PHILIP MORRIS
PRODUCTS S.A.

RESPONSE TO MARCH 2, 2017 INFORMATION REQUEST for MR0000059-MR0000061 and AMENDMENT to MR0000059-MR0000061

16 March 2017

Contents

This response/amendment contains confidential commercial and/or trade secret information. Protection of this information from public disclosure is hereby claimed under the applicable provisions of United States law. To facilitate FDA's publication of the disclosable portions of this response/amendment, as required by Section 911(e) of the FD&C Act, PMP S.A. will submit proposed redactions under separate cover.

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FDA QUESTION 1

In Section 7.3.3, you provided study protocols with information on study design, study population, measures, procedures, statistical analysis, and detailed study reports, including study findings and conclusions concerning the Whole Offer Test (WOT) conducted in five study countries (Japan, S. Korea, Italy, Germany and Switzerland).

You provided approximately 100 pages of summary tables (Transition Tables, Patterns of Usage Behavior Tables) aggregating results derived from WOT participants including the frequency and percentage of participants who report exclusive use of the IQOS system, exclusive use of traditional cigarettes, and combined use of both tobacco products, by study country and by study week. We cannot locate in your submission the underlying raw dataset compiled from the pencil and paper diaries recorded by study participants during the WOT from which the summary tables were developed.

Your applications should provide the underlying raw data from which the summary tables were developed so that FDA can fully assess the applications. These data may include, but are not limited to, the individual-level information concerning tobacco product use (IQOS, combustible cigarette, or combined use of both), study country, study site, date of diary entry, demographic information (age, gender, etc.), diary information collected, consent forms, confidentiality forms, CAPI questionnaire on cigarette use prior to study selection, and remuneration fee structure by country. We need this information to ensure a full review of the MRTP applications. If you have already provided this information, point us to the exact location within your applications (i.e., section number, page number, and paragraph). If you do not possess this information, please inform us of that fact. If you do not have access to the full datasets, including all raw data, consider providing this information through a right of reference to a Tobacco Product Master File (TPMF).

PMP S.A. RESPONSE:

The WOT studies were conducted outside the US as market research to provide data for the marketing of THS in the 5 countries in which they were conducted. The findings were included in the Applications to provide supportive data to the Actual Use Study of THS (THS-PBA-07-US) conducted in the U.S.

The WOT study raw data files listed in Appendix 1 of this response are provided in complement to the information contained in Module 7.3.3 of the Applications.

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FDA QUESTION 2

In Section 2.7, Executive Summary, you provided estimates from two online cross-sectional studies in Japan for initiation of the IQOS among never smokers (1.2%) and relapse using the IQOS among adult former smokers (1.5%). We could not locate further information about these studies in the applications. Your applications should provide information about the design of these cross-sectional studies, whether there are additional results available from these studies, and the data used to calculate these estimates for initiation and relapse. If you have already provided this information, point us to the exact location within your applications (i.e., section number, page number, and paragraph). If you do not possess this information, please inform us of that fact. If you do not have access to this information, consider providing it through a right of reference to a Tobacco Product Master File (TPMF).

PMP S.A. RESPONSE:

PMI has conducted two online cross-sectional studies in Japan. Both online cross-sectional studies were conducted as market research for the marketing of IQOS in Japan. The first study (two waves respectively in March 2015 and May 2015) evaluated the use of an online methodology to assess the effect of IQOS among Japanese adults of legal age to purchase tobacco and nicotine-containing products, in terms of prevalence, initiation and relapse. This study was conducted in the test area where IQOS was initially marketed in November 2014 (Nagoya prefecture). The second study (single wave in September 2016) was undertaken to gather more recent data at the national level.

The design of those studies does not reflect current cross-sectional studies design.

The documents for the online cross-sectional studies in Japan listed in Appendix 2 are provided with this response. They include raw data files and existing study reports, which also provide information about the design of these cross-sectional studies.

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FDA QUESTION 3:

In Section 3.3.2, you included data for PMI-58 testing for 54 HPHCs, glycerol, nicotine, TPM, and tar. Additionally, Section 7.1 includes mean, standard deviation (SD) and number of replicates for the PMI-58 data. In the three reports in Section 7.1 describing these analyses, you indicate that details of the analytical methodology are reported in Labstat reports NS308-H, NS336-H, and NS309-H, abstracts of which are included in the applications. You provide the reference for these Labstat reports, but we cannot locate them in your submission:

> "Analytical Test Report, NS336-H revision 1, Peter Joza, Labstat International ULC, September 21st 2016"
> "Analytical Test Report, NS309-H, Peter Joza, Labstat International ULC, April 13th 2016"
> "Analytical Test Report, NS308-H, Peter Joza, Labstat International ULC, April 13th 2016"

In addition, we cannot locate in your submission the full datasets, including all raw data generated from these analyses. On page 3 of Appendix A3.3-2, you indicate that Labstat is the owner of this data, and that release of this data cannot be made without authorization from Labstat:

> "The information given in the appendix are data provided by Labstat UCL, who performs analysis for PMI (see Section 3.2.2).
>
> Those Labstat information are proprietary, and cannot be disclosed without prior authorization from Labstat." (p. 3, Appendix A3.3-2)

The full datasets including all raw data, along with the details of the analytical methodology, are necessary to ensure a full review of the applications. Please confirm that you do not possess this information. If you do not have access to the full datasets, including all raw data and the details of the analytical methodology, consider providing this information through a right of reference to a Tobacco Product Master File (TPMF).

PMP S.A. RESPONSE:

In complement to the information contained in Module 7.1 of the Applications, the requested Labstat reports and corresponding raw data files are provided:

- Analytical Test Report, NS308-H, Peter Joza, Labstat International ULC, April 13th 2016 (Filename: NS308-H_Report_R1.pdf)

  Raw data files: NS308-H_ms_dataCF.xls (test item Regular)
  NS308-H_ms_controlsCF.xls (reference 3R4F)

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- Analytical Test Report, NS309-H, Peter Joza, Labstat International ULC, April 13th 2016 (Filename: NS309-H_Report_R1.pdf)

  Raw data files: NS309-H_ms_dataCF_R1.xls (test item Menthol 1)
  NS309-H_ms_controlsCF_R1.xls (reference 3R4F)

- Analytical Test Report, NS336-H revision 1, Peter Joza, Labstat International ULC, September 21st 2016 (Filename: NS336-H_Report_R1.pdf)

  Raw data files: NS336-H_ms_dataCF.xls (test item Menthol 2)
  NS336-H_ms_controlsCF_R1.xls (reference 3R4F)

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FDA QUESTION 4:

You submitted study plans, study reports, and published manuscripts for in vitro systems toxicology studies involving human organotypic bronchial epithelial, nasal, and oral epithelial cultures. Recently you published a systems toxicology study to investigate the effects of the THS 2.2 on human organotypic gingival epithelial cultures (Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A 3-day repeated exposure study. Food Chem Toxicol. 2016 Dec 23;101:15-35). Provide your study plan, study report, and raw data for the study involving gingival epithelial cultures to ensure a full review of the scientific merit of the MRTP applications. If you have already provided this information, point us to the exact location within your applications (i.e., section number, page number, and paragraph).

PMP S.A. RESPONSE:

The Human Organotypic Gingival Epithelial Cultures study plan and study report related to the recent publication mentioned above are provided herewith:

Filename: 1798_Organotypic_Gingival_SP.pdf
Filename: 1798_Organotypic_Gingival_SR.pdf

As the folder structure containing the raw data for the Human Organotypic Gingival Epithelial Cultures study cannot be submitted through the FDA ESG, the raw data has been sent separately on virus-checked external media on March 16, 2017.

These files are provided in complement to the information contained in Module 7.5 of the Applications.

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FDA QUESTION 5:

We have identified two published clinical studies of the Tobacco Heating System 2.1 sponsored by Philip Morris Products S.A.:

> Ludicke, F., Baker, G., Magnette, J., Picavet, P., & Weitkunat, R. (2017). Reduced Exposure to Harmful and Potentially Harmful Smoke Constituents With the Tobacco Heating System 2.1. *Nicotine Tob Res*, 19(2), 168-175.
>
> Picavet, P., Haziza, C., Lama, N., Weitkunat, R., & Ludicke, F. (2016). Comparison of the Pharmacokinetics of Nicotine Following Single and Ad Libitum Use of a Tobacco Heating System or Combustible Cigarettes. *Nicotine Tob Res*, 18(5), 557-563.

These studies do not appear to be referenced in your applications and we could not locate in your submission any documents related to these studies (e.g., raw data, original study protocol, study reports). Provide all documents for studies of Tobacco Heating System 2.1. Alternatively, if you believe that the findings from studies conducted using THS 2.1 are not relevant to an evaluation of the proposed MRTPs, consider providing a scientific rationale for that position. If you have already provided this information, point us to the exact location within your applications (i.e., section number, page number, and paragraph).

PMP S.A. RESPONSE:

The studies on THS 2.1 referenced above, clinical studies ZRHX-EX-01 and ZRHX-PK-02, were submitted to the FDA first in the form of study result summary reports with the meeting preparation package in support of the meeting held on March 7, 2013 (Submission Tracking Number: TC0000533) related to the protocol submission for clinical study ZRHM-PK-06-US on THS 2.2 (Submission Tracking Number: IU0000015). The clinical study reports on clinical studies ZRHX-EX-01 and ZRHX-PK-02 were submitted to the FDA as part of the protocol submission for study ZRHM-PK-06-US (Submission Tracking Number: IU0000015). In addition, the safety results for both studies, ZRHX-EX-01 and ZRHX-PK-02, were also submitted to the FDA in the Safety Summary Report submitted as part of the same submission (Submission Tracking Number: IU0000015).
As the subject of the Applications (MR0000059-MR0000061) is THS 2.2, the study data concerning THS 2.1 was not submitted in the Applications, as THS 2.1 was an earlier developmental prototype precedent to THS 2.2 with differences in terms of product specifications.

The main differences between THS 2.1 and THS 2.2 are highlighted in Table 1 below:

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Table 1 - Excerpt from Table 2 of FDA meeting information package (22 January 2013) - Submission Tracking Number: TC0000533, Page 17

Name of the product	Years of development and commercial status	Key characteristics	Improvements
THS 2.0	Development timing 2007-2010. No commercial or marketing activity	• Internal Tobacco Stick heating • Temperature control of the heating blade • Usage limited to 6 minutes • Revised cigarette design using shredded cast leaf tobacco processing and new filter element. • Heating blade temperature of 375°C • Significant Device size reduction • Introduction of a two-piece system including a Charger and Holder	• Overall reduction of HPHCs delivery compared to THS 1.0 • Consumer acceptability improved (taste and ergonomics) • Potential for consumer misuse more limited than in THS 1.0
THS 2.1	Development in 2011	Changes from THS 2.0: • Tobacco Plug manufacturing changed to crimped tobacco	• Increased manufacturing consistency • Improved consistency of sensory experience
THS 2.2	Development from 2011	Changes from THS 2.1: (b) (4) • Overall blade temperature reduction (320-350 °C) compared to THS 2.1	• Further reduction in the scope of potential consumer misuse • Improved puff by puff consistency • Improved sensory satisfaction compared to THS 2.1

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However, as the clinical studies ZRHX-EX-01 and ZRHX-PK-02 were used to inform the study designs submitted to the FDA that were conducted as part of the THS 2.2 clinical assessment program and, therefore, served as proof of concept for the methodology used for clinical studies part of the THS 2.2 clinical assessment program, we are submitting the following documents and data as requested:

- The study reports for studies ZRHX-EX-01 and ZRHX-PK-02
- SDTM data submission packages (datasets, define.xml and Reviewer Guide) for studies ZRHX-EX-01 and ZRHX-PK-02
- ADaM data packages (datasets and ADaM Specifications) for studies ZRHX-EX-01 and ZRHX-PK-02
- The Safety Summary Report originally submitted as part of the ZRHM-PK-06-US protocol submission (Submission Tracking Number: IU0000015).

As these documents and data are contained in a folder structure that cannot be submitted via the FDA ESG, the files have been sent on virus-checked external media on March 16, 2017.

This data is submitted in complement to information contained in Module 7.3.1 of the Applications.

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FDA QUESTION 6:

In Module 1 (section 1.5) of your submission, you provided a letter of authorization for FDA to review the Tobacco Product Master File (TPMF) MF0000042 for a Tobacco Heating System (THS) to support your MRTP applications. This letter is not signed by the TPMF owner (or authorized agent) for MF0000042. Additionally the TPMF file does not contain any amendments authorizing you to reference the TPMF for these applications. To allow for a right of reference to support your MRTP applications, the TPMF owner (or authorized agent) will need to grant authorization to reference MF0000042 for these three MRTP applications.

PMP S.A. RESPONSE:

We would like to confirm that the Letter of Authorization to review the Tobacco Product Master File (TPMF) MF0000042 for a Tobacco Heating System (THS) was signed by the TPMF owner, Dr. Karsten Merkel, Director QA & Compliance, PMP S.A.

He is designated as the owner of TPMF MF0000042 in the TPMF update submitted to FDA on November 28th, 2016 and as the key contact for all our MFs in the Authorization Letter dated October 15, 2015.

Furthermore, in the update to the TPMF MF0000042, the right to reference the master file information in support of these Applications is specified. FDA has acknowledged receipt (TI0000979) on November 28th, 2016.

The following documents are included in Appendix 3 of this response for reference:

- MF0000042 TPMF Update Letter, dated November 4, 2016 (submitted Nov. 28, 2016)
- FDA Acknowledgement of receipt (STN: TI0000979), dated November 28, 2016
- Master File Authorization Letter, dated October 15, 2015

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FDA QUESTION 7:

Within your MRTPAs, different names are used to describe the product under study. For example, is THS 2.2 the same as the IQOS system? We request that you clarify which product names apply to the IQOS system and/or previous versions. One way to do this would be to provide a table outlining each name associated with each version. If you have already provided this information, point us to the exact location within your applications (i.e., section number, page number, and paragraph).

PMP S.A. RESPONSE:

We confirm that THS 2.2 is the same as the IQOS system.

Subject of the application	**Investigational Product**	**Commercial Product**
Denomination:	THS 2.2	IQOS system

No previous versions of the Tobacco Heating System were called IQOS.

THS 2.1, was a development phase prototype used in pilot / exploratory human studies in UK (ZRHX-PK-02) and in Poland (ZRHX-EX-01). Additional information regarding THS 2.1 is provided in response to Question 5 above.

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FDA QUESTION 8:

To allow for FDA to independently test the products that are the subject of these applications, we request that you submit the following samples to the Southeast Regional Laboratory (SRL):

- 65 20-stick packs of Marlboro Heatsticks (6.5 cartons)
- 45 20-stick packs of Marlboro Smooth Menthol Heatsticks (4.5 cartons)
- 20 20-stick packs of Marlboro Fresh Menthol Heatsticks (2 cartons)
- 22 IQOS Holders
- 12 IQOS Chargers

Samples should be submitted in accordance with manufacturer recommended storage conditions and within original packaging. To ensure integrity of testing for your samples, when they are being shipped we request that you observe the following:

- 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.
- Each sample should be clearly labeled with the product name, submission tracking number (STN) assigned to the product, manufacturing date, and quantity enclosed.
- Samples containing menthol should be packaged separately from non-mentholated tobacco products.

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

Southeast Regional Laboratory
Attn: Sample Custodian-Tobacco
U.S. Food and Drug Administration
60 8th Street
Atlanta, GA 30309

PMP S.A. RESPONSE:

The requested samples, prepared in accordance with the above-mentioned instructions, have been sent to the Southeast Regional Laboratory on March 16, 2017.

A copy of the letter to SRL is provided in Appendix 4 of this response.

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APPENDICES

Appendix 1: Q1 - WOT studies

The files listed below are provided with this response:

Japan

File	Description
P1 WOT JP Data.xlsx	Raw data at individual-level
P1 WOT JP Variables.xlsx	Description of the variables used in the raw data file
P1 WOT JP Consent Form.pdf	Informed consent form and confidentiality declaration
P1 WOT JP Questionnaire.pdf	Questionnaire used on cigarette use prior to study selection
P1 WOT JP Diary.pdf	Blank diary sample
P1 WOT JP Remuneration fee.pdf	Remuneration fee

South Korea

File	Description
P1 WOT KO Data.xlsx	Raw data at individual-level
P1 WOT KO Variables.xlsx	Description of the variables used in the raw data file
P1 WOT KO Consent Form.pdf	Informed consent form and confidentiality declaration
P1 WOT KO Questionnaire.pdf	Questionnaire used on cigarette use prior to study selection
P1 WOT KO Diary.pdf	Blank diary sample
P1 WOT KO Remuneration fee.pdf	Remuneration fee

Italy

File	Description
P1 WOT IT Data.xlsx	Raw data at individual-level
P1 WOT IT Variables.xlsx	Description of the variables used in the raw data file
P1 WOT IT Consent Form.pdf	Informed consent form and confidentiality declaration
P1 WOT IT Questionnaire.pdf	Questionnaire used on cigarette use prior to study selection
P1 WOT IT Diary.pdf	Blank diary sample
P1 WOT IT Remuneration fee.pdf	Remuneration fee

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Germany

File	Description
P1 WOT DE Data.xlsx	Raw data at individual-level
P1 WOT DE Variables.xlsx	Description of the variables used in the raw data file
P1 WOT DE Consent Form.pdf	Informed consent form and confidentiality declaration
P1 WOT DE Questionnaire.pdf	Questionnaire used on cigarette use prior to study selection
P1 WOT DE Diary.pdf	Blank diary sample
P1 WOT DE Remuneration fee.pdf	Remuneration fee

Switzerland

File	Description
P1 WOT CH Data.xlsx	Raw data at individual-level
P1 WOT CH Variables.xlsx	Description of the variables used in the raw data file
P1 WOT CH Consent Form.pdf	Informed consent form and confidentiality declaration
P1 WOT CH Questionnaire.pdf	Questionnaire used on cigarette use prior to study selection
P1 WOT CH Diary.pdf	Blank diary sample
P1 WOT CH Remuneration fee.pdf	Remuneration fee

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Appendix 2: Q2 - Online cross-sectional studies

The files listed below are provided with this response:

File	Description
Online CS Data Mar 2015.xlxs	Raw data at individual-level March 2015-Nagoya
Online CS Questionnaire Mar 2015.pdf	Questionnaire March 2015
Online CS Data May 2015.xlxs	Raw data at individual-level May 2015-Nagoya
Online CS Questionnaire May 2015.pdf	Questionnaire May 2015
Online CS Report Mar-May 2015.pdf	PMI internal report March-May 2015
Online CS Data Sep 2016.xlxs	Raw data at individual-level September 2016-Japan national
Online CS Questionnaire Sep 2016.pdf	Questionnaire September 2016
Online CS Report Sep 2016.pdf	PMI internal report September 2016

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Appendix 3: Q6 - Tobacco Product Master File

- MF0000042 TPMF Update Letter, dated November 4, 2016 (submitted Nov. 28th, 2016)

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November 4, 2016

U.S. Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Update of the Tobacco Product Master File reference STN MF0000042 and submission of product-related ingredient information in support of PMP S.A. premarket submissions for a Tobacco Heating System (THS)

To whom it may concern,

Philip Morris Products S.A. intends to submit a Modified Risk Tobacco Product application and a Premarket Tobacco application for a Tobacco Heating System (THS). THS is composed of a tobacco product, referred to as Tobacco Stick, and a Tobacco Heating Device.

Information regarding confidentiality within PMP S.A.:

PMP S.A. considers the individual composition of any of its product as highly confidential and as trade secret.

Consequently, the ingredient reports of the Tobacco Sticks are being sent separately, in a dedicated Tobacco Product Master File, from the Modified Risk Tobacco Product and Premarket Tobacco applications for the Tobacco Heating System (THS). This procedure was already applied for the submission of ingredient related information in support of the request for the Investigational Use Exemption.

For ease of reference, we are using the most recent FDA Submission Tracking Number (STN), i.e. **MF0000042** for the submission of ingredient related data in support of PMP S.A. Modified Risk Tobacco Product and Premarket Tobacco applications for a Tobacco Heating System (THS).

Quai Jeanrenaud 3 / CH-2000 Neuchâtel / Switzerland
Phone +41 58 242 33 84 / e-mail: karsten.merkel@pmi.com

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Update of the Tobacco Product Master File/Table of Contents:

The Tobacco Product Master File reference STN MF-0000042 was updated to include product-related ingredient information, in accordance with FDA's Guidance for Industry - Listing of Ingredients in Tobacco Products, for the following three products:

- Tobacco Sticks Regular "*Marlboro HeatSticks*"
- Tobacco Sticks Menthol 1 "*Marlboro Smooth Menthol HeatSticks*"
- Tobacco Sticks Menthol 2 "*Marlboro Fresh Menthol HeatSticks*"

A letter granting authorization to the U.S. Food and Drug Administration to review this information within the scope of PMP S.A. applications is provided attached.

Information on Tobacco Product Master File owner:

Name:	Dr. Karsten Merkel
Title:	Director QA & Compliance, PMP S.A
Mailing address:	Quai Jeanrenaud 3, CH-2000 Neuchatel, Switzerland
e-mail address:	Karsten.Merkel@pmi.com
Phone number:	+41 58 242 3384

Information on authorized representatives:

Name:	Dr. Sabine Gacond Mignon,
Title:	Manager Product Information Reporting, PMP S.A.
Mailing address:	Quai Jeanrenaud 3, CH-2000 Neuchatel, Switzerland
e-mail address:	Sabine.Gacond@pmi.com
Phone number:	+41 58 242 3610

Name:	Judith Clerc
Title:	Senior Officer Regulatory Affairs, PMP S.A.
Mailing address:	Quai Jeanrenaud 3, CH-2000 Neuchatel, Switzerland
e-mail address:	Judith.Clerc@pmi.com
Phone number:	+41 58 242 2282

Information on PMP S.A. US Agent:

Name:	Jeffrey P. Walker
Title:	Teton Regulatory Sciences, CEO
Mailing address:	PO Box 4876, 877 Cache Creek Drive, 83001-4978 Jackson, Wyoming
e-mail address:	jpwalkermd1@mac.com
Phone number:	866-661-0170

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We will notify the U.S. Food and Drug Administration through an amendment to the Tobacco Product Master File of any addition, change, or deletion of information in the Tobacco Product Master File.

Please contact us in case of any further questions.

Very truly yours,

Dr. Karsten Merkel
Director QA & Compliance
PMP S.A.

Quai Jeanrenaud 3 / CH-2000 Neuchâtel / Schweiz
Phone +41 58 242 33 84 / e-mail: karsten.merkel@pmi.com

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November 4, 2016

U.S. Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

LETTER OF AUTHORIZATION

Re: Authorization for the U.S. Food and Drug Administration to review the Tobacco Product Master File reference STN MF0000042 submitted by PMP S.A. for a Tobacco Heating System (THS) in support of our Modified Risk Tobacco Product and Premarket Tobacco applications.

We hereby grant authorization to the U.S. Food and Drug Administration to review the ingredient information submitted under the Tobacco Product Master File reference STN MF0000042 when considering applications filed by PMP S.A., e.g. Modified Risk Tobacco Product application, Pre-market Tobacco application, for a Tobacco Heating System (THS), without limitations.

Sincerely,

Dr. Karsten Merkel
Director QA& Compliance
PMP S.A.

Quai Jeanrenaud 3 / CH-2000 Neuchâtel / Switzerland
Phone +41 58 242 3384 / e-mail: karsten.merkel@pmi.com

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- FDA Acknowledgement of receipt (STN: TI0000979), dated November 28th, 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

11/28/2016

Philip Morris Products S.A.
Attention: Mr. Karsten Merkel
Director QA and Compliance
Quai Jeanrenaud 3
Neuchatel, Neuchatel 2000, Swiss Confederation
Submission Tracking Number: TI0000979

Dear Mr. Merkel:

On 11/28/2016, the Center for Tobacco Products (CTP) received your Listing of Ingredients in Tobacco Products submitted under section 904(c) of the Food, Drug, and Cosmetic Act as amended by the Family Smoking Prevention and Tobacco Control Act. This acknowledgement does not constitute review or approval of your submission.

If you require assistance regarding your submission or with any information in this letter, please contact us at 1-877-CTP-1373 or at CTP_DCC@fda.hhs.gov. Please use the Submission Tracking Number (STN) identified above in all references to this submission.

We encourage you to visit our website at http://www.fda.gov/TobaccoProducts, which includes up-to-date information about the regulations that have been promulgated and any actions CTP is taking with respect to implementing the Tobacco Control Act. You can sign up for automatic notification when there is any new information on the website.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal (http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/ucm515047.htm) using eSubmitter (http://www.fda.gov/ForIndustry/FDAeSubmitter). The FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal. If necessary, submissions may be mailed to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The CTP Portal and FDA Electronic Submission Gateway (ESG) are both generally available 24 hours a day, seven days a week. Submissions delivered to DCC by couriers or physical mail will be considered timely if received during delivery hours on or before the due date (see

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http://www.fda.gov/TobaccoProducts/AboutCTP/ContactUs/default.htm); if the due date falls on a weekend or holiday the delivery must be received on the prior business day. We are unable to accept regulatory submissions by e-mail.

Sincerely,

Patricia S. Baur
Project Manager
Document Control Center
Center for Tobacco Products

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- Master File Authorization Letter, dated October 15, 2015

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PMI RESEARCH & DEVELOPMENT

15 October 2015

David Ashley, Ph.D.
Director Office of Science
Center for Tobacco Products (CTP)
US Food and Drug Administration
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Teleconference with CTP on 15 October 2015
PMI Authorization Letter for Dr. Karsten Merkel and Dr. Beate Miller - MF0000013, MF0000034, MF0000042

Hereby, we would like to inform you that Dr. Karsten Merkel, employee of Philip Morris International (PMI) Research and Development will be the key contact to act on behalf of PMI on matters related to the Masterfile numbers MF0000013, MF0000034 and MF0000042 related to the investigational Tobacco Heating System 2.2 (THS 2.2).
Dr. Beate Miller, employee of Philip Morris International (PMI) Research and Development is authorized as additional contact to act on behalf of PMI on matters related to the Masterfile numbers MF0000013, MF0000034 and MF0000042 related to the investigational Tobacco Heating System 2.2 (THS 2.2).

The contact details of Dr. Merkel and Dr. Miller are given below:

Karsten Merkel, Ph.D.
Director R&D QA & Compliance
PMI Research and Development
Rue des Usines 90
2000 Neuchatel, Switzerland
e-Mail: Karsten.Merkel@pmi.com
Tel: +41 58 242 3384
Fax: + 41 58 242 3110

Beate Miller, Ph.D.
Program Manager, Regulatory Operations
PMI Research and Development
Quai Jeanrenaud 5
2000 Neuchatel, Switzerland
e-Mail : Beate.Miller@pmi.com
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Fax: + 41 58 242 2811 18

Very truly yours,

Dr. Karsten Merkel
Director R&D QA & Compliance
PMI Research and Development

QUAI JEANRENAUD 5 CH-2000 NEUCHATEL SWITZERLAND TELEPHONE (41-58) 242 21 13 TELEFAX (41-58) 242 28 11
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PHILIP MORRIS
PRODUCTS S.A.

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PMI RESEARCH & DEVELOPMENT

15 October 2015

David Ashley, Ph.D.
Director Office of Science
Center for Tobacco Products (CTP)
US Food and Drug Administration
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Teleconference with CTP on 15 October 2015
PMI Withdrawal of Authorization Letter for Dominique Andrey - MF0000042

Hereby, we would like to inform you that I, Dominique Andrey, employee of Philip Morris International (PMI) Research and Development, will no longer act as contact on behalf of PMI on matters related to the Masterfile number MF0000042 related to the investigational Tobacco Heating System 2.2 (TSH 2.2).

Very truly yours,

D. Andrey

Dominique Andrey
Manager Product Regulatory Compliance
PMI Research and Development

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Appendix 4: Q8 - Letter to Southeast Regional Laboratory

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March 16, 2017

Southeast Regional Laboratory
Attn: Sample Custodian-Tobacco
U.S. Food and Drug Administration
60 8th Street
Atlanta, GA 30309
USA

By Air Freight

Re: PRODUCT SAMPLES ACCORDING TO MARCH 2, 2017 INFORMATION REQUEST (Question 8) for MR0000059-MR0000061 from US-FDA

Dear Sir or Madam,

In accordance with instructions provided in the above-mentioned request from FDA (see attached), we are submitting herewith Tobacco Heating System (THS) 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 product samples provided are listed below:

Product Name	STN	Item Code	Batch Number	Manufacturing Date	Quantity
Marlboro HeatSticks	MR0000059	ME000004.02	41-2769125	29 Dec. 2016	70 20-stick packs (7 cartons)
Marlboro Smooth Menthol HeatSticks	MR0000060	ME000041.01	41-2697700	24-25 Oct. 2016	50 20-stick packs (5 cartons)
Marlboro Fresh Menthol HeatSticks	MR0000061	ME000006.01	41-2697701	25 Oct. 2016	20 20-stick packs (2 cartons)

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Product Name	STN	Item Code	UID** Number	UID Date	Quantity
IQOS Holder*	MR0000059 MR0000060 MR0000061	DVC.000023	T5A8PWQ7BMXLSH TV8WN14PBJC990 T7A0YW0NU4TYBC TFNZA45NRHCZL7 TJH2UPRESUSCCE TVRKS1GCN5R45E TPY8X6FFFMX5D6 T2NVB0LHVJFZLL TDUJ3KYY5JKEKG T59BZQ97QEAQS5 TJB5XL7MHTVAY3 TXRFSYRPC5D63E TJSBTU6EH5F63T TTX3Z48QQP66KN TK2NFNQFB4P0PC TWXLT801ZB3JGN TQQPBH81E1NR0E TFX68RCDVWBSPM TFELKVNRZVU0V9 TNLA6B2TCZG2ZG TF2DLWWNKAZ37H TLKJSANLP3H7B0	11 Nov. 2016 11 Nov. 2016	22
IQOS Charger*	MR0000059 MR0000060 MR0000061	DVC.000033	TPK7596F3ZX3MR TFXLEWT0RKLPLP T1G8CTVGB0AR85 TUVT3RKXUD1TAU T89QU6QMPJN5N7 TLU634JBMSRU8U TQTLLYEGKK96MA T99LPY7MSVHTEN TX907EYZYD115D T58CGKFCT8404E TUD3XWXWDXX14W TAPR2DFVNQJXWQ T0F4T3UE7DA3S1 TNAGA8F7C3K0WJ TWSBLWLYF8K5Q8 T1G7KAXQCDJ751 TQXH8U15THCSAE TX25CMPYJCF8YS TG34ZHHVUAXDKQ T00EG4RB9C6NJZ TWV4YLYYQ1M0BZ TMZANXVWXAQLGH	09 Nov. 2016 09 Nov. 2016 30 Oct. 2016 04 Nov. 2016 04 Nov. 2016 09 Nov. 2016 09 Nov. 2016 04 Nov. 2016 04 Nov. 2016 09 Nov. 2016 30 Oct. 2016 30 Oct. 2016 30 Oct. 2016 09 Nov. 2016 09 Nov. 2016 09 Nov. 2016 09 Nov. 2016 09 Nov. 2016 28 Oct. 2016 09 Nov. 2016 09 Nov. 2016 03 Nov. 2016	22

* Packaged in a kit containing: 1 Holder, 1 Charger, 1 USB cable, 1 A/C power adapter and 1 cleaning brush per box.

** UID: Unique Identifier

The samples are identified with the product name, submission tracking number (STN), batch/UID no., manufacturing/UID date and quantity enclosed.

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PRODUCTS S.A.

The HeatSticks and IQOS kit samples are labelled for the Japanese and UK markets, respectively. Please find enclosed the instructions for using IQOS, as submitted in the MRTPA.

The samples should be stored in their original packaging. The products can be stored under ambient conditions and are recommended to be stored between 5-30°C and Max. 60% R.H.

Authorized Contacts:

Malgorzata Wronowska
Director Regulatory and Scientific Affairs
Philip Morris Products S.A.
Phone: +41 58 242 2708
Email: Malgorzata.Wronowska@pmi.com

U.S. 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: jpwalkermd1@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: Jeffrey Walker, US Agent for PMP S.A.

Enclosures:

- US-FDA Advice/Information Request dated March 2, 2017
- A3.4.1 User Guide
- A3.4.2 Quick Start Guide