	(b) (4)	THS2.2	3R4F
Acid derivatives						
16. Acetamide	µg/mg nicotine		9.69 ± 1.01		3.063 ± 0.283	7.17 ± 0.399
17. Acrylamide	µg/mg nicotine		N.D.		1.918 ± 0.188	2.03 ± 0.157
18. Acrylonitrile	µg/mg nicotine		40.8 ± 1.48		0.166 ± 0.013	14.4 ± 0.894
Epoxides						
19. Ethylene oxide	µg/mg nicotine		N.D.		0.167 ± 0.011	12.9 ± 0.998
20. Propylene oxide	µg/mg nicotine		N.D.		0.094 ± 0.008	0.723 ± 0.0234
Nitro compounds						
21. Nitrobenzene					N.D.	N.D.
Aromatic Amines						
22. 1-aminonaphthalene	ng/mg nicotine		N.D.		0.065 ± 0.007	9.95 ± 0.6
23. 2-aminonaphthalene	ng/mg nicotine		N.D.		3/4 < 0.024	5.11 ± 0.186
24. 3-aminobiphenyl	ng/mg nicotine		N.D.		0.043 ± 0.005	1.64 ± 0.213
25. 4-aminobiphenyl	ng/mg nicotine		1.35 ± 0.13		4/4 < 0.032	1.31 ± 0.115
26. o-toluidine	ng/mg nicotine		61.4 ± 3.44		0.962 ± 0.076	43.5 ± 1.45
27. benzidine	ng/mg nicotine		N.D.		4/4 < 0.0007	N.D.
N-heterocyclic aromatics						
28. Pyridine	µg/mg nicotine		N.D.		6.343 ± 0.283	18 ± 0.833
29. Quinoline	µg/mg nicotine		N.D.		0.016 ± 0.001	0.273 ± 0.0276
Halogen compounds						
30. Vinyl chloride	ng/mg nicotine		46.5 ± 3.39		4/4 < 2.477	50.2 ± 2.75
Inorganic compounds						
31. Ammonia	µg/mg nicotine		N.D.		10.18 ± 0.611	19.4 ± 0.847

(table continues)

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Product tested	Units	pMRTP	Cigarette	pMRTP	cMRTP	Cigarette
Product code		(b) (4)	3R4F	(b) (4)	THS2.2	3R4F
32. Hydrogen cyanide	µg/mg nicotine		147 ± 5.35		2.905 ± 0.201	215 ± 17.2
33. Nitric oxide	µg/mg nicotine		N.D.		11.37 ± 0.521	218 ± 10.3
34. Nitrogen oxides	µg/mg nicotine		359 ± 3.38		11.48 ± 0.516	240 ± 12.3
Monocyclic aromatics						
35. Benzene	µg/mg nicotine		59.8 ± 1.25		0.538 ± 0.037	46.8 ± 1.7
36. Styrene	µg/mg nicotine		14.2 ± 0.55		0.578 ± 0.048	11.9 ± 0.497
37. Toluene	µg/mg nicotine		112 ± 4.56		2.172 ± 0.231	97.8 ± 3.8
N-nitrosamines						
38. N-nitrosoanabasine (NAB)	ng/mg nicotine		N.D.		4/4 < 2.173	18 ± 1.24
39. N-nitrosoanatabine (NAT)	ng/mg nicotine		N.D.		11.67 ± 1.224	173 ± 10.1
40. 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/mg nicotine		144 ± 8.28		4.631 ± 0.387	117 ± 5.56
41. N-nitrosonornicotine (NNN)	ng/mg nicotine		148 ± 8.00		10.37 ± 1.039	155 ± 4.31
Phenols						
42. Catechol	µg/mg nicotine		52.9 ± 0.91		15.53 ± 1.698	43.8 ± 2.17
43. m+p-cresol	µg/mg nicotine		N.D.		0.123 ± 0.02	6.04 ± 0.448
44. o-cresol	µg/mg nicotine		N.D.		0.102 ± 0.014	2.08 ± 0.18
45. Hydroquinone	µg/mg nicotine		N.D.		6.614 ± 0.859	40.2 ± 1.85
46. Phenol	µg/mg nicotine		8.94 ± 0.37		1.617 ± 0.269	6.59 ± 0.497
47. Resorcinol	µg/mg nicotine		N.D.		0.049 ± 0.004	0.894 ± 0.0364
PAHs						
48. Benzo[a]pyrene	ng/mg nicotine		9.02 ± 0.28		3/4 < 0.696	4.66 ± 1.87

(table continues)

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Product tested	Units	pMRTP	Cigarette	pMRTP	cMRTP	Cigarette
Product code		(b) (4)	3R4F	(b) (4) (b)	THS2.2	3R4F
49. Benz[a]anthracene	ng/mg nicotine		16.6 ± 0.57	(b)	1.078 ± 0.051	9.21 ± 3.19
50. Dibenz[a,h]anthracene	ng/mg nicotine		5/5 < 1.41	(b) (4)	4/4 < 0.07	3/8 < 0
51. Pyrene	ng/mg nicotine		N.D.	(b) (4)	4.085 ± 0.24	25.5 ± 15.2
Metals/Elements						
52. Arsenic	ng/mg nicotine		5.22 ± 0.33	(b)	3/3 < 0.787	3.32 ± 0.209
53. Cadmium	ng/mg nicotine		70.4 ± 2.16	(b) (b)	0.371 ± 0.008	63.7 ± 3.28
54. Chromium	ng/mg nicotine		3/4 < 3.72	(b) (4)	3/3 < 0.118	4/4 < 0.257
55. Lead	ng/mg nicotine		22.5 ± 3.50	(b) (4)	3/3 < 2.332	14.8 ± 0.773
56. Mercury	ng/mg nicotine		N.D.	(b) (b)	1.024 ± 0.105	1.86 ± 0.0981
57. Nickel	ng/mg nicotine		4/4 < 4.89	(b) (4)	2/3 < 0.118	4/4 < 0.257
58. Selenium	ng/mg nicotine		N.D.	(b) (4)	3/3 < 0.383	0.687 ± 0.126

N.D.: not determined. In case at least one value was it of quantitation (LOQ), the number of values below LOQ per total number of determinations and the valu were given: 3 / 4 < 3.35 means 3 of 4 values were below the LOQ of 3.35.

(b) (4)

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FDA QUESTION 18:

All of your MRTPAs include inconsistent statements between the User Guide and the Environmental Impact Assessment related to disposing of a used tobacco heating device (THD). Page 37 of the User Guide (File A3.4.1 in Module 3, Product Description) states the following:

> "This symbol on the device or on its packaging indicates that this product and its individual parts (including batteries) must not be disposed of with your other household waste. Instead, it is your responsibility to dispose of your waste equipment by handing it over to a designated collection point for the recycling of waste electrical and electronic equipment.
>
> Your iQOS Device contains a Lithium-ion rechargeable battery. When discarded, it must be recycled or dispose of properly in accordance with state and local requirements. Do not crush battery (*e.g.*, such as in a trash compactor). Do not dispose of any part of this product in fire or flame. For further information on recycling and disposal of the battery call 1-877-RECYCLE (1-877-723-2925). Or contact your local waste management officials."

In contrast, Module 5, Environmental Impact Assessment, states "The reusable THD, when eventually discarded, would be managed as solid waste" (Page 5 in Section 5.1.2 of the file "5.1 THS Regular Public.pdf" and parallel sections in files 5.2, A5.1.1, and A5.2.1). Resolve the inconsistent statements. If the THD cannot be managed as nonhazardous municipal solid waste, provide an analysis of the potential environmental effects from proper and improper consumer disposal of a used THD, if available.

PMP S.A. RESPONSE:

The Environmental Impact Assessment included in the applications focused on the components of the tobacco stick, based on the assumption that the THD (including the battery) and packaging will be responsibly managed as solid waste at the end of their useful life, and therefore will not pollute terrestrial or aquatic environments (Module 5.1.1 and 5.2.1, §3.3 in the applications).

The Environmental Impact Assessment also assumed a more conservative approach than the User Guide, i.e. that the device (as a whole) would be disposed of as household solid waste instead of being recycled. The environmental impacts would be considered less if the devices enter the recycling stream instead of the 'waste disposal' stream. A consumer could potentially discard the device in household waste (nonhazardous municipal solid waste). The User Guide leaves this possibility open in the statement "When discarded, it must be recycled or dispose of properly in accordance with state and local requirements".

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FDA QUESTION 19:

All of your MRTPAs describe the chemical components of three different types of tobacco Heatsticks. It also includes a user guide (File A3.4.1 in Module 3) and a quick start guide (File A3.4.2 in Module 3) that direct users to dispose of heatsticks "responsibly." Users of combusted cigarettes litter a significant proportion of cigarette ends (butts), so it is likely that some proportion of used Heatsticks would also be littered. In accordance with 21 CFR 25.40, "[an] EA shall focus on relevant environmental issues relating to… disposal from use of FDA-regulated articles." To support this analysis, if available, provide a description of the physical and chemical properties of a used Heatstick compared to an unused Heatstick. Also, if available, provide information on the chemicals that would leach from a used Heatstick in the environment, for example, results from a standard analytical method designed for this purpose such as *SW-846 Test Method 1311: Toxicity Characteristic Leaching Procedure*.[4]

PMP S.A. RESPONSE:

(b) (4)

[redacted]

[4] U.S. Environmental Protection Agency. 1992. Test Methods for Evaluating Solid Waste: Physical/Chemical Methods (SW-846): Test Method 1311: Toxicity Characteristic Leaching Procedure. www.epa.gov/hw-sw846/sw-846-test-method-1311-toxicity-characteristic-leaching-procedure

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FDA QUESTION 20:

All of your MRTPAs, in Section 5.1.2, references "the potential shipping forecast for THS Regular and associated Tobacco Stick" as having "formed the basis for the environmental exposure estimates provided in the environmental assessment." FDA could not locate this information in your MRTPAs. Define and provide the details of this shipping forecast or indicate where in the applications this information is located. If available, also provide the first- and fifth-year market projections for each product with detailed separate information for the starter kit (Charger and Holder) and Heatsticks (specified by individual Heatstick or pack of 20).

PMP S.A. RESPONSE:

In Module 5 of the applications, both public and confidential versions of Environmental Impact Assessments were provided. The above-mentioned excerpts are drawn from the public versions in Section 5.1 (THS Regular Public) and Section 5.2 (THS Menthol Public). The potential shipping forecast information can be found in the confidential versions of the Environmental Impact Assessments, which are appendices to Module 5.

(b) (4)

These potential shipping forecasts were made solely for the purposes of the Environmental Impact Assessment and likely overstate the actual shipping quantities to create a worst-case scenario from an environmental impact perspective. This is consistent with the statement by Environmental Resources Management, Inc. in the Environmental Impact Assessments that its calculations used conservative formulation and production forecasting information provided by PMP S.A.

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FDA QUESTION 21:

All of your MRTPAs, in studies PBA05-RRC, PBA05-RRC2, and PBA05-REC, evaluate perceptions of IQOS, intent to use IQOS, comprehension, and changes in intentions to quit smoking, all among people who viewed IQOS materials with modified risk information. The analyses are descriptive in nature, providing estimates of levels of perceptions, intentions, and comprehension after people have viewed IQOS materials with modified risk information. However, we did not identify any analyses of how perceptions, intentions, and comprehension *change* (within each of the five identified smoker groups) depending on whether the IQOS materials contain modified risk information.

We note that you have submitted an additional study (PMTA05-NOC) that is similar to the PBA05 studies but had participants view IQOS materials with no modified risk information. One approach to evaluating the potential effects of the various modified risk claims you tested would be to conduct analyses in which you compare perceptions, intentions, and comprehension across these studies (i.e., comparing relevant Study Arms and smoker groups across studies), while controlling for factors (*e.g.*, demographic characteristics) that differ across study samples. These analyses would be useful to our review by helping us understand whether providing the modified risk information would benefit public health, such as by increasing the likelihood that current smokers (but not non-smokers) will switch to the product. If you have such information, provide it.

PMP S.A. RESPONSE:

To address the questions raised, new analyses have been performed. We outline the methods and results for these new analyses. In line with the information requested, the objective of this post hoc analysis was to compare perceptions, intentions, and comprehension between subjects receiving IQOS materials containing modified risk/harm/exposure claims (herein referred to as 'claims studies' i.e. the THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US studies) and those receiving IQOS materials containing no claims (i.e. the THS-PMTA-05-NOC-US study).

It should be noted that there are limitations with this additional analysis, which arises because the analysis goes beyond the aims and design of the studies, which were planned to be descriptive and not for hypothesis testing. The four studies included in this analysis were balanced on age group and sex, because they had an identical design in terms of sampling quotas on these factors. However, it remains that the comparison in the current analysis (i.e. the PBA05 studies compared to the THS-PMTA-05-NOC-US study) was not based on randomization. Thus there may be factors influencing the outcome measures which were not measured in the studies or which are not being adjusted for. For example, it is possible that the study results could be confounded by seasonal factors and/or trends over time (the PBA-05 studies were conducted between July 2015

and December 2015, and the THS-PMTA-05-NOC-US study was conducted in September 2016). Further, the analysis could be potentially confounded by geographical differences in sampling, as the THS-PMTA-05-NOC-US study was conducted in different sites than the PBA05 studies. We do not expect that these potential confounds are serious, but such issues remain a possible source of bias.

The main result of this additional analysis is that the claims were associated with smaller differences in Perceived Health Risk scores between CC and THS compared to no claims, in all smoking status groups. This is consistent with the claim being successful in lower risk perceptions of THS relative to CC, however there was no reliable effect of claims on Intent to Use THS.

The claims studies were combined for analysis. This analysis only considered arms which were directly comparable between the claims studies and the no claims study, i.e. the data associated with the Brochure and HeatSticks Pack with the Surgeon General's warnings. For the claims studies, this meant arms 1 and 3 respectively. For the no claims study this meant Arms 1 and 2, respectively.

Outcome measures

The outcome measures in the current analyses were comprised of the four main study outcome measures assessed in each of the studies:

1. ***Perceived Health Risk*** **and** ***Perceived Addiction Risk***

   We present data for the absolute perceived risk scores for THS and also for the difference in scores between CC and THS. We used these derived data (i.e. the difference in scores between CC and THS) as it would be expected that these would provide a less biased method of comparing Perceived Risk across the different studies.

   Perceived risk data were analyzed separately on the basis of the five smoking status groups:

   1. Adult Smokers with no Intention to Quit (SNIQ)
   2. Adult Smokers with Intention to Quit (SIQ)
   3. Adult Former Smokers (FS)
   4. Adult Never Smokers (NS)
   5. Legal smoking age to 25 years Never Smokers (LA-25 NS)

2. **Intent to Use, comprised of:**
    i. Positive Intention to Try THS ("Definitely" or "Very likely")
    ii. Positive Intention to Try THS, if offered by a friend ("Definitely" or "Very likely")
    iii. Positive Intention to Try THS ("Definitely" or "Very likely")

    The Intention to Try and Intention to Use THS use the same definitions as presented in the analyses presented in the study reports.

    Intent to Use data were analyzed separately on the basis of the five smoking status groups:

    1. Adult Smokers with no Intention to Quit
    2. Adult Smokers with Intention to Quit
    3. Adult Former Smokers
    4. Adult Never Smokers
    5. Legal smoking age to 25 years Never Smokers

3. **Change in Intention to Quit All Tobacco**

    Change in Intention to Quit All Tobacco was analyzed only within the smoking status group for which it was assessed, i.e. Adult Smokers with the Intention to Quit.

4. **Comprehension** that:
    - IQOS is intended only for smokers who want to continue using tobacco (assessed for the Brochure only).
    - IQOS heats tobacco but does not burn it (assessed for the Brochure and HeatSticks Pack)

    These comprehension endpoints are the only ones in common between the claims studies and no claims study (THS-PMTA-05-NOC-US).

    Comprehension data were considered for the main samples, i.e. the first four smoking status groups.

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Statistical Methods

To compare the differences between the claims studies and the no claims study for the continuous perceived risk endpoints, a general linear regression model was fitted and included the following covariates:

- claim status (with claim, without claim - identified by study),
- age (continuous),
- sex (male, female),
- race (white, black, other),
- education ($\leq$high school graduate, some college, $\geq$ college graduate),
- employment status (employed, not employed),
- IQOS material (Brochure with Surgeon General's warnings, HeatSticks Pack with Surgeon General's warnings).

The least squares (LS) means within the claims studies and the no claims study is presented along with the LS mean difference between these comparison groups and the associated 95% confidence intervals (CIs).

For the binary outcomes (intentions and comprehension), a generalized linear model assuming a Poisson distribution and an identity link function was fitted and included the same covariates listed above. The identity link function was used to estimate the absolute differences in percentages between the claim studies and no claims study groups. The LS percentage within the claim studies and no claims study groups is presented along with the LS absolute percentage difference between the groups and the associated 95% confidence intervals (CIs). A similar model was used for change in intention to quit (ITQ) all tobacco, with the addition of repeated measures by subject, i.e. ITQ all tobacco pre- and ITQ all tobacco post- exposure to IQOS material. The LS percentage pre- minus post- ITQ all tobacco is presented within the claim studies and no claims study groups, along with the LS absolute percentage difference between the groups and the associated 95% confidence intervals (CIs).

The models were initially run separately for each claims study (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US) and material type (Brochure and HeatSticks Pack). Due to the similarity of the results between studies and IQOS material, they were combined to provide estimates at the outcome by smoking status level. In some cases, the full model with all covariates listed above did not converge due to limited events. In these cases the model was re-run with only the claim status covariate.

Results

There were lower absolute levels of Perceived Health Risk for THS, for the claims studies compared to the no claim study, in Adult Smokers with no Intention to Quit, Adult Former Smokers and Adult Never Smokers. Considering the differences in Perceived Health Risk

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between CC and THS, there were lower levels for the claims studies compared to the no claim study in all smoking status groups (Table 20).

There were lower absolute levels of Perceived Addiction Risk for THS, for the claims studies compared to the no claim study, in Adult Former Smokers, Adult Never Smokers and LA-25 Never Smokers. Considering the differences in Perceived Addiction Risk between CC and THS, there were lower levels for the claims studies compared to the no claim study in Adult Never Smokers only (Table 21).

Table 20 Perceived Health Risk

Object	Smoking Status	Claims studies		No Claim study		Mean Difference (and 95% CI) Claim studies – No Claim study
		n	Adjusted Mean Score (95% CI)	n	Adjusted Mean Score (95% CI)	
THS	Group 1: SNIQ	514	41.5 (39.4 , 43.6)	170	45.9 (42.9 , 48.9)	-4.4 (-7.5 , -1.4) *
	Group 2: SIQ	512	46.2 (43.9 , 48.5)	169	48.1 (44.8 , 51.4)	-1.9 (-5.1, 1.3)
	Group 3: FS	496	51.8 (49.1 , 54.6)	174	57.5 (53.9 , 61.1)	-5.7 (-9.3 , -2.2) *
	Group 4: NS	524	55.2 (52.7 , 57.8)	170	62.6 (58.9 , 66.2)	-7.3 (-10.8 , -3.8) *
	Group 5: LA-25 NS	561	56.6 (54.6 , 58.6)	183	59.4 (56.3 , 62.4)	-2.7 (-5.9, 0.4)
CC - THS	Group 1: SNIQ	513	18.6 (16.6, 20.6)	170	12.1 (9.2, 15.0)	6.5 (3.5, 9.4) *
	Group 2: SIQ	512	19.8 (17.6, 22.0)	169	16.1 (13.0, 19.3)	3.7 (0.6, 6.8) *
	Group 3: FS	496	17.1 (14.9, 19.4)	174	12.4 (9.5, 15.3)	4.7 (1.8, 7.6) *
	Group 4: NS	522	17.8 (15.7, 20.0)	170	12.9 (9.9, 16.0)	4.9 (2.0, 7.9) *
	Group 5: LA-25 NS	560	15.8 (14.1, 17.4)	183	12.9 (10.4, 15.5)	2.8 (0.2, 5.5) *

* Confidence intervals do not include zero, i.e. providing evidence of an effect.

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Table 21 Perceived Addiction Risk

Object	Smoking Status	Claims studies		No Claim study		Mean Difference (and 95% CI) Claim studies – No Claim study
		n	Adjusted Mean Score (95% CI)	n	Adjusted Mean Score (95% CI)	
THS	Group 1: SNIQ	507	47.3 (44.3 , 50.3)	173	45.4 (41.1 , 49.6)	1.9 (-2.5, 6.3)
	Group 2: SIQ	512	50.5 (47.4 , 53.6)	170	50.0 (45.6 , 54.4)	0.5 (-3.8, 4.7)
	Group 3: FS	509	53.0 (49.4 , 56.5)	181	58.0 (53.4 , 62.6)	-5.0 (-9.6 , -0.4) *
	Group 4: NS	528	59.4 (56.0 , 62.9)	178	67.1 (62.4 , 71.9)	-7.7 (-12.3 , -3.1) *
	Group 5: LA-25 NS	562	56.8 (53.9 , 59.7)	184	62.4 (58.1 , 66.8)	-5.6 (-10.1, -1.1) *
CC - THS	Group 1: SNIQ	507	20.4 (17.7, 23.0)	172	18.5 (14.7, 22.2)	1.9 (-1.9, 5.8)
	Group 2: SIQ	512	22.9 (20.0, 25.8)	170	20.3 (16.3, 24.4)	2.6 (-1.4, 6.5)
	Group 3: FS	507	14.3 (11.5, 17.0)	181	11.0 (7.5, 14.6)	3.2 (-0.3, 6.8)
	Group 4: NS	527	18.2 (15.6, 20.9)	177	14.0 (10.3, 17.7)	4.2 (0.6, 7.8) *
	Group 5: LA-25 NS	558	17.4 (15.1, 19.7)	184	15.1 (11.6, 18.6)	2.3 (-1.3, 5.9)

* Confidence intervals do not include zero, i.e. providing evidence of an effect.

Intent to Use

There was evidence of lower absolute levels of positive Intention to Use THS regularly, for the claims studies compared to the no claim study, in LA-25 Never Smokers only (Table 23), based on the unadjusted confidence intervals.

Table 22 Intent to Use THS

Outcome	Smoking Status	Claims studies		No Claim study		Absolute Difference (95% CI) Claim studies – No Claim study
		n	Adjusted % (95% CI)	n	Adjusted % (95% CI)	
Positive Intention to Try THS	Group 1: SNIQ	560	40.0 (32.6 , 47.3)	191	41.9 (31.6 , 52.2)	-2.0 (-12.5, 8.6)
	Group 2: SIQ	566	42.0 (34.2 , 49.7)	192	40.2 (29.5 , 51.0)	1.7 (-8.7 , 12.2)
	Group 3: FS†	565	6.7 (4.6, 8.9)	188	6.4 (2.8 , 10.0)	0.3 (-3.9, 4.5)
	Group 4: NS†	571	0.5 (-0.1, 1.1)	192	0.5 (-0.5, 1.5)	0.0 (-1.2, 1.2)
	Group 5: LA-25 NS†	575	0.9 (0.1, 1.6)	188	1.1 (-0.4, 2.5)	-0.2 (-1.9, 1.5)
Positive Intention to Try THS, if Offered by a Friend	Group 1: SNIQ	560	65.9 (56.5 , 75.3)	191	64.5 (51.5 , 77.4)	1.4 (-12.0 , 14.8)
	Group 2: SIQ	566	60.9 (51.5 , 70.4)	192	57.3 (44.4 , 70.2)	3.6 (-9.3 , 16.5)
	Group 3: FS†	565	14.7 (11.5 , 17.9)	188	15.4 (9.8 , 21.0)	-0.7 (-7.2, 5.7)
	Group 4: NS†	571	2.3 (1.0, 3.5)	192	3.1 (0.6, 5.6)	-0.8 (-3.6, 1.9)
	Group 5: LA-25 NS†	575	3.1 (1.7, 4.6)	188	6.4 (2.8 , 10.0)	-3.3 (-7.1, 0.6)

(table continues)

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Outcome	Smoking Status	Claims studies		No Claim study		Absolute Difference (95% CI) Claim studies – No Claim study
		n	Adjusted % (95% CI)	n	Adjusted % (95% CI)	
Positive Intention to Use THS regularly	Group 1: SNIQ	560	33.3 (26.6 , 40.0)	191	32.0 (23.1 , 40.9)	1.3 (-7.7 , 10.3)
	Group 2: SIQ	566	30.4 (23.7 , 37.1)	192	32.6 (23.1 , 42.1)	-2.1 (-11.3, 7.0)
	Group 3: FS†	565	4.4 (2.7, 6.2)	188	1.6 (-0.2, 3.4)	2.8 (0.3, 5.3)
	Group 4: NS	571	0.0 (0.0, 0.6)‡	192	1.6 (0.3, 4.5)‡	-1.6 (-3.3, 0.2)‡
	Group 5: LA-25 NS	575	0.0 (0.0, 0.6)‡	188	2.1 (0.6, 5.4)‡	-2.1 (-4.5, -0.1)‡ *

* Confidence intervals do not include zero, i.e. providing evidence of an effect.
† Final model fit with the covariate claim status only as the full model with all covariates did not converge.
‡ Wald confidence intervals (all others are Poisson confidence intervals)

There was no evidence of any differences between the claims studies and no claims study in terms of Change in Intention to Quit All Tobacco or Comprehension. These results are shown below in Table 23 and Table 24.

Table 23 Change in Intention to Quit All Tobacco

Outcome	Smoking Status	Claims studies		No Claim study		Absolute Difference (95% CI) Claim studies – No Claim study
		n	Adjusted % (95% CI)	n	Adjusted % (95% CI)	
Change in Intention to Quit All Tobacco (Post-Pre) exposure to the material	Group 2: SIQ	566	5.7 (2.3, 9.0)	192	8.3 (1.5, 15.2)	-2.7 (-10.3 , 5.0) †

† Model fit with claim status only due to convergence issues using the full model.

Table 24 Comprehension

Outcome	Claims studies		No Claim study		Mean Difference (and 95% CI) Claim studies – No Claim study
	n	Adjusted Mean % (95% CI)	n	Adjusted Mean % (95% CI)	
IQOS heats tobacco but does not burn it (assessed for the Brochure and HeatSticks Pack)	1889	94.0 (87.7 ,100.0)	762	93.2 (85.1 ,100.0)	0.8 (-7.5, 9.0)
IQOS is intended only for smokers who want to continue using tobacco (assessed for the Brochure only)	1135	91.9 (83.7 ,100.0)	383	93.3 (81.7 ,100.0)	-1.4 (-12.7, 9.9)

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Conclusion

In summary, this new analysis revealed that there were lower levels in the differences in Perceived Health Risk scores between CC and THS in the claims studies compared to the no claim study, in all smoking status groups. There were lower levels in the differences in Perceived Addiction Risk scores between CC and THS, in Adult Never Smokers but not in the other smoker status groups. However, it should be noted that the overall pattern of results was similar between the claims studies and the no claim study, in that in all four studies, CC was ranked as the highest perceived risk object, THS and E-cigarettes were ranked as having a similar level of perceived risk and NRTs and Cessation were ranked as the lowest perceived risk objects. As noted in the study reports included in Module 7.3.2 of the applications, the finding that subjects tended to perceive THS as having lower health risks than CC should be seen in the context of the wide understanding of the US public that smoking CC involves very serious health risks, following decades of public health campaigns (U.S. Department of Health and Human Services 2014). Hence people may perceive some tobacco or nicotine-containing products (such THS and e-cigarettes) as less harmful than CC, due to their being new, electronic and not involving combustion.

There was evidence of lower absolute levels of positive Intention to Use THS regularly, for the claims studies compared to the no claim study, in LA-25 Never Smokers only (see Table 22).

For Comprehension and Change in Intention to Quit All Tobacco, there was no evidence of differences between the claims studies and the no claim study.

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FDA QUESTION 22:

All of your MRTPAs, in the Perception and Behavior Assessment (PBA) studies, provide information about the sources of research participants, stating that they were recruited from lists and databases maintained by research agencies. You did not provide information about how people became a part of those lists or databases, aside from stating that they had expressed interest in participating in market research studies. Provide information about the sources of participants for the above mentioned PBA studies (i.e., how people came to be listed in the databases, such as through address sampling, recruiting from websites or social media, or by stopping passersby in a public location). Also, you did not describe how people meeting quota criteria were selected from these databases for screening. For example, if the recruiter was looking for a female current smoker aged 51+, how did the recruiter decide which female smoker aged 51+ to call from the database? If you have information about the method used to select people from the database (*e.g.*, if the recruiter used any additional selection criteria, or if the selection was randomized), provide it. Providing this information would help FDA evaluate the generalizability of the results of the studies concerning the potential public health impact of marketing the proposed MRTPs. If you do not have this information, provide a statement to that effect.

PMP S.A. RESPONSE:

The research agencies used for the recruitment of participants in the PBA studies, used a range of methods to populate their databases with people who have indicated an interest in participating in market research studies. In particular, database enrollment is done directly through the research agencies' website, referrals from friends and family already in the database, word of mouth, social media (advertising/recruitment banner), telephone recruiting (random digital dialing (i.e. cold calling) or specifically targeted population lists) and in-person recruiting.

Those research agencies selected people from the database based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, Individuals identified as meeting the pre-defined sampling frame were contacted and screened in a random order by individuals employed by the research agencies. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

A summary of database enrolment methods and sample selection methods used for the conduct of the Perception and Behavior Assessment studies can be found in Table 25.

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Table 25 Summary of Database Enrolment Method(s) and Sample Selection Method(s) - Perception and Behavior Assessment Studies

Study	Research Agency	Study Sites	Database Enrolment Method(s)	Sample Selection Method(s)
THS-PBA-02-US	(b) (4)		Company websites (awareness to websites driven by e-mail campaigns, social media, direct marketing and digital advertising/banner placements on specific websites). Referrals from current database members. Telephone recruiting (random digital dialing or specifically targeted population lists) In-person recruiting.	Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by the research agencies contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.
THS-PBA-03-US **THS-PBA-05-RRC-US** **THS-PBA-05-RRC2-US** **THS-PBA-05-REC-US** **THS-PMTA-05-NOC-US**			Referrals Company website Social media	Individuals identified as meeting the study criteria from the database information were contacted and screened in a random order. The random ordering was undertaken at the stratum level.

(table continues)

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Study	Research Agency	Study Sites	Database Enrolment Method(s)	Sample Selection Method(s)
THS-PBA-05-RRC-US **THS-PBA-05-REC-US**	(b) (4)		Company website Social media Cold calling and e-mailing Online survey outreach	Individuals identified as meeting the study criteria from the database information were contacted and screened in a random order. The random ordering was undertaken at the stratum level.
THS-PMTA-05-NOC-US			Referrals Company website Mass mailing Cold calls of general phone book Intercepts Social media	Individuals identified as meeting the study criteria from the database information were contacted and screened in a random order. The random ordering was undertaken at the stratum level.
THS-PBA-05-REC-US	Baltimore Research	Baltimore	Referrals Company website	Individuals identified as meeting the study criteria from the database information were contacted and screened in a random order. The random ordering was undertaken at the stratum level.

(table continues)

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Study	Research Agency	Study Sites	Database Enrolment Method(s)	Sample Selection Method(s)
THS-PBA-04-US	(b) (4)		Company websites (awareness to websites driven by e-mail campaigns, social media, direct marketing and digital advertising/banner placements on specific websites). Referrals from current database members. Telephone recruiting (random digital dialing or specifically targeted population lists). In-person recruiting.	Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by the research agencies contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

(table continues)

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Study	Research Agency	Study Sites	Database Enrolment Method(s)	Sample Selection Method(s)
THS-PBA-06-US	(b) (4)		Company websites (awareness to websites driven by e-mail campaigns, social media, direct marketing and digital advertising/banner placements on specific websites). Referrals from current database members. Telephone recruiting (random digital dialing or specifically targeted population lists). In-person recruiting.	Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by the research agencies contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.
THS-PBA-07-US			Mall intercept Word of mouth (b) (4) website (b) (4)	Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by (b) (4) contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

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Below we provide detailed information about the sources of participants for each PBA study (i.e., how people came to be listed in the databases, such as through address sampling, recruiting from websites or social media, or by stopping passersby in a public location).

THS-PBA-02-US study:

As stated in the study report (Page 49) and in the study protocol (Page 16 of 26) in Module 7.3.2 of the applications, "recruitment was conducted over the telephone using recruitment lists and databases maintained by the research agency/local recruitment agencies". The study fieldwork was conducted in 4 cities (b) (4)) and the recruitment of the potential study participants was done by two suppliers: (b) (4) (b) (4) .

Database enrollment practices are similar for both suppliers. Database enrollment is mainly sourced through their company websites and referrals from current members of the databases. Awareness to the websites is driven by e-mail campaigns, social media such as Facebook, direct marketing and digital advertising/banner placements on specific websites. At times, telephone recruiting either using random digital dialing or specifically targeted population lists and in-person recruiting is done.

THS-PBA-03-US study, the PBA05 studies (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US) and the THS-PMTA-05-NOC-US study:

The recruitment databases used for the THS-PBA-03-US study the PBA05 studies and the PMTA study (THS-PMTA-05-NOC-US), are populated over time using a range of methods including: referrals, enrollment directly from the research agencies' website, social media, cold calling, and intercepts. The most frequently used research agency, (b) (4) , has developed their databases from word of mouth referrals from friends and family already in the database. (b) (4) (b) (4) rely on frequent use of social media, to target specific types of recruits.

THS-PBA-04-US study:

As stated in the study report (Page 43), "recruitment was conducted over the telephone using recruitment lists and databases maintained by the local recruitment agencies". As further described in the study protocol (Page 22 of 36) "These companies (b) (4) (b) (4)] maintain recruitment lists and databases containing several thousand people who have indicated an interest in participating in market research studies such as individual interviews, focus groups, and surveys. These proprietary recruitment lists and databases include basic demographic information about the potential research volunteers".

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The THS-PBA-04-US study fieldwork was conducted in 2 cities (b) (4)) and the recruitment of the potential study participants was done by (b) (4)
(b) (4)

Database enrollment practices are similar for both suppliers. Database enrollment is mainly sourced through their company websites and referrals from current members of the databases. Awareness to the websites is driven by e-mail campaigns, social media such as Facebook, direct marketing and digital advertising/banner placements on specific websites. At times, telephone recruiting either using random digital dialing or specifically targeted population lists and in-person recruiting is done.

THS-PBA-06-US study:

As stated in the study report (Page 19 of 62), "subjects were recruited from four cities ((b) (4)
(b) (4)) to provide a geographically diverse sample of the U.S. population. (b) (4) provided the interviewing facilities in all cities and recruited subjects through outbound calling to participants in their in-house panel of database participants in each respective city." Database enrollment is mainly sourced through their company website and referrals from current members of the databases. Awareness to the websites is driven by e-mail campaigns, social media such as Facebook, direct marketing and digital advertising/banner placements on specific websites. At times, telephone recruiting either using random digital dialing or specifically targeted population lists and in-person recruiting is done.

THS-PBA-07-US study:

The study protocol (Page 33 of 62) states that "Candidate participants will be recruited from (b) (4) consumer-based databases according to the sampling structure […] to approximate the composition of the US adult smoking population. To ensure a good representation of the U.S. adult daily smokers of CC population, multiple sites, geographically spread across the U.S., will be used to recruit potential study participants". For reference, the study was conducted in 8 cities and the study sites were located in research facilities located in the following malls ((b) (4)
(b) (4)

The study report (Page 38 of 274) states that "The recruitment of candidate participants was handled by (b) (4) . Candidate participants were pre-recruited from ((b) (4)
(b) (4) s consumer-based databases (b) (4) maintains databases of candidate participants who voluntarily join to participate in various research studies for which they may be qualified (b) (4) databases consist of approximately 400,000 individuals nationwide. The (b) (4)

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databases are maintained and operated by each local site. Any candidate participant is allowed to join the site database via local facility or online. Interested participants complete a demographic survey and once completed they are added to the site database. The only exclusion criteria applied pertain to a participant's immediate disqualification for standard screening based on responses to "sensitive industry" related questions. Examples of sensitive industries would include: marketing brand management or marketing research, advertising agency or public relations firm, radio or television, newspaper or magazine. Candidate participants are recruited to join the site database via mall intercept, word of mouth or by visiting the (b) (4) website(b) (4) Database enrollment via mall intercept occurs in one of two ways; 1) potential participants are intercepted / screened solely for the purpose of enrolling in the database, or 2) at the end of completing a particular survey, participants are asked if they wish to enroll in the database so as to participate in future research.

Below we provide detailed information about the method used to select people from the database for each PBA study (e.g., if the recruiter used any additional selection criteria, or if the selection was randomized).

THS-PBA-02-US study:

The study report (Page 49) states that "recruiting for both research phases was done by telephone and handled by individuals employed by the various research facilities in each of the four cities. Recruitment was conducted over the telephone using recruitment lists and databases maintained by the local recruitment agencies". Profiles of participants who took part in the focus group discussion (FGD) (Phase 1) and individual interview (IDI) (Phase 2), as well as information by city about the number of persons contacted for the research who did not make it through the screener, were submitted in the applications and can be found in Appendix i and Appendix k of the study report, respectively. The study report (Page 49 and Page 50) also states that "A good mix of different ethnicities, level of education, level of income, different family situations (i.e. single, married, living together, divorced with or without children), working situations (i.e. studying, working part time, working full time, retired, unemployed) was attempted and achieved across the research. In addition, a good mix was attempted and achieved in terms of number of cigarettes smoked per day as well as brands (lower to premium priced) for groups of both adult smokers with no intention to quit as well as adult smokers motivated to quit. During the recruitment process, subjects were screened to ensure that they met the inclusion/exclusion criteria and then were assigned to the appropriate FGD/IDI". Lastly, and based on the information stated in the study protocol (Page 16 of 26), the telephone calls took place at different times of the day to avoid any recruitment bias.

Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by (b) (4) contacted, at random, potential study participants meeting the pre-defined sampling frame. No

specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

THS-PBA-03-US study and the PBA05 studies (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US, THS-PMTA-05-NOC-US):

For the THS-PBA-03-US study, the PBA05 studies and the PMTA study (THS-PMTA-05-NOC-US), all research agencies stated that they selected subjects at random from their database for screening potential subjects. Using the demographic and smoking status information, where available, on the database they identified potentially eligible subjects within each study stratum and then screened subjects at random until the quotas were filled.

There was one research vendor (b) (4) who were used to manage the recruitment for the (b) (4) site, for the THS-PBA-05-REC-US study, who did not respond to requests for information on their method of database building or sample selection from the databases.

THS-PBA-04-US study:

The study report (Page 43) states that "Recruiting was done by telephone and handled by individuals employed by the research facilities in each city. Recruitment was conducted over the telephone using recruitment lists and databases maintained by the local recruitment agencies". Profiles of participants who took part in the IDIs, as well as information by city about the number of persons contacted for the research who did not make it through the screener, were submitted in the applications and can be found in the Appendix d and Appendix e of the study report, respectively.

The study report (Page 43 and Page 44) also states that "the IDIs were stratified using the following variables: Gender – both male and female subjects were included; Age - quotas were set for subjects 18-25; 26-35; 36-50 and 51+; City – the sample was equally split between (b) (4) Beyond that, a good mix of different ethnicities, level of education, level of income, different family situations (i.e., single, married, living together, divorced with or without children), working situations (i.e., studying, working part time, working full time, retired, unemployed) was attempted and achieved across the research. In addition, a good mix was attempted and achieved in terms of number of cigarettes smoked per day as well as brands (lower to premium priced) for adult current smokers of CC. During the recruitment process, subjects were screened to ensure that they met the inclusion/exclusion criteria and then were assigned to the appropriate IDI". Lastly, and based on the information stated in the study protocol (Page 22 of 36), the telephone calls took place at different times of the day to avoid any recruitment bias.

Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by (b) (4)

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contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

THS-PBA-06-US study:

As stated in the study report (Page 21 of 62), "subjects were recruited using the research facilities' consumer panels consisting of people who had indicated an interest in participating in market research studies. These proprietary consumer panels included basic demographic information about potential research participants that helped the recruitment firm (b) (4) (b) (4)) to identify potential subjects to contact about the study. […] All screening was done over the phone." Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by (b) (4) contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

THS-PBA-07-US study:

The study report (Page 38 of 274) states that "The (b) (4) site database does pre-identify smokers who were contacted first, via telephone, as candidate participants. As needed, to meet recruitment quotas, screening was extended to the whole (b) (4) site database or via further recruitment. Further recruitment was done via mall intercept procedures, with candidate participants being first recruited to the (b) (4) site database and then screened against study qualification criteria. During the screening process, the candidate participants contacted were identified based on their socio-demographic characteristics related to sex, age, race and income. The study did not restrict enrollment using quotas, however, the sampling approximated the adult smoker distribution contained in the Centers for Disease Control and Prevention (CDC) report (CDC, 2012)".

Based on information available for each person (e.g., age, gender, smoker/non-smoker, etc…) within the database, individuals employed by (b) (4) contacted, at random, potential study participants meeting the pre-defined sampling frame. No specific method or particular order was utilized for the selection of study participants beyond ensuring the quotas were met.

The study report (Page 40 of 274) further states that "In a first step, (b) (4) screened candidate participants against all inclusion and exclusion criteria via telephone [see above]. Subject to eligibility determination, candidate participants were [then] invited to the study site for rescreening and enrollment into the study".

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FDA QUESTION 23:

All of your MRTPAs include several studies in which you classified participants based on their responses to questions about their intentions to try or use IQOS. Specifically, in studies PBA03, PBA05-RRC, PBA05-RRC2, and PBA05-REC, you classified participants as having a "positive intention" to use IQOS if they responded that they would either "Definitely" or "Very likely" use IQOS, but not if they would "Somewhat likely," "Somewhat unlikely," "Very unlikely," or "Definitely not" use IQOS. You did not submit any data or analyses supporting the validity of this classification. If you have such data or analyses, submit it to FDA. Providing data or analyses regarding why the "positive intention" category should include individuals responding "Definitely" or "Very likely" but exclude those responding "Somewhat likely" would help FDA with the scientific review of your MRTPAs. You may have data or analyses supporting this classification (*e.g.*, psychometric testing) from your scale development research completed as part of PBA01, given that you mention conducting Rasch measurement theory analysis and classical test theory analyses. However, your MRTPAs do not appear to include results or other scientific justification concerning the classification of "positive intention" to try or use IQOS. Providing this information would help FDA understand the likelihood of current cigarette smokers and non-smokers initiating use of the proposed MRTPs. If you do not have this classification information, provide a statement to that effect.

PMP S.A. RESPONSE:

We could not have performed a validation of the predictive ability of the chosen cut point, as the product is currently not on the market. In this situation, we chose a cut point that prioritized specificity (the 'true negative rate') over sensitivity (the 'true positive rate'), i.e. to minimize false positive predictions of actual (post-market) trial/use. For this reason, we sought to identify those subjects with a level of interest in THS which was strong or moderately strong (i.e. those using the top two categories), rather than using a broader definition (i.e. using the top three categories). This approach should exclude the somewhat undecided subjects from the 'positive' intent to use category, maximizing the probability of those included as actually trying/using the product in the real world.

Qualitative research was used in the development of the Intent to Use questionnaire (ITUQ) and this established content and face validity for the different items constituting the ITUQ. This developmental work is contained in the PBA01 – Scales Development and Validation Project (PBA01Sum) in the 732 PBA section of Module 7 of the applications.

It is important to note that there is currently no consensus in the literature on how intention to use should be measured, or what kind of assessment most accurately predicts uptake. However, the approach we took is consistent with standard practice laid out by European Society for Opinion and Marketing Research, which states "The mean, median and top two box percentages undoubtedly are the most widely used summary measures in quantitative market research." (ESOMAR, Market Research Best Practice 2009).

The interpretation of the 'top two categories' as a summary statistic will change according to the number of response options. A recent study reported analyses of 'interest' in a hypothetical MRTP using the top two of four categories ('very likely', 'somewhat likely', 'somewhat unlikely' and 'very unlikely'; Pearson et al. 2017). This more inclusive method of collapsing data was appropriate because it reflected that 'interest' is a wide ranging concept. By contrast, 'intention to try/use' is more concrete, and a stricter method of deriving a summary measure is appropriate. Despite the methodological differences between Pearson et al. 2017 and our PBA05 studies, there is a broad consistency in the reported data on interest/ Intent to Use THS. Pearson and colleagues reported that interest in an MRTP was 54.4% within current established smokers, and the THS-PBA05-RRC-US study (for example) reported that positive Intention to Use THS regularly was between 28% to 39% within Adult Smokers with No Intention to Quit CC, across arms. Thus both studies provided broadly comparable results in that both interest in a hypothetical MRTP and positive Intention to Use THS regularly was substantial within smokers. Similarly, Pearson and colleagues reported that interest in a hypothetical MRTP was 3.0% within never tobacco users and the THS-PBA05-RRC-US study reported that positive Intention to Use THS regularly was between 0% and 1% within Adult Never Smokers across arms. Overall, this consistency provides some support to the validity of our method of assessing Intent to Use THS.

A literature search did not find any published research specifically on how a combination of the top two of six categories for intention to use/purchase translate into use/purchase. However, the combination of the top two of five categories of an intention to try response scale is reported to be associated with a greater probability of trial after six months* (Jamieson and Bass, 1989). Although there are limitations in the predictive accuracy of intentions as a guide to actual behavior, it remains that intentions of use are the best predictor of future actual use. Further, purchase intention questionnaires are considered, in general, to be empirically unbiased and it has been stated that "researchers can have confidence in the use of such scales" (Wright and MacRae 2007).

For each of the PBA05 studies, the Intent to Use data is presented by the different response options separately in the study tables of results. This would allow the intention to try/use data to be considered in various ways, including using the top three categories rather than the top two.

* Probability of trial was a mean of 36% across non-durable products given the top two boxes of an intention to try response scale and 12.6% given the bottom two boxes. Probability of trial was a mean of 10% across durable products given the top two boxes of an intention to try response scale and a mean of 4.1% given the bottom two boxes.

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FDA QUESTION 24:

All of your MRTPAs, in the study protocols for qualitative studies PBA02 and PBA04, state that you would develop analysis schemes to "assess similarities and differences among various subpopulations," such as based on smoking status and quitting intentions (p. 24 of 26 in the PBA02 Protocol; p. 30 of 36 in the PBA04 Protocol). If you developed analysis schemes to guide analyses of results from PBA02 or PBA04, provide them. Providing these documents would help FDA understand how you reached your conclusions from these studies. If you have not developed analysis schemes, provide a statement to that effect.

PMP S.A. RESPONSE:

No written analysis schemes were documented. The analysis and subsequent reporting followed a multi-step detailed process consisting of a) observations made during the interviewing, including the observed non-verbal cues, b) a systematic analysis of the transcripts and visual aids to assess intention to use and risk perception and c) discussions within the study team (e.g. Principal Investigator, the professional moderators, etc…) regarding the interpretation of the study results.

As it is commonly done for qualitative studies, the systematic analysis based on the transcripts and the visual aids was done by reviewing subjects' responses by subpopulation (e.g. on the basis of gender, age, smoking status, etc…) to identify consistent patterns in responses and assess similarities and differences across subpopulations. The outcome of those analysis are only summarized in the respective final study report.

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FDA QUESTION 25:

All of your MRTPAs include PMTA05-NOC, in which you evaluate perceptions of IQOS, intent to use IQOS, comprehension, and changes in intentions to quit smoking CCs. You note that the Heatsticks Pack used in Arm 3 is an experimental condition intended to provide a comparison with Arm 2 "to enable an assessment of the impact of the presence or absence of product information on study outcome measures" and "to provide a basis for assessing outcomes measures for 'the product itself'" (p. 21, csr-app-16_1_1-protocol). You did not provide statistical analyses comparing perceptions and intentions between Arms 2 and 3. If you have conducted analyses to compare perceptions and intentions between Arm 2 and Arm 3 of PMTA05-NOC, provide them. These analyses could provide useful information about the effects of the different study arm stimuli on potential users of the products.

PMP S.A. RESPONSE:

The THS-PMTA-05-NOC-US study took a descriptive approach to the study data and, as such, tests of differences between arms were not performed nor presented in the study report. The study report presented means and 95% confidence intervals. Differences between arms 2 and 3 can potentially be inferred from the distances between the confidence intervals.

Subsequent to the production of the THS-PMTA-05-NOC-US study report, we did perform some additional statistical analysis on an exploratory basis, of the main outcome measures, including comparisons between arms 2 and 3 of the THS-PMTA-05-NOC-US study. These analyses were as follows.

Intention to Use THS regularly

This analysis included only smokers because there was such a small number of non-smokers who had positive Intention to Use THS. A Chi^2 test was used to explore for a difference between the four study arms. This analysis found that there was no difference between the groups (χ^2=5.3, p=0.15), because the p-value was above 0.05. Pairwise comparisons between arms were not performed.

Change in Intention to Quit

The analysis on Change in Intention to Quit All Tobacco included only smokers with the intention to quit. A Chi^2 test was used to explore for a difference between the four study arms. This analysis found that there was a difference between arms 2 and 3 (χ^2=12.2 p=0.007). Because the p-value was below 0.05, pairwise comparisons of the arms were performed, using pairwise Chi^2 tests. This post hoc analysis found that there was no difference between arms 2 and 3 in terms of Change in Intention to Quit All tobacco (χ^2=0.006, p=0.94).

Perceived Risk

In the post hoc analysis performed on the THS-PMTA-05-NOC-US Perceived Risk data, the data from all smoking status groups were combined. We present data for the absolute perceived risk

scores for THS and also for the difference in scores between CC and THS. We used these derived data (i.e. the difference in scores between CC and THS), as these provide a potentially valuable alternative method of analyzing Perceived Risk.

Perceived Health Risk

Main Sample

There was a difference in Perceived Health Risk between the arms (F=4.5, p=0.0040). Therefore, pairwise comparisons for differences between means of the arms were performed. This post hoc analysis found that there was no difference between arms 2 and 3 (Mean Perceived Health Risk = 51.7 for arm 2 and 55.2 for arm 3; $p > 0.05$; Tukey's Studentized Range test).

Considering the difference in Perceived Health Risk scores between CC and THS, there was a difference in Perceived Health Risk scores between the arms (F=6.5, p=0.0002). Therefore, pairwise comparisons for differences between means of the arms were performed. This post hoc analysis found that there was no difference between arms 2 and 3 (Mean Perceived Health Risk = 15.8 for arm 2 and 12.6 for arm 3; $p > 0.05$; Tukey's Studentized Range test).

Legal smoking age to 25 years Never Smokers (LA-25 NS)

There was no difference in Perceived Health Risk between the arms (F=0.84, p=0.47). Therefore, pairwise comparisons for differences between means of the arms were not performed. Similarly, considering the difference in Perceived Health Risk scores between CC and THS, there was no difference between the arms (F=1.72, p=0.16). Therefore, pairwise comparisons for differences between means of the arms were not performed.

Perceived Addiction Risk

Main Sample

There was a difference in Perceived Addiction Risk between the arms (F=4.7, p=0.003). Therefore, pairwise comparisons for differences between means of the arms were performed. This post hoc analysis found that there was no difference between arm 2 and 3 (Mean Perceived Addiction risk = 53.6 for arm 2 and 58.0 for arm 3; $p > 0.05$; Tukey's Studentized Range test).

Considering the difference in Perceived Addiction Risk scores between CC and THS, there was a difference in Perceived Addiction Risk scores between the arms (F=5.2, p=0.0014). Therefore pairwise comparisons for differences between means of the arms were performed. This post hoc analysis found that there was no difference between arms 2 and 3 (Mean Perceived Health Risk = 16.8 for arm 2 and 15.6 for arm 3; $p > 0.05$; Tukey's Studentized Range test).

LA-25 Never Smokers sample

There was no difference in Perceived Addiction Risk between the arms (F=1.35, p=0.26). Therefore, pairwise comparisons for differences between means of the arms were not performed. Similarly, considering the difference in Perceived Addiction Risk scores between CC and THS,

there was no difference in Perceived Addiction Risk between the arms (F=2.0, p=0.11). Therefore, pairwise comparisons for differences between means of the arms were not performed.

Summary

In summary, a comparison of arms 2 and 3 of the THS-PMTA-05-NOC-US study did not provide evidence that product information was associated with differences in:

a) Positive Intention to Use THS within smokers
b) Change in Intention to Quit All Tobacco within smokers with the Intention to Quit or
c) Perceived Health Risk or Perceived Addiction Risk within all subjects combined

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FDA QUESTION 26:

All of your MRTPAs, in PBA-07 and WOT studies, provide definitions for different usage categories of Heatsticks and CCs (*e.g.*, combined use [30-70% Heatstick use]), Heatstick use [over 70% Heatstick use]). If you have an explanation for why you decided to use these percentage thresholds for classifying people into usage categories, provide it.

PMP S.A. RESPONSE:

We decided to use the above-mentioned percentage thresholds to define usage groups, as this pre-defined symmetrical classification allows for practical and meaningful operationalized categorization, description and analysis. Such approach also facilitates the comparison of usage categories between different studies (e.g. THS-PBA-07-US and WOT studies). We provided this classification as part of the THS-PBA-07-US Statistical Analysis Plan to increase transparency and provided the raw data to allow to create further (more refined) categories for ad-hoc analysis, if needed.

Analysis of the Japanese Market Research Panel, comparing HeatStick use after 3 weeks and after 3 months from IQOS purchase, indicates that exclusive IQOS users tend to remain exclusive IQOS users over time, whilst predominant IQOS users have a higher tendency to become exclusive IQOS users than to remain predominant IQOS users. In particular, the data revealed that:

- 80% of the exclusive IQOS users [over 95% Heatstick use] at week 3 remained exclusive IQOS users after 3 months;
- 63% of the predominant IQOS users [over 70% but less than 95% Heatstick use] at week 3 became exclusive IQOS users after 3 months, whilst a lower proportion (24%) remained predominant IQOS users.

This provides additional support on the definition of IQOS users as those using over 70% HeatSticks.

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FDA QUESTION 27:

To allow for FDA to independently test the batteries used in the products that are the subject of these applications, we request that you submit the following samples to the Winchester Engineering Analytical Center (WEAC):

- 50 model 10370 batteries
- 50 model 18650 batteries

Samples should be submitted in accordance with manufacturer recommended storage conditions and within original packaging. Battery samples should be from one representative manufacturer for each battery type (10370 and 18650). To ensure integrity of testing for your samples, when they are being shipped we request that you observe the following:

a. Multiple samples can be shipped in the same outer shipping container, however; samples should be placed in sealed waterproof packaging within the outer shipping container.
b. Each sample should be clearly labeled with the product name, submission tracking number (STN) assigned to the product, manufacturing date, and quantity enclosed.

Product samples for WEAC should be sent to the following address:

Winchester Engineering Analytical Center
Attn: Sample Custodian-TOBACCO
109 Holton Street
Winchester, MA 01890-1152

PMP S.A. RESPONSE:

The requested batteries were sent to the Winchester Engineering Analytical Center in accordance with the above instructions and were delivered to the WEAC on September 1, 2017.

A copy of the cover letter is provided hereafter.

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August 30, 2017

Winchester Engineering Analytical Center
Attn: Sample Custodian-TOBACCO
109 Holton Street
Winchester, MA 01890-1152
USA

By Air Freight

Re: BATTERY SAMPLES ACCORDING TO AUGUST 4, 2017 INFORMATION REQUEST (Question 27) for MR0000059-MR0000061 from US-FDA

Dear Sir or Madam,

In accordance with instructions provided in the above-mentioned request from FDA, we are submitting herewith battery samples for independent testing in relation to PMP S.A.'s Modified Risk Tobacco Product Applications (MRTPAs):

MR0000059: IQOS system with Marlboro HeatSticks
MR0000060: IQOS system with Marlboro Smooth Menthol HeatSticks
MR0000061: IQOS system with Marlboro Fresh Menthol HeatSticks

The battery samples provided are listed below:

STN	Battery Usage	Battery Model	Battery Reference	Manufacturer	Man-ufacturing date	Quantity
MR0000059 MR0000060 MR0000061	IQOS Charger	18650	BAT. 000064.RD	Panasonic	Year 2017 Week 26	50 per box
MR0000059 MR0000060 MR0000061	IQOS Holder	10370	BAT. 000040.RD	FullRiver	Year 2017 Week 08	50 per box

The samples are identified with the battery model, reference, manufacturer, manufacturing date and quantity enclosed, as well as the related submission tracking numbers (STNs).

The battery samples can be stored under ambient conditions.

QUAI JEANRENAUD 3 CH-2000 NEUCHATEL SWITZERLAND TELEPHONE (41-58) 242 21 13 TELEFAX (41-58) 242 28 11

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US Agent for PMP S.A.:

Jeffrey Paul Walker, CEO
Teton Regulatory Sciences
PO Box 4876
877 Cache Creek Drive
Jackson, Wyoming 83001-4876 USA

Phone: 1-866-661-0170
Fax: 1-866- 661-6025
Email: jpwalkermdl@mac.com

Do not hesitate to contact us if any further information is required.

Sincerely,

Malgorzata Wronowska, PhD
Director Regulatory and Scientific Affairs
Philip Morris Products S.A.

cc. Jefferey Walker, US Agent for PMP S.A.

Enclosures:

- Page 16 (Question 27) of US-FDA Advice/Information Request dated 4 August, 2017, addressed to Philip Morris Products S.A.

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APPENDICES

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

Filename	Title / Description
SR1_Q03-A1_THS-TempProfile-00mm.xls	THS Temperature Profile data at 0.0 mm from Heating Blade
SR1_Q03-A2_THS-TempProfile-02mm.xls	THS Temperature Profile data at 0.2 mm from Heating Blade
(b) (4)	
SR1_Q04-A2_Factory-Heater-Calibration.pdf	Specification: ZRH CH Factory Heater Calibration
SR1_Q04-A3_HolderSequenceDesign-Report.pdf	Manufacturing Test Sequence Design Description Report: SFT.000079_R1, P1 Holder 2.4 MT4 (Calibration)
SR1_Q04-A4_Holder-Energy-Profile.pdf	Requirements Specifications: C28 Energy Profile for Platform Model 2.X Devices
SR1_Q05-A1_Aerosol-Deliveries-THS-reuse.pdf	Determination of Aerosol Deliveries of THS 2.2 Sticks when Re-used
SR1_Q08-A1_HPHC-MarketMap-Results.xls	Philip Morris USA 2012 HPHC Test Results for 31 Products and 3R4F, Altria Client Services
SR1_Q08-A2_MarketMap-Test-Mtds.pdf	2014 Letter from Altria Client Services describing test methods for HPHC analysis of 31 US conventional cigarette brands and 3R4F
SR1_Q12-A1_Compositions-Regular.pdf	Comparison of the Characteristics for the Regular Tobacco Stick used in the Studies Listed
SR1_Q12-A2_Compositions-Menthol1.pdf	Comparison of the Characteristics for the Menthol 1 Tobacco Stick used in the Studies Listed
SR1_Q12-A3_Compositions-Menthol2.pdf	Comparison of the Characteristics for the Menthol 2 Tobacco Stick used in the Studies Listed
SR1_Q12-A4_SER_SS0122014042.pdf	Sensory Evaluation Report: Dorado Dry Blends TO-04796
SR1_Q12-A5_SER_SS0152014052.pdf	Sensory Evaluation Report: QDP Consumer Test Platform 1 ZRH

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- The documents listed below are provided with this response in amendment to the applications:

Filename	Title	Status
Module 3 Product Description		
3.2.3 Dev Manuf.pdf	3.2.3 (v2) Device Manufacturing	Replaces 3.2.3 in the original submission
A3.2.1-21 Changes.pdf	A3.2.1-21 (v2) Changes	Replaces A3.2.1-21 in the original submission
A3.2.2-2 Regular Tobacco Stick BOM.pdf	A3.2.2-2 (v2) Regular Tobacco Stick BOM	Replaces A3.2.2-2 in the original submission
A3.2.2-3 Menthol Tobacco Stick BOMs.pdf	A3.2.2-3 (v2) Menthol Tobacco Stick BOMs	Replaces A3.2.2-3 in the original submission
A3.2.3-2 Device BOMs.pdf	A3.2.3-2 (v2) Device Bill of Materials	Replaces A3.2.3-2 in the original submission
A3.2.3-5 Contact-PCBA-Schem-Layout.pdf	A3.2.3-5 Contact PCB Assembly Schematics and Layout	New
A3.2.3-6 Heater-Ctrl-PCBA-Schem-Layout.pdf	A3.2.3-6 Heater Control PCB Assembly Schematics and Layout	New
A3.2.3-7 Charger-PCBA-Schem-Layout.pdf	A3.2.3-7 Charger PCB Assembly Schematics and Layout	New
A3.2.3-8 Holder-Mechanical-dwgs.pdf	A3.2.3-8 Holder Mechanical Drawings	New
A3.2.3-9 Charger-Mechanical-dwgs.pdf	A3.2.3-9 Charger Mechanical Drawings	New
A3.2.3-10 Heating-Blade-Spec.pdf	A3.2.3-10 Heating Blade Specification	New
A3.3-4 Final-Stab-Report-Regular.pdf	A3.3-4 (v2) Stability Final Results (12 months) – Regular	Replaces A3.3-4 Stability Intermediate Results (6 months) – Regular in the original submission [A3.3-4 Inter Stab Report Regular]
A3.3-8 Final-Stab-Report-Menthol-1.pdf	A3.3-8 (v2) Stability Final Results (12 months) – Menthol 1	Replaces A3.3-8 Stability Intermediate Results (6 months) – Menthol 1 in the original submission [A3.3-8 Inter Stab Report Menthol 1]

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- In response to Q13 above, the following reports/data, have been submitted on electronic media in amendment to the applications:

Folder	Title	Status
Module 7.3.1 Clinical		
\MedSafeReport2016	Safety Update Report - Tobacco Heating System / *IQOS* THS 2.2 and 2.4 Products with HeatSticks / *IQOS,* 01-Jan-2016 to 31-Dec-2016 and associated documents	New
Module 7.3.2 PBA\PBA07		
\30-d Addendum	THS-PBA-07-US - Actual Use Study of THS 2.2 Study Report Addendum - 30-Day Follow-Up Interview, Version 1.0, 01 Dec. 2016 and associated documents	New
\data	THS-PBA-07-US full study datasets (ADaM and SDTM), inclusive of the PBA07 30-day follow up data	Replaces the data submitted in Module 732PBA\PBA07 of the applications
\PostHoc-HSType	THS-PBA-07-US - Actual Use Study of THS 2.2 Study Report Addendum - Posthoc Analysis by HeatSticks Order Type, Version 1.0, 28 April 2017 and associated documents	New