U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

MODIFIED RISK GRANTED ORDER–
EXPOSURE MODIFICATION

Philip Morris Products S.A.
Attention: Adam Susser, Esq., Senior Counsel, Regulatory Affairs, U.S. Agent for PMP S.A.
8800 Harness Trail
Potomac, MD 20854

FDA Submission Tracking Number (STN): MR0000192

Dear Adam Susser:

We completed review of your MRTPA[1,2] and are issuing a modified risk granted order (MRGO) for the tobacco product identified in Appendix A.

Based on our review of your MRTPA, we determined that the proposed modified risk tobacco product, as described in your application and specified in Appendix A, as actually used by consumers, has satisfied the requirements of section 911(g)(2)(A) and (B), including that it is appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. Therefore, we authorize the marketing of the modified risk tobacco product with the following reduced exposure claim:

"AVAILABLE EVIDENCE TO DATE:

- **The IQOS system heats tobacco but does not burn it.**
- **This significantly reduces the production of harmful and potentially harmful chemicals.**
- **Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."**

Under the provisions of section 911, you may introduce or deliver for introduction into interstate commerce the modified risk tobacco product, in accordance with this exposure modification order. Under section 911(g)(2)(C)(ii), this order is conditioned on your agreement to conduct postmarket surveillance and studies (PMSS) in accordance with a protocol approved by FDA and to submit the results of such PMSS annually. See Appendix B for information on required PMSS. This order also includes requests related to other record retention and reporting, as outlined in all attached appendices.

[1] Modified Risk Tobacco Product Application (MRTPA) submitted under section 911(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

[2] The IQOS 3 System has already received a marketing order for its premarket (PMTA) submission (PM0000634) and it represents an updated version of the IQOS 2.4 System, which can be legally marketed and has a modified risk granted order

This order for this MRTPA expires July 07, 2024 to align with the expiration of the MRTPA MRGO for the IQOS 2.4 System. If you wish to renew your order, we recommend a request for renewal is received by FDA at least 360 days prior to the expiration date. Your renewal may cross-reference your MRTPA for the IQOS 2.4 system and the MRTPA that is subject to this order.

The requirements in this exposure modification order are intended to help ensure that your modified risk tobacco product will continue to satisfy the requirements of section 911(g)(2)(A) and (B). However, compliance with these requirements alone is not a guarantee that the modified risk tobacco product will continue to be appropriate to promote public health and continue to be expected to benefit the health of the population as a whole, particularly if, despite these measures, there is a significant increase in youth initiation or initiation by non-users. FDA will continue to monitor the marketing of your product and its impact on the population. FDA will continue to monitor the marketing of your modified risk tobacco product and its impact on the population.

This order authorizing the marketing of this modified risk product does not mean FDA "approved" the product specified in Appendix A; therefore, you may not make any express or implied statement or representation directed to consumers that conveys, promotes, or would mislead consumers into believing, among other things that the tobacco product specified in Appendix A, as being "approved" by FDA (see Section 301(tt) of the FD&C Act). Moreover, because these products have not been authorized under section 911(g)(1) (risk modification order), you may not market these products with reduced risk claims.

The modified risk tobacco product subject to this exposure modification order is subject to withdrawal as described in section 911(j) of the FD&C Act.

The modified risk tobacco product specified in Appendix A is subject to the requirements of the associated December 7, 2020, PMTA order and appendices, FD&C Act, and its impending regulations.

We remind you that all regulated tobacco products, including the tobacco product specified in Appendix A, are subject to the requirements of the FD&C Act and its implementing regulations. These requirements include, but are not limited to, annual registration, listing of products, listing of ingredients, reporting of harmful and potentially harmful constituents, packaging, labeling, and advertising requirements, and payment of user fees. It is your responsibility to ensure the tobacco product specified in Appendix A complies with all applicable statutory and regulatory requirements. FDA will monitor your compliance with all applicable statutes and regulations.

In accordance with 40 CFR 1506.6, we will make your Environmental Assessment (EA) publicly available.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[3,4] using eSubmitter.[5] Alternatively, 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's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; if the upload is successful, submissions are considered received by DCC on the day of upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date[6]; if the due date falls on a weekend or holiday, the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

If you have any questions regarding this order, please contact Barbara Banchero, Regulatory Health Project Manager, at (301) 796-1937 or Barbara.Banchero@fda.hhs.gov.

If you have any questions regarding postmarket activities for the tobacco products subject of this order, please contact Lillian Ortega, Director, Division of Enforcement and Manufacturing, at CTP-OCE-Postmarket@fda.hhs.gov.

Sincerely,

/S/

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures:

Appendix A – Tobacco Product Subject of This Letter
Appendix B – Required Postmarket Surveillance and Studies
Appendix C – Recordkeeping and Retention
Appendix D – Conditions of Marketing

[3] https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal
[4] FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.
[5] https://www.fda.gov/industry/fda-esubmitter
[6] https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp

Appendix A[7]

Tobacco Product Subject of This Letter

Attributes of MRTPA	
Submission date	March 18, 2021
Receipt date	March 18, 2021
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Product category	Heated Tobacco Product (HTP)[8,9]
Product subcategory	Open HTP
Order type	Exposure Modification 911(g)(2) order
Proposed claims	AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.
Attributes	**Tobacco Product**
STN	MR0000192
Product name	IQOS 3 System Holder and Charger
Package type	Box
Product quantity	1 Holder, 1 Charger
Characterizing flavor	None
Length	92.25 mm (Holder) 114. 80 mm (Charger)
Diameter	14.40 mm (Holder) (smallest) 14.90 mm (Holder) (largest area with protruding button)
Wattage	Not provided
Battery Capacity	> 110 milliAmpere hour (mAh) (Holder) > 2600 mAh (Charger)
Additional property	Ventilation: Not provided Source of energy: Electric (rechargeable battery) Thickness: 23.00 mm (Charger) Width: 46.35 mm (Charger)

[7] Brand/sub-brand or other commercial name used in commercial distribution.

[8] Upon scientific review, the product category and product subcategory were revised.

[9] The IQOS products are also regulated as cigarettes and cigarette components and parts. Cigarettes and their components and parts must be in compliance with the FD&C Act and applicable regulations.

Appendix B

Required Postmarket Surveillance and Studies (PMSS)

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco product that is the subject of this order continues to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by use behavior. Therefore, monitoring use of the tobacco product that is the subject of this order in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTP and the extent to which new users of the MRTP become exclusive IQOS users, dual users with combusted cigarettes or other tobacco products, or transition to combusted cigarette smoking over time. Relatedly, such surveillance must include an assessment of consumers' understanding of the claim and perceptions of the product. These studies should be designed to observe behavior over a sufficient period of time to examine, for instance, the extent to which dual use of IQOS and combusted cigarettes is a transitional versus stable pattern of use.

Given the novelty of these products and the uncertainty related to the impact of modified risk information on youth, your studies must also be designed to monitor individuals under the age of 18 to assess: (a) youth awareness of IQOS, to evaluate how effectively your marketing is limiting unintended exposure to youth, and (b) youth use of the IQOS system, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. Your surveys must also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20).

Your studies must also include an assessment of consumers' understanding of the claim and perceptions of the products. In particular, your PMSS must assess the extent to which users of the product understand that reducing their exposure to harmful and potentially harmful chemicals is relative to smoking, as described in the modified risk information, and that current smokers must use the IQOS system exclusively and stop smoking. Thus, current smokers who take up IQOS, must understand that they should switch completely to IQOS and stop smoking and that cutting down on combusted cigarettes per day while using IQOS is not sufficient. Other tobacco users who switch to IQOS must understand that the reduction in harmful and potentially harmful chemicals is relative to combusted cigarette smoking and not to other types of tobacco use.

Your studies must have clear research objectives, including assessing whether the modified risk tobacco product leads to changes in product use behaviors that are expected to benefit population health. Your protocol must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives.

In addition, FDA has determined that assessing the impact of your MRTP order on uptake of the product requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the product is sold (e.g., IQOS stores and kiosks, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the tobacco product by quarter since the date of issuance of your modified risk granted order (for the initial reporting period) or the previous reporting period (for all reports that follow), including total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold during the reporting period (e.g., IQOS stores, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).
- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly growth rate (percent change) in total U.S. sales and distribution of the tobacco product, post-MRTP authorization.

MRTP Use and Health Risk – Toxicology

Although your applications demonstrated that switching completely from combusted cigarettes to the IQOS system would, in general, significantly reduce exposure to harmful or potentially harmful chemicals, there were some chemicals that were higher in Heatstick aerosol than in combusted cigarette smoke. Additional research must be conducted to better characterize the potential impact of these exposures. In your applications, you reported computational toxicology predictions on chemicals found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke. However, your applications lacked details of the quantitative structure-activity relationship (QSAR) modeling prediction results including, information to judge reliability of the modeling results, information on how you made interpretations of the model predictions, and a description of the training sets used in the models and why they are appropriate for tobacco constituents to predict adverse effects at the endpoints that were tested. An adequate computational toxicology assessment of Heatstick aerosols must be conducted in order to predict potential adverse effects in users before toxicity may be evident.

Given that the chemicals analyzed by QSAR are found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke and that Heatsticks are novel tobacco products for which long term health consequences have not been established, you must conduct a rigorous computational toxicology study using a battery of genotoxicity and carcinogenicity models (modeled endpoints: in vitro bacterial mutagenicity, mammalian cell mutagenicity, clastogenicity, rodent carcinogenicity) that have been validated in the published literature. A well-designed computational toxicology study must use both structure-activity-relationship (SAR), as well as QSAR models, and provide a full explanation of the computational basis for each prediction from the models. This includes probabilistic information of the prediction from a statistical model (i.e., probability of being positive), how the predictions were interpreted, model training set information including structurally similar compounds in the training set to the query compound, information on external validation testing and applicability domain of the models to understand reliability of the results for assessing the tobacco compounds.

MRTP Use and Health Risk – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the modified risk product that is the subject of this order, as actually used by consumers, continues to be appropriate to promote the public health and continues to be expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(A-B)), your PMSS must include ongoing surveillance of all adverse experiences including those that are both serious and unexpected associated with the use of the MRTP. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and unexpected adverse experiences for the tobacco product, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list, including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.

In addition, the PMTA order for your tobacco product, issued on December 07, 2020, requires you to report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for this product. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT FOR STNs PM0000424-PM0000426, PM0000419, PM0000634, MR0000059-MR0000061, MR0000133 and MR0000192**.

For purposes of this reporting, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;

- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTP and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the tobacco product that is the subject of this order, as actually used by consumers, continues to be appropriate to promote the public health and continues to be expected to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTP and consumer perception, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTP and consumer perception, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco product from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order.
- A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the MRTP and consumer perception, behavior, or health.

Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTPs on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using IQOS; the percentage of current smokers who start using IQOS and become dual users; the percentage of current smokers who switch completely to IQOS; the percentage of youth and young adults below the legal age of purchase who start using IQOS; and the percentage of individuals who start using IQOS and then initiate or re-initiate combusted cigarette smoking. Postmarket modeling must incorporate the latest information on acute and long-term health effects of using IQOS relative to combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

II. Submitting PMSS Protocols and Reports

As required under section 911(g)(2)(C)(ii) of the FD&C Act, your modified risk order is conditioned on your agreement to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of determinations on which the order is based. Within 30 days of receiving this notice, you must submit your agreement to conduct PMSS and complete protocols for your PMSS. **FDA expects that modifications of previously approved protocols for the original MRTPA (MR0000133) that incorporate the product subject of this order would be appropriate for the PMSS required under this order.** Label your submission clearly as a "PMSS Protocol," and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, submit each protocol as a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA intends to review the protocol(s) and evaluate if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of data or other information that has the potential to enable FDA to accurately determine the impact of the order on consumer perception, behavior and health and to review of accuracy of the determinations upon which the order was based, pursuant to section 911(g)(2)(C)(ii) of the FD&C Act. FDA will notify you of, and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(g)(2)(C)(iii) requires that the results of the PMSS be submitted on an annual basis. As this product will be modifying the previously approved protocol for MR0000133, it should be submitted when the PMSS report is submitted for MR0000133. These reports must be identified as "PMSS Report", and the MRTPA STNs should be referenced for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.

Appendix C

Recordkeeping and Retention

The exposure modification order for your modified risk tobacco product is effective for a period to end on July 07, 2024. If you wish to renew your order, we recommend you submit a request for renewal 360 days prior to the end of your effective timeframe. In order to help ensure that your exposure modification order meets the standard for renewal and to help expedite the review of any renewal applications, we request that you establish and maintain the records listed below. The records should be retained for a period of not less than four years from the date of distribution of the last batch of the tobacco products listed in your orders under section 911(g)(2). The records should be legible, written in English, and upon request, available for inspection and copying by officers or employees duly designated by the Secretary. Please note that Appendix B requires you to periodically submit some of these records to FDA (e.g., in PMSS reports). Additionally, we remind you that the PMTA order for your tobacco product issued on December 07, 2020, also requires you to establish and maintain records, some of which overlap with the records listed below:

- The MRTPAs submitted prior to the orders
- Postmarket reports, as described in the Required PMSS Appendix, including adverse experience reports and all relevant documentation associated with the experience
- Records of all nonclinical or clinical studies, including:
  - Source data;
  - Study protocols (including statistical analysis plan);
  - Amendments showing the dates and reasons for any protocol revisions;
  - Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals or non-approvals;
  - Informed consent forms;
  - Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC;
  - Investigator financial disclosure statements;
  - Progress reports;
  - Monitoring reports;
  - Adverse experience reports;
  - Case report forms/subject diaries/medical records/laboratory reports;
  - Subject data line listings/observation records;
  - Test article accountability records;
  - Study results/protocol summaries/study reports; and
  - Certifications and amendments to certifications
- Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls), packaging, storage, and stability monitoring and testing (including protocol and results) of the products
- Records pertaining to the sale, distribution, or other disposition of the products, specifically:
  - A list of distributors and retailers of the products, including brick-and-mortar and digital. For the purposes of this order, here and throughout the document, “digital” includes internet/online and mobile;
  - Any available information (not to include personally identifiable information) about product purchases, such as purchasers’ demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use);

  - Policies and procedures regarding verification of the age and identity of purchasers of the products; and
  - Policies and procedures regarding restrictions on youth access to the products
- Health hazard analyses, if performed voluntarily or directed by FDA
- Records pertaining to any and all complaints associated with any of the products that you receive or of which you are aware
- Records pertaining to the products' labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
  - Specimens of all labeling (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information;
  - Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers;
  - Copies of any formative research studies conducted among any audiences in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
  - Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
  - Copies of any contractual agreements regarding the creation and/or dissemination of the products' labeling, advertising, marketing, and/or promotional materials, including for example, in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction;
  - Copies of all advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any:
    - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
    - Targeting of specific adult audiences by age-range(s), including young adult audiences, ages 18-24, and other demographic and/or psychographic characteristics that reflect your intended target audience;
    - With respect to individuals under the federal minimum age of sale of tobacco products, actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
    - Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the product;
    - Use of broadcast, satellite, or cable TV media, or broadcast or satellite radio media, including copies of media buy schedules pre-launch, program lists, projected percent audience compositions by age breakouts (i.e., 21+, 2-11, 12-17, 18-24, 25-54, 55+) by program, audience indices by age breakouts (i.e., 2-11, 12-17, 18-24, 25-54, 55+) by program, reach and frequency goals, and any targeting or purchasing parameters;
    - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the product;

- Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; and/or
- Use of public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the product;

- Copies of all records pertaining to the actual delivery of advertising impressions, including media tracking and optimization, by channel, by product (if applicable), by program (where applicable), and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), media buy summaries, program lists, number of units by program, percent audience compositions by age breakouts (i.e., 21+, 2-11, 12-17, 18-24, 25-54, 55+) by program, audience indices by age breakouts (i.e., 2-11, 12-17, 18-24, 25-54, 55+) by program, reach and frequency, any other parameters purchased against the buying demographics, post-logs that verify TV/radio ads ran within the approved parameters, and all post-launch delivery-verification reports for other paid media submitted to you or entities working on your behalf or at your direction from an accredited source; and
- Policies and procedures for real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, including documentation of such monitoring activities and implementation of corrective and preventive measures.

Appendix D

Conditions of Marketing

The PMTA order for your tobacco product[11], issued on December 07, 2020, requires you to report to the FDA manufacturing information. We request that when submitting such reports, you reference both your PMTA and your MRTPA for the product. When cross-referencing, please provide the date of submission and location in the submission where the information is covered.

For each twelve-month reporting period, the annual reports should include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for PM0000424-PM0000426, PM0000419, PM0000634, MR0000059-MR0000061, MR0000133 and MR0000192**. The cover letter should include the STN(s), static product ID if applicable, and corresponding tobacco product name(s), firm name, date of report, reporting period.
- A description of each change made to the manufacturing process, facilities, or controls during the reporting period including:
  - A comparison of each change to what was described in the PMTA/MRTPA;
  - The rationale for making each change; and
  - A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the tobacco products and the basis for concluding that each manufacturing change did not result in any modification to the products.[12]
- A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution and indicate any deviation(s) that may affect the characteristics of the products. For additional information on manufacturing deviations, see below.

Manufacturing Deviations

You should promptly investigate all manufacturing deviations including, but not limited to, those associated with processing, testing, packing, labeling, storage, holding, and distribution. The PMTA order for your tobacco product, issued on December 07, 2020, requires that, for products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death you are required to report the deviation to FDA within 15 calendar days of identification. We request that when submitting such reports, you reference both your PMTA and your MRTPA for the product.

Discontinuation and Reintroduction

If you discontinue the manufacture, preparation, compounding, or processing for commercial distribution of the modified risk tobacco product and later decide to reintroduce the modified risk

[11] PMP SA has requested a modification to the required Cigarette Health Warnings for the IQOS brand. This is still under discussion with FDA. What is listed within this order does not convey any decision from FDA on that topic.

[12] We note that any modifications made to a tobacco product that render it a new tobacco product are subject to the premarket review requirements under section 910 of the FD&C Act.

tobacco product into the market, please contact the Office of Compliance and Enforcement prior to reintroduction. Section 905(i)(3) of the FD&C Act requires you to update your product listing biannually to reflect any products that have been discontinued and/or reintroduced into interstate commerce.