FDA Briefing Document

January 24-25, 2018
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Modified Risk Tobacco Product Applications (MRTPAs)
MR0000059-MR0000061
Philip Morris Products S.A.

Office of Science
Center for Tobacco Products
Food and Drug Administration

DISCLAIMER STATEMENT

The attached briefing document contains information prepared by the Food and Drug Administration (FDA) for the members of the Tobacco Products Scientific Advisory Committee (TPSAC). The FDA background package includes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are referring Philip Morris Products S.A.'s Modified Risk Tobacco Product Applications (MRTPAs) for the *IQOS* Tobacco Heating System and three associated *Marlboro HeatSticks* to TPSAC in order to gain TPSAC's insights and recommendations. This briefing package may not include all issues relevant to FDA's decision on the applications and instead is intended to focus on issues identified by FDA for discussion by TPSAC. The FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting. The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy. The information is being provided to TPSAC to facilitate its evaluation of the issues and questions referred to the Committee.

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FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date:	December 22, 2017
To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Matthew Holman, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for January 24-25, 2018 discussion of Philip Morris Products S.A. MRTPAs for its *IQOS* system and three tobacco *HeatSticks* (FDA Submission Tracking Numbers MR0000059, MR0000060, & MR0000061)

Introduction

We would like to thank the TPSAC members in advance for their efforts to provide FDA recommendations on the modified risk tobacco product applications (MRTPAs) submitted by Philip Morris Products S.A. (PMP S.A.).

On December 5, 2016, FDA received MRTPAs from PMP S.A., which state that PMP S.A. is seeking orders under Section 911(g)(1) and 911(g)(2) of the Federal Food, Drug and Cosmetic Act (FD&C Act) for its *IQOS* system with *Marlboro HeatSticks*, *IQOS* system with *Marlboro Smooth Menthol HeatSticks*, and *IQOS* system with *Marlboro Fresh Menthol HeatSticks*. See Appendix A for additional information on the statutory requirements for MRTPs and Appendix B for the regulatory history of the *IQOS* submissions.

The applicant describes the *IQOS* Tobacco Heating System as a "heat-not-burn tobacco product," consisting of three main components (Figure 1):

1. ***IQOS HeatStick*:** The *HeatStick* contains a tobacco plug consisting of crimped cast tobacco sheet made from ground tobacco powder. It is designed to function with the *IQOS* Holder to produce an aerosol when the plug is heated. It is a filtered non-combusted cigarette.
2. ***IQOS* Holder:** The *HeatStick* is inserted into the Holder and heats the tobacco material by means of an electronically controlled heating blade. The Holder is activated by the user by pressing the activation button for a set period until the Holder light begins to blink, signaling that the product may be used. The Holder is designed to function for a maximum of six minutes or 14 puffs, whichever comes first, after which it must be recharged and a new *HeatStick* must be inserted.
3. ***IQOS* Charger:** The Charger is used to recharge the Holder after each use. The Charger stores sufficient energy for the use of approximately 20 *HeatSticks* and can be recharged from household power.

Figure 1: Components of *IQOS* Tobacco Heating System
(Source: Section 2.7 of MRTPAs)

For additional information about the *IQOS* system, see Section 3 of the applications.

PMP S.A. requests modified risk orders to market these products as follows:

Modified Risk Claim #1:

- 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 cigarettes to the *IQOS* system can reduce the risks of tobacco-related diseases.

Modified Risk Claim #2:

- Switching completely to *IQOS* presents less risk of harm than continuing to smoke cigarettes.

Modified Risk Claim #3:

- 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 cigarettes to the *IQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

Furthermore, although the applicant acknowledges that the statutorily mandated cigarette warnings are applicable to the products that are the subject of these applications, given their regulatory classification as cigarettes, the applicant has developed and tested alternative warnings intended to improve comprehension and understanding.

Enclosed is the FDA's background package for your review prior to the meeting in which the three modified risk tobacco product applications will be discussed. This background package may not include all issues relevant to FDA's decision on the applications and instead is intended to focus on issues identified by FDA for discussion by TPSAC. This package does not contain a comprehensive review of the applications. Rather, the package contains a summary of the specific issues FDA identified during scientific review to date for which we are specifically seeking recommendations from TPSAC, as well as the key issues and topics for discussion at the meeting.

It must be emphasized that this document does not represent final findings, recommendations, or conclusions, and that no regulatory decision on the status of these applications has been made. Indeed, an important aspect of our thinking on these applications will be a full consideration of public comments and whatever advice the TPSAC provides on the applications, including these important issues. To reiterate the above, this document contains statements of preliminary findings and interpretations of the data and information reviewed to date.

The focus of TPSAC, as described below, will be in regard to scientific topics as they relate to the proposed modified risk information, the relative health risks to individual users, and the impact on the population as a whole for the products that are the subject of these applications.

Draft Topics for TPSAC Discussion

FDA is reviewing the scientific information submitted in the MRTPAs to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met. The evidence submitted by the applicant includes data from chemical analyses of the products and their emissions; non-clinical studies of the products' toxicological properties; clinical studies of pharmacokinetics/pharmacodynamics (PK/PD) and biomarkers of exposure and potential harm; actual use studies, studies of comprehension, perception, behavioral intentions, and post-market surveillance from other countries, as well as other scientific information. FDA is also reviewing public comments submitted in accordance with Section 911(e).

FDA intends to raise the following matters for discussion with TPSAC:

1. **Evidence related to the relative health risks of *IQOS* use**

    - The implications of the results of *IQOS* aerosol testing, nonclinical studies, and clinical studies for health risk of *IQOS* use
    - The likelihood that any exposure reductions due to switching from combusted cigarettes would translate to a measurable and substantial reduction in morbidity and mortality
    - The interpretation of changes in biomarkers of potential harm in terms of tobacco-related disease risk

2. **Evidence related to substantiation of the proposed modified risk claims**

3. **Evidence related to consumer understanding of the proposed modified risk labeling and advertising and "PMI Important Warnings"**

4. **Evidence related to the behavioral impact of *IQOS* and its proposed modified risk labeling and advertising on tobacco product users**

    - The likelihood that U.S. smokers would initiate use of the *IQOS* system
    - The likelihood that, if U.S. smokers did initiate, they would completely switch to *IQOS*
    - The potential for long-term dual use of *IQOS* and combusted cigarettes and implications for health risks
    - The potential impact on the use of other tobacco products, including e-cigarettes

5. **Evidence related to the behavioral impact of *IQOS* and its proposed modified risk labeling and advertising on non-users of tobacco products**

    - The likelihood that U.S. never smokers, particularly youth, will experiment with *IQOS*
    - The likelihood that U.S. never smokers, particularly youth, who experiment will become established users of *IQOS* or other tobacco products
    - The likelihood that former smokers will re-initiate tobacco with *IQOS*

The following sections provide a summary of FDA's preliminary evaluation of certain evidence included in the MRTPAs. This summary includes a discussion of some specific issues FDA identified during scientific review of the applications for which FDA specifically seeks recommendations from TPSAC.

Preliminary FDA Review Findings

I. EVIDENCE RELATED TO THE HEALTH RISKS OF *IQOS* USE

In order to inform the evaluation of the relative health risks of the *IQOS* system with *HeatSticks*, the applicant submitted a range of studies, including those related to aerosol chemistry, in vitro and in vivo toxicological studies, and clinical studies evaluating the impact of switching from combusted cigarettes to *HeatSticks* on biomarkers of exposure and potential harm. The studies are summarized briefly below, along with a preliminary evaluation of the evidence to inform the TPSAC discussion.

> The applicant uses different terms to describe the products tested in the studies presented below, including the Tobacco Heating System (THS). In a March 2017 amendment to the applications, the applicant stated that THS2.2 is the investigational product name for the product they plan to market as the *IQOS* system. In this section, we predominantly refer to the product by its proposed commercial name, the *IQOS* system.

A. Product Chemistry

***HeatStick* Ingredients**

The three tobacco *HeatStick*s that are the subject of these MRTPAs, *Marlboro HeatSticks* (MR0000059), *Marlboro Smooth Menthol HeatSticks* (MR0000060), and *Marlboro Fresh Menthol HeatSticks* (MR0000061), are identical in appearance, general form and dimensions. The tobacco blend in the *HeatStick*s includes only reconstituted cast-leaf[1] tobacco. This is in contrast to combusted cigarettes, which typically include other types of tobacco in the blend, such as tobacco leaf (e.g., flue cured, burley, oriental tobacco leaf) and expanded tobacco, in addition to reconstituted tobacco. Reconstituted tobacco can produce higher levels of carbon monoxide, nitrogen oxides, and tobacco-specific nitrosamines (TSNAs) during combustion compared to other types of tobacco (Ding et al., 2008).

In addition to tobacco and other ingredients commonly found in combusted cigarettes, the *HeatStick*s also contain glycerol (52.3 mg/*HeatStick*) and propylene glycol (2.57-2.04 mg/*HeatStick*). This is notable because glycerol and propylene glycol are two of the main ingredients in e-liquids and generate an aerosol when heated in e-cigarettes. Glycerol degradation produces mainly glycidol and acrolein, while propylene glycol degradation produces acetol and 2-propen-1-ol. Both glycerol and propylene glycol produce formaldehyde in e-cigarettes (Sleiman et al., 2016). As described below, the applicant submitted the concentration in aerosol of glycerol, nicotine, tar, water, total particulate matter (TPM)[2], and 54 harmful and potentially harmful constituents (HPHCs) for the three *HeatSticks*. The reported HPHCs are known to be present in combusted cigarette smoke. The HPHCs reported include compounds that could be produced by degradation of glycerol and propylene glycol, such as acrolein and formaldehyde. The levels of other compounds known to be produced by thermal degradation of glycerol and propylene glycol, such as glycidol, acetol, and 2-propen-1-ol, were not included in the original applications. However, the applicant included a comparison of the quantity of glycidol and

[1] Large sheets of tobacco formed by casting and drying the tobacco slurry (tobacco powder, water, glycerin, guar gum and cellulose fibers).

[2] Mass of the condensed phase of the smoke determined by a gravimetric filter collection in a Cambridge filter pad.

acetol in the aerosol of the three *HeatSticks* with the Kentucky reference cigarette (3R4F[3]), in an amendment submitted on December 8, 2017.[4] Glycidol, acetol, and 2-propen-1-ol could be formed from glycerol under pyrolytic conditions (Laino et al., 2011). Pyrolysis is a thermal process that starts at 200-350°C, which is within range of the heating temperature in the *IQOS* system.

The tobacco blend and other ingredients are slightly different among the three *HeatStick*s, with the main difference being that *Marlboro Smooth Menthol HeatStick*s (MR0000060) and *Marlboro Fresh Menthol HeatStick*s (MR0000061) are mentholated and *Marlboro HeatStick*s (MR0000059) is not mentholated. The total amount of menthol is 7.3 mg/*HeatStick* in *Marlboro Smooth Menthol HeatStick*s and 13.6 mg/*HeatStick* in *Marlboro Fresh Menthol HeatStick*s. A study of mentholated cigarettes for 23 brands available in the U.S. market indicates that menthol content ranges from 2.9 to 7.2 mg/cigarette with an average menthol content of 4.8 mg/cigarette (Ai et al., 2016). The total amount of menthol in *Marlboro Smooth Menthol HeatStick*s is at the upper limit of the published menthol cigarette concentrations. The total amount of menthol in *Marlboro Fresh Menthol HeatStick*s exceeds the upper limit by 89%. The applicant reports the level of menthol in the aerosol (1.77 mg/*HeatStick* for *Marlboro Smooth Menthol HeatStick*s and 2.42 mg/*HeatStick* for *Marlboro Fresh Menthol HeatStick*s using a "modified" Canadian Intense smoking regimen[5]).

Aerosol and Tobacco Filler Testing

In the *IQOS* system, the tobacco is heated at temperatures below 350°C, while a combusted cigarette burns to a temperature of 600°C. Given the lower temperature at which the *HeatStick*s are heated, the HPHC levels in aerosol of the *IQOS* system formed by combustion and pyrolysis are significantly lower than those in mainstream smoke from combusted cigarettes. Examples of products formed by combustion are carbon monoxide, carbon dioxide, and nitrogen oxides. Compounds generated by pyrolysis include heterocyclic amines, benzene, and toluene (CDC, 2010). A full characterization of the chemical composition of the aerosol produced by the *IQOS* is unknown. In the *IQOS* system, compounds could be released directly in the aerosol instead of being burned as in combusted cigarettes. Tobacco leaf constituents could be extracted from the tobacco by glycerol and water and released directly into the aerosol. In a similar way, flavors and additives could be released directly into the aerosol at temperatures below 350°C. In addition, compounds formed by thermal degradation of glycerol, which is included at a high concentration in the *HeatStick*s, could be present in the aerosol of the *IQOS*.

In Section 3.3.2 of the applications, PMP S.A. submitted three separate datasets of the tar, nicotine, and carbon monoxide (TNCO) and HPHC analyses for the *IQOS* system with three *HeatStick* styles (*Marlboro HeatStick*s, *Marlboro Smooth Menthol HeatStick*s, and *Marlboro Fresh Menthol HeatStick*s) manufactured under commercial manufacturing conditions:

[3] The Kentucky reference cigarette 3R4F contains the highest level of nicotine, tar, and HPHCs among all the reference cigarettes.

[4] FDA plans to provide more information about these findings at the TPSAC meeting.

[5] Canadian Intense smoking regimen: Puff volume: 55 mL, puff frequency: 30 s, duration: 2 s, vents: 100% blocked. Modified Canadian Intense smoking regimen: Puff volume: 55 mL, puff frequency: 30 s, duration: 2 s, vents: no vent blocking applied.

a. Study #1: TNCO yields (using the ISO smoking regimen).[6]
b. Study #2: "FDA 18 + 6"; yields of 18 HPHCs in aerosol (using the ISO and Canadian Intense smoking regimens) and 6 HPHCs in tobacco filler.[7]
c. Study #3: "PMI-58"; yields of 54 HPHCs (using the Canadian Intense regimen) plus glycerol, nicotine, tar, TPM, and water.

The applicant compares the quantity of HPHCs in the *HeatStick*s PMI-58 dataset with data obtained for the 3R4F. The comparison is performed per unit (quantity in *HeatStick* aerosol vs. quantity in mainstream cigarette smoke) and also normalized by nicotine level.[8] In Section 6.1.1.3.2 of the applications, the applicant compared the quantity in aerosol of 18 HPHCs from the PMI-58 dataset in all three *HeatStick*s styles with the median quantity in mainstream smoke from 31 Philip Morris USA cigarettes.

Table 1 includes a summary of the findings from across the various analyses. The data is presented in quantity per *HeatStick* and normalized by nicotine. TNCO and HPHC yields in *Marlboro HeatStick*s, *Marlboro Smooth Menthol HeatStick*s, and *Marlboro Fresh Menthol HeatStick*s are lower compared to combusted cigarettes.

Table 1: Reduction of Constituent Levels in *HeatSticks* Aerosol Compared to Cigarette Smoke (Data Source: Section 3.3.2.1.2, Section 3.3.2.2.2., Section 3.3.2.3.2, Section 6.1.1.3.4 of MRTPAs, and Ghosh et al, 2014)

Constituent	Test Product	Comparator Product	Reduction (%)			
			ISO Smoking Regimen		Canadian Intense Smoking Regimen	
			On Unit Basis[a]	On Nicotine Basis[b]	On Unit Basis[a]	On Nicotine Basis[b]
Tar[c, d]	*Marlboro HeatStick*	3R4F	45%	11%	56%	36%
		Commercial cigarette	38%	16%	51%	40%
Nicotine	*Marlboro HeatSticks Marlboro Smooth Menthol HeatSticks Marlboro Fresh Menthol HeatSticks*	3R4F	-		28 – 36%	
	Marlboro HeatStick Marlboro Smooth Menthol HeatSticks	Mean of combusted cigarettes in the US market	-		36 – 42%	

[6] ISO smoking regimen: Puff volume: 35 mL, puff frequency: 60 s, vents: open. Note: there are no ventilation holes in the *HeatSticks*.

[7] As described by the applicant, the HPHCs tested are from the abbreviated list of HPHCs in the *Draft Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the FD&C Act*.

[8] The applicant compares the level of HPHC in the aerosol of the *IQOS HeatSticks* and in the smoke of the cigarette per mg of nicotine. This is particularly important because there is a possibility that the user will smoke a larger number of *HeatSticks* than cigarettes to get the same amount of nicotine.

Constituent	Test Product	Comparator Product	Reduction (%)			
			ISO Smoking Regimen		Canadian Intense Smoking Regimen	
			On Unit Basis[a]	On Nicotine Basis[b]	On Unit Basis[a]	On Nicotine Basis[b]
Carbon Monoxide (CO)	*Marlboro HeatSticks Marlboro Smooth Menthol HeatSticks Marlboro Fresh Menthol HeatSticks*	3R4F	-	-	99%	98%
	Marlboro HeatSticks Marlboro Smooth Menthol HeatSticks	Mean of combusted cigarettes on the US market	-	-	99%	98%
53 HPHCs (excluding CO)[e]	*Marlboro HeatSticks Marlboro Smooth Menthol HeatSticks Marlboro Fresh Menthol HeatSticks*	3R4F	-	-	47 – 99.9%	25 – 99.8%
16 HPHCs (excluding CO)[e]	*Marlboro HeatSticks Marlboro Smooth Menthol HeatSticks*	Mean of combusted cigarettes on the US market	-	-	69 – 99.9%	54 – 99.8%

[a]Data per unit; concentration in *HeatStick* aerosol vs. concentration in cigarette smoke.
[b]Data normalized by nicotine; concentration in *HeatStick* aerosol per mg of nicotine vs. concentration in cigarette smoke per mg of nicotine.
[c]Ghosh et al., 2014
[d]The tar produced by the *IQOS* system contains larger amount of water and glycerol compared to the tar from combusted cigarettes (Schaller et al., 2016)
[e]See Appendix C for full list of HPHCs

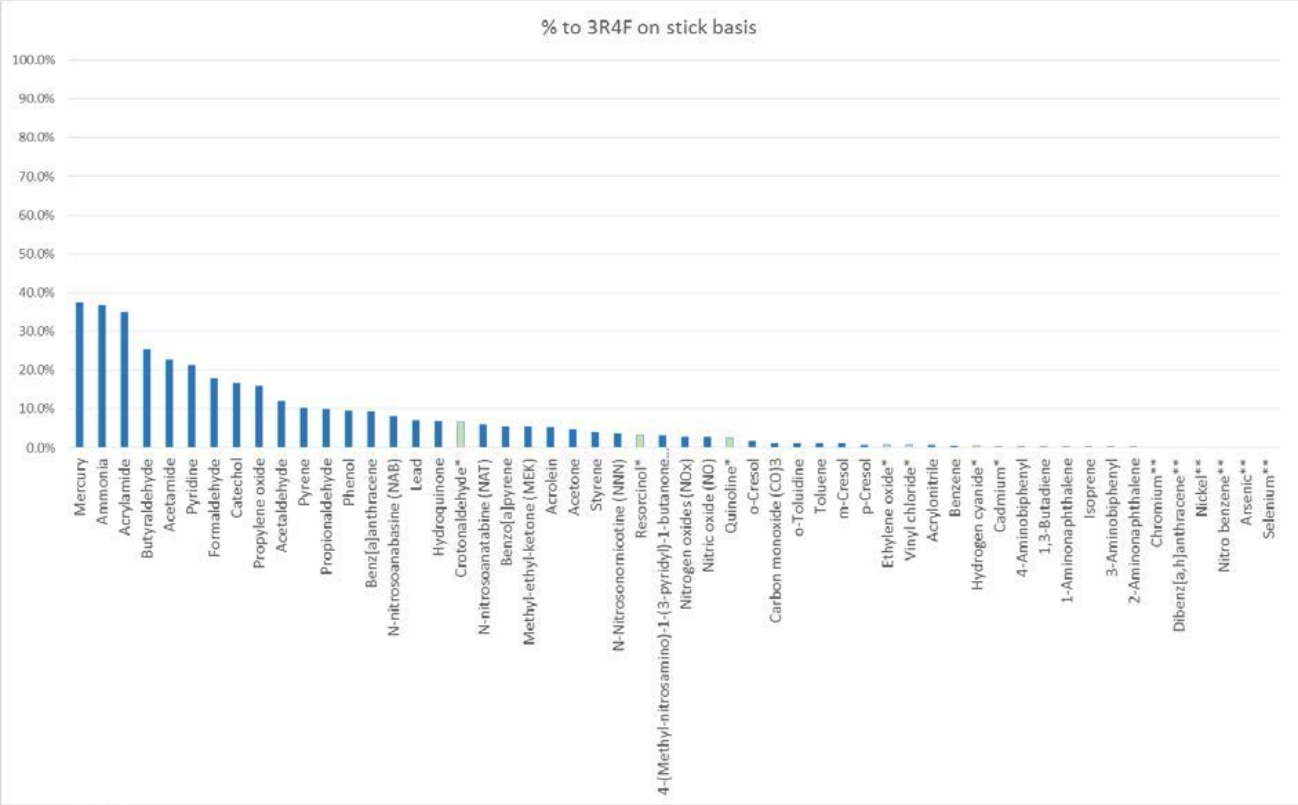

Figure 2: Reduction of 54 HPHCs in *Marlboro HeatSticks* Compared to Reference Cigarette 3R4F (Source: Section 3.3.2.1.2 of MRTPAs)**. Similar graphs are included for *Marlboro Smooth Menthol HeatSticks* in Section 3.3.2.2.2 of MRTPAs and *Marlboro Fresh Menthol HeatSticks* in Section 3.3.2.3.2 of MRTPAs.**

Figure 2 shows the percentage reduction of 54 HPHCs in *Marlboro HeatSticks* compared to the reference cigarette 3R4F. Appendix C compares mean estimates for all the HPHCs reported across the 3R4F reference cigarette, 31 combusted cigarettes on the U.S. market, and the *IQOS* aerosol for each of the three Marlboro *Heatsticks*.

TPM is 20-32% higher in the aerosol of the *HeatSticks* than in combusted cigarettes. The composition of the TPM produced by the *IQOS* system is different from the one produced by the reference cigarette 3R4F. The TPM produced by the *IQOS* system contains 76% water and 10% glycerol, while the TPM produced by the reference cigarette 3R4F contains 32% water and 5% glycerol (Schaller et al., 2016).

The tobacco blend and ingredients other than tobacco included in the *HeatSticks* could increase the concentration of certain compounds in the aerosol. For example, the reconstituted tobacco included in the *HeatSticks* could produce higher levels of NNN and NNK. In addition, the high level of glycerol and propylene glycol could increase the level of formaldehyde, acrolein, carbon monoxide, and nitrogen oxides in the aerosol. The findings from the applicant's aerosol testing of these constituents are described below.

Formaldehyde and Acrolein: Formaldehyde and acrolein are produced by glycerol and propylene glycol (Sleiman et al., 2016). Despite the higher level of glycerol and propylene glycol in the *HeatSticks* than in cigarettes, the levels of acrolein and formaldehyde in the aerosol of the *HeatSticks* are lower than in cigarette smoke. Acrolein is 89-95% lower and formaldehyde is 66-91% lower in the aerosol of the *HeatSticks* than in cigarette smoke.

NNN and NNK: NNN and NNK are 92-98% lower in the aerosol of the *HeatStick*s than in cigarette smoke. CDC studies show that the mainstream smoke of burley and reconstituted tobaccos contain much higher TSNA levels than bright and oriental tobacco (Ding et al., 2008). NNN and NNK are formed by nitrosation of alkaloids present in the tobacco plant during tobacco processing, curing, and storage. PMP S.A. scientists Schaller et al. (Schaller et al., 2016) studied the influence of tobacco blends on the formation of HPHCs in the *IQOS* system and stated that, "Selecting tobaccos with low concentrations of TSNAs should reduce exposure to these HPHCs." While NNN and NNK levels can be lower in the aerosol of the *IQOS* system due to the lower temperature at which the tobacco is heated, the main reduction is likely caused by selecting tobacco blends with lower propensity for TSNA formation and by limiting the use of nitrogen fertilizer (CDC, 2010).

Carbon Monoxide and Nitrogen Oxides: Carbon monoxide and nitrogen oxides are 97-99% lower in the aerosol of the *HeatStick*s compared to mainstream cigarette smoke. Reconstituted tobacco can produce high levels of carbon monoxide and nitrogen oxides during combustion (Ding et al., 2008). Carbon monoxide is produced by an oxidative reaction at a higher range of combustion temperature (>350°C) (Bekki et al., 2017).

Ammonia and Acrylamide: Ammonia and acrylamide are 63-68% lower in the aerosol of the *HeatStick*s compared to mainstream cigarette smoke. While there are lower levels of ammonia and acrylamide in the aerosol of the *IQOS* system, it is not as significant as the reduction observed for other HPHCs, such as carbon monoxide. Ammonia and acrylamide can be formed through the pyrolysis of amino acids at temperatures of 180-210°C (Moldoveanu, 2010; Stadler et al., 2002). Both ammonia and acrylamide could be formed at the temperature of operation of the *IQOS* system.

In a December 8, 2017 amendment, the applicant included non-targeted studies of the chemical composition of the aerosol of the *HeatSticks* compared to the quantity of selected chemicals with data obtained for the 3R4F. The non-targeted studies were additional studies that screened for the identification and semi-quantification of the full chemical composition of the aerosol. The studies included in the original MRTP applications were specific for certain HPHCs. The applicant identified 53 compounds in the Marlboro *HeatSticks*, 60 compounds in the Marlboro Smooth Menthol *HeatSticks*, and 62 compounds in the Marlboro Fresh Menthol *HeatSticks* with higher quantities in the aerosol of the *Heatsticks* compared to the smoke of the 3R4F. Among the chemicals listed are glycidol, acetol, and propylene glycol. The quantity of glycidol, acetol, propylene glycol are higher by 108 – 295%, 35 – 67%, and 383 – 638%, respectively, in the aerosol of the *HeatSticks* compared to the smoke of the 3R4F. FDA plans to provide more information about these findings at the TPSAC meeting.

Independent Testing by FDA

In order to verify chemical and physical data submitted in the MRTPAs, analytical testing of tar, nicotine, acrolein, formaldehyde, and benzo[a]pyrene in mainstream aerosol and ammonia, NNN, and NNK in the tobacco filler was completed at FDA's Southeast Tobacco Laboratory (STL) in October 2017. The constituents tested were selected based on the characteristics of the *HeatSticks*. For example, acrolein and formaldehyde were chosen based on the high level of glycerol in the *HeatSticks*; NNN, and NNK were selected because the *HeatSticks* include reconstituted tobacco; benzo[a]pyrene was selected as a surrogate for polycyclic aromatic hydrocarbons (PAHs) because there are strong associations between benzo[a]pyrene and other PAHs as well as total PAHs (Vu et al, 2015). There are some differences between the applicant's analytical methods and the methods used by STL (e.g., for the aerosol testing,

the applicant used a 20-port linear smoking machine and STL used an e-cigarette smoking machine). Preliminary assessment of the data indicates that the levels of acrolein, formaldehyde, and benzo[a]pyrene in the *IQOS* aerosol measured by STL are higher than the values reported by the applicant; however, these three HPHCs are still significantly lower than the levels in the mainstream smoke of the reference cigarette 3R4F. Greater than 90% reduction was observed for acrolein and benzo[a]pyrene, and greater than 80% reduction was observed for formaldehyde in the aerosol compared to 3R4F. The levels of tar and nicotine determined by STL were similar to the levels reported by the applicant. Finally, the levels of ammonia, NNN, and NNK in the *HeatSticks* tobacco filler measured by STL were similar to the levels reported by the applicant.

Review of Published Literature

FDA searched the published, peer-reviewed literature and identified four additional studies that reported on the chemical analysis of heat-not-burn tobacco products. The main findings from these studies are summarized below.

Auer et al. (2017) compared the concentrations of eight volatile organic compounds (VOCs), 16 PAHs, three inorganic compounds, and nicotine in mainstream aerosol at 330 °C of the *IQOS* system with *HeatStick*s and in mainstream smoke at 684°C of combusted cigarettes. A summary of key data is presented in Table 2.

Table 2: Proportion of Key Constituent Levels in *HeatSticks* Aerosol Compared to Cigarette Smoke in Auer et al. (2017) and in PMP S.A. MRTPAs (Data Source: Section 3.3.2.1.2, Section 3.3.2.2.2, Section 3.3.2.3.2, and Section 6.1.1.3.4 of MRTPAs)

Compound	Auer et al. (2017)					PMP S.A.
	Heat-Not-Burn Cigarette		Combusted Cigarette		Proportion of the Chemical in Heat-Not-Burn Cigarette Compared with Combusted Cigarette (%)	Proportion of the Chemical in Heat-Not-Burn Cigarette Compared with Combusted Cigarette (%)
	Mean (SD)	N	Mean (SD)	N		
Acenaphthene (ng/cigarette)	145 (54)	4	49 (9)*	7	295	NA
Acrolein (µg/cigarette)	0.9 (0.6)	2	1.1	1	82	5 – 7
Formaldehyde (µg/cigarette)	3.2 (2.7)	5	4.3 (0.4)	2	74	11 – 22

*Value reported in Vu et al., 2015.

Personal communication between FDA reviewers and the paper's authors indicated that Auer et al. used a smoking device designed in their facility to capture mainstream aerosol with a modified ISO smoking regimen to perform the analysis. They used the recommended ISO smoking regimen puff volume (35 mL), but puffed twice per minute for six minutes (12 puffs) as in the Canadian Intense smoking regimen. They stated that they used smoking conditions that closely mimic typical user behavior. Their smoking device and their smoking regimen do not mimic those of the applicant. Auer et al. conducted the analysis over two consecutive days and some of the data included too few replicates. Data published in the article lack the appropriate number of replicates, and do not include testing of some compounds in cigarettes, such as acenaphthene. In addition, the identity of some of the compounds,

such as acenaphthene, cannot be confirmed since the method used is not selective. The data published is not considered adequate for comparing the levels of HPHCs between the *IQOS* products and combusted cigarettes. There are significant analytical issues in the Auer et al. study, such as lack of testing reference samples, low number of replicates, lack of selectivity on some analytical methods. In comparison, we have not identified specific issues with the applicant's methods.

S. Maeder and M. Peitsch, scientists at PMP S.A., published a comment on the Auer et al. study in pmiscience.com on May 30, 2017. The comment includes their review of Auer et al.'s data and methodology. With regard to the high level of acenaphthene reported by Auer et al., the scientists at PMP S.A stated, "Acenaphthene is not part of the list of 58 substances we routinely quantify, nor is it part of any regulatory lists (including the most extensive list, the FDA 93). It is, however, a compound we have measured in the smoke of 3R4F, but could not detect in the *IQOS* aerosol."

Farsalinos et al. (2017) compared nicotine levels among *IQOS*, e-cigarettes, and commercially available cigarettes. The article concludes that the "HnB product delivers nicotine to the aerosol at levels higher than ECs but lower than a tobacco cigarette when tested using Health Canada Intense puffing regime."

Savareear et al. (2017) reported on a list of 205 compounds identified in the aerosol of *HeatStick*s, including flavor and fragrance agents, humectants, natural substances, and a plasticizer. The paper lists 82 compounds that were not previously reported in cigarette smoke, including 43 compounds previously reported in tobacco leaves. The presence in the aerosol of compounds known to be present in tobacco leaves suggests that the heating process in the heat-not-burn products can release tobacco constituents in aerosol without the combustion or pyrolysis of combusted cigarettes. Savareear et al. stated that the chemical composition of the aerosol of *HeatSticks* is significantly less complex compared to the smoke of a combustible product. However, the full characterization of the aerosol of the *HeatSticks* is unknown.

Finally, Bekki et al. (2017), compared nicotine, tar, carbon monoxide, and TSNA[9] levels in mainstream smoke and tobacco filler between the *IQOS* products and the reference cigarettes 1R5F and 3R4F. Carbon monoxide was found to be 99% lower in the *HeatStick* aerosol compared to mainstream cigarette smoke. While the reduction reported in this article for NNN (90-94%) and NNK (87-95%) are lower than the reduction reported by the applicant (NNN: 93-97%; NNK: 92-98%), the levels were significantly lower in the *IQOS* aerosol compared to cigarette smoke.

Summary and Conclusions

In the MRTPAs, the applicant argues that the *IQOS* system heats, but does not burn tobacco, resulting in significantly reduced concentrations of HPHCs. HPHCs were present at lower levels in aerosol from the *HeatStick*s compared to mainstream cigarette smoke. HPHCs are 54-99.9% lower in the *IQOS* system when compared per unit (*HeatStick* vs. cigarette) and 25-99.8% lower when the compared to normalized nicotine levels. The independent testing performed by STL confirmed the lower levels of selected HPHCs in the aerosol from the *HeatSticks* compared to mainstream cigarette smoke.

Since the *IQOS* system heats tobacco at a temperature lower than 350°C, it is expected that the levels of compounds formed by combustion and pyrolysis will be substantially lower than for combusted

[9] NNN, NAT, NAB, and NNK.

cigarettes. However, other compounds would still be expected to be present in the aerosol. These compounds could include, but are not limited to, compounds produced by the pyrolysis of glycerol and propylene glycol and evaporated at temperatures less than 350°C; compounds transferred intact from the *IQOS* system to the aerosol by evaporation; and pesticides that are not burned and evaporated at temperatures less than 350°C. In a December 8, 2017 amendment to the applications, the applicant identified between 53 and 62 compounds that are at higher levels in the aerosol of the *HeatSticks* compared to the smoke of the reference cigarette 3R4F. The compounds identified include propylene glycol and the known degradation products of glycerol, glycidol and acetol. Two additional compounds produced by pyrolysis of glycerol, acrolein and formaldehyde, were independently tested by STL. The levels of acrolein and formaldehyde measured by STL in the aerosol of the *IQOS* system were significantly lower than in the smoke of cigarettes.

B. Nonclinical Studies

HPHCs and Aerosol Constituents

As summarized above, all the 54 measured HPHCs produced by the three *HeatSticks* were substantially reduced compared to the 3R4F cigarette on a per-cigarette basis. However, based on the results, consuming 10 *HeatSticks* exposes users to levels of acetaldehyde, acetamide, acrylamide, ammonia, butyraldehyde, catechol, formaldehyde, mercury, propylene oxide, and pyridine that are comparable to smoking 1-3 cigarettes. Formaldehyde is carcinogenic to humans while acetaldehyde, acetamide, acrylamide, butyraldehyde, catechol, and propylene oxide are possibly carcinogenic to humans. For carcinogens that are mutagenic, such as the HPHCs listed above, the cancer potency is assessed using a linear extrapolation from the low-dose region of the dose-response model. Using this model, any increased exposure increases cancer risk. In a December 8, 2017 amendment to the applications, the applicant provided additional aerosol testing information indicating there were compounds of toxicological concern present in higher quantities in *HeatSticks* aerosols than in reference cigarette smoke. This will be discussed further at the TPSAC meeting.

In Vitro and Organotypic Studies

The applicant submitted in vitro cytotoxicity and mutagenicity assays (Neutral Red Uptake [NRU], Mouse Lymphoma Assays [MLA], and Ames test) using OECD guidelines for regular and menthol *IQOS HeatSticks* and compared the results to 3R4F cigarettes. The tobacco smoke and aerosol used in the NRU, MLA, and Ames tests were generated under a Canadian Intense smoking regimen. Approximately 12 puffs were generated for each *HeatStick* and approximately 10 puffs for the 3R4F cigarette. Collection methods, however, varied between product types. For instance, there were differences in numbers of products used in each aerosol collection session (five *HeatSticks* and four cigarettes), the number of "accumulations" collected (35 for *HeatSticks* and four for cigarettes), and differing volumes of phosphate-buffered saline (PBS) for gas-vapor phase (GVP) collection (26 ml for *HeatSticks* and 36 ml for cigarettes).

The NRU test detects cytotoxicity in a mammalian cell line. When normalized to nicotine yield, *IQOS* TPM and GVP were 90% less cytotoxic than 3R4F TPM and GVP. The MLA detects mutagenicity in a mammalian cell line. The lowest observed genotoxic levels (LOGEL) of 3R4F TPM were 15-30 times lower than the *IQOS* TPM. The LOGEL of 3R4F GVP were 8-24 times lower than the *IQOS* GVP. These findings demonstrate that it takes less cigarette smoke than *IQOS* aerosol to cause a detectable mutation in the MLA. The Ames test detects mutagenicity in bacteria. The 3R4F TPM was mutagenic in

three of five Sa*lmonella typhimurium* strains (TA98, TA1537, and TA100), but only with metabolic activation (+S9). In contrast, TPM from regular and menthol *IQOS* products was not mutagenic in any of the five strains with or without metabolic activation. The GVP from *IQOS* or 3R4F cigarettes was not evaluated in the Ames test. It is important to note that assay limitations affect the conclusions that can be drawn from these in vitro tests. For example, while the Ames assay can robustly detect DNA damage from mutagens that directly interact with DNA, the bacterial strains used in these assays do not possess the complex DNA repair mechanisms that mammalian cells have. Notably, some mutagenic compounds (e.g., acetaldehyde, formaldehyde, benzene) in cigarette smoke that are also found in *IQOS* aerosol, are weakly positive or produce a negative response in the Ames test and yet are known to be either possibly carcinogenic or carcinogenic in humans.

The applicant submitted data from five separate in vitro organotypic studies assessing the effects of *IQOS* aerosol from regular *HeatSticks* compared to 3R4F cigarette smoke on human gingival, buccal, nasal, bronchial, and coronary arterial epithelium cultures. The results showed that exposure to *IQOS* aerosol has a lower impact on pathophysiological changes and adverse effects in human gingival, buccal, nasal, bronchial, and coronary artery cell cultures when compared to 3R4F cigarette smoke. For example, smoke from the 3R4F cigarette produced significant cytotoxicity and histological changes in the bronchial epithelium that persisted for at least 72 hours, while *IQOS* aerosols produced fewer effects that were less severe. Similar results were observed in nasal, buccal, and gingival cell cultures. Also, *IQOS* aerosol only increased cell adhesion and reduced monocyte migration in coronary artery cell cultures at considerably higher concentrations than 3R4F cigarette smoke. Similarly, *IQOS* aerosol can have pro-inflammatory effects as well as adverse pathophysiological effects in buccal cell cultures, and alters responses to oxidative stress in gingival cell cultures, but those changes are less pronounced than effects from the 3R4F cigarette smoke and generally occur at higher concentrations. The applicant also provided evidence of recovery after acute exposure to *IQOS* aerosol, but the relevance of these data is unclear since consumers are anticipated to use the product on an ongoing basis. In addition, organotypic tests were based on a single exposure to tissue samples derived from a single human donor. A high level of variability would be expected from the diverse user population and, thus, data generated from cells derived from a single donor may not reflect this variability. These studies alone do not resolve what impact the changes induced by *IQOS* would have on these tissues in vivo during long-term, chronic exposures.

90-Day Nose-Only Inhalation Studies in Sprague-Dawley Rats

The applicant submitted two separate 90-day nose-only inhalation studies in male and female Sprague-Dawley rats with a 42-day post-exposure recovery period per OECD Guideline 413. The first study was designed to compare the toxicity induced by sub-chronic exposure (6 hours/day, 5 days/week, 13 weeks) to aerosol generated from *IQOS* regular *HeatSticks* to mainstream smoke generated from 3R4F cigarettes or filtered air (sham control). Target atmosphere (inhalation chamber) nicotine concentrations for *IQOS* regular aerosol were 15, 23, and 50 µg/L; those for the 3R4F cigarette smoke were 8, 15, 23 µg/L. The exposure concentrations for *IQOS* aerosol were based on a previously-conducted dose range finding study in rodents that established a maximum tolerable nicotine concentration of 50 µg/L and a maximum tolerable carbon monoxide exposure from cigarette smoke equivalent to 23 µg/L nicotine. Due to lower carbon monoxide levels in *IQOS* aerosol, rodents can be exposed to twice the amount of *IQOS* aerosol compared to 3R4F cigarette smoke. The second study was designed to determine whether menthol altered the toxicity profile of the *IQOS HeatSticks*. In this study, rats were exposed to mainstream smoke from 3R4F cigarettes, smoke from two mentholated cigarettes (1XMIS and 2XMIS), or aerosol from an *IQOS* menthol *HeatSticks* for 6 hours/day, 5 days/week

for 13 weeks. The target atmosphere nicotine concentrations for the *IQOS* menthol aerosol were 15, 23, and 50 µg/L and a nicotine concentration of 23 µg/L was used for all three cigarettes. The menthol exposure concentrations for the *IQOS* menthol aerosol were 32, 50, and 100 µg/L, 0 µg/L for the 3R4F cigarette, 56 µg/L for the 1XMIS cigarette, and 80 µg/L for the 2XMIS cigarette. In addition to assessing general toxicity endpoints, both studies included a subset of animals that were used for "omics" (e.g., genomic, lipidomic, transcriptomic) analyses on selected organs.

Animals exposed to 50 µg/L nicotine in both studies experienced tremors. Plasma carboxyhemoglobin (HbCO) levels in all *IQOS*-exposed groups were similar to sham controls (3%), while those exposed to cigarette smoke ranged from 10-27%. Plasma nicotine and cotinine levels were only measured in the *IQOS* menthol study and ranged from 200-1200 ng/mL and 500-1400 ng/mL, respectively. Urine cotinine levels (measured in both studies) ranged from 20-175 µmol/L. Urine biomarkers of exposure (BoE) for NNK (total NNAL), acrolein (HPMA, 3-hydroxypropylmercapturic acid), benzene (SPMA, S-phenylmercapturic acid), and acrylonitrile (CMEA, 2-cyanoethylmercapturic acid) in all *IQOS* regular and menthol exposure groups were similar to the sham control, while groups exposed to cigarette smoke showed concentration-dependent increases. Respiratory frequency showed a concentration-dependent decrease in 3R4F-exposed animals, but no effect was observed in *IQOS* regular- and menthol-exposed animals. Respiratory minute volume and tidal and peak inspiratory flow rate were adversely affected by cigarette smoke, but not by aerosol from *IQOS* regular *HeatSticks* (data was not captured in the menthol study due to technical error). Immune cell infiltration and nonspecific biomarkers of inflammation within the bronchial alveolar lavage fluid (BALF) were elevated to a greater extent in all cigarette smoke-exposed groups compared to *IQOS*-exposed groups. Matrix metalloproteinase (MMP), an enzyme closely associated with lung disease (Hiroyuki, 2002), was not elevated in the lungs of *IQOS*- or cigarette-exposed animals. Hematology and clinical chemistry parameters were within normal ranges for all exposure groups. Digital images of slides at 20X magnification from the respiratory tract of animals in the *IQOS* regular study were sent to Laboratory of Pharmacology and Toxicology (LPT)/Histovia in Germany for a histopathological evaluation. In the *IQOS* menthol study, an in-house pathologist at PMI conducted the first histopathological assessment of respiratory tissues. Subsequently, digital images of slides at 20X magnification from the respiratory tract were sent to AnaPath in Switzerland for a second independent evaluation. While all pathology reports stated that the digital images of the slides were of high quality, one pathology report noted that 20X magnification was too low to evaluate subtle changes (15025 THS SR Part 8.pdf, page 12).

Overall, the reports indicate that the incidence of basal cell hyperplasia (nose and larynx) and squamous cell hyperplasia (nose and larynx) were similar in cigarette and *IQOS*-exposed animals (Figure 3), while goblet cell hyperplasia/hypertrophy (lung) and macrophage aggregation (lung) were present in cigarette smoke-exposed groups only. Hyperplasia, metaplasia, and immune cell infiltration are adaptive responses to acute stressors, which often reverse once the causative agent is removed. However, if the exposure continues, as with smoking, hyperplasia and metaplasia can be interpreted as preneoplastic changes while intra-alveolar macrophage aggregation can be an early indicator of fibrosis and goblet cell hyperplasia an early sign of chronic bronchitis (Burger et al., 1989). The applicant considers such findings to be adaptive as they partially reverse during the recovery period, yet the data suggest that not all effects are reversible (Figure 3). Though a recovery period is recommended by OECD Guideline 413, this practice is designed for the toxicological evaluation of individual, non-chronic, noncancer-causing chemicals and may be less relevant for studies of smoke mixtures since smoking is a life-long behavior for which the adverse effects in humans are caused by multiple chemical entities and are often not reversible. Other findings including necrosis (nose), nerve bundle loss (nose and olfactory bulb), ulceration (nose), edema (nose), inflammation (nose and base of epiglottis of the larynx), and atrophy

(nose) occurred only in cigarette-exposed groups, not *IQOS*-exposed animals. Some degeneration was observed in the larynx of both cigarette and *IQOS* menthol exposure groups. Concentration-dependent increases in the epithelial thickness of the floor of the larynx and vocal cords occurred to a lesser extent in *IQOS*-exposed animals compared to those exposed to cigarette smoke. No significant pathological findings were observed in other organs. A 90-day exposure can be informative to detect some non-cancerous toxicological adverse effects, but it is not sensitive enough to determine chronic systemic toxicities associated with repeated inhalation exposures during long-term tobacco use.

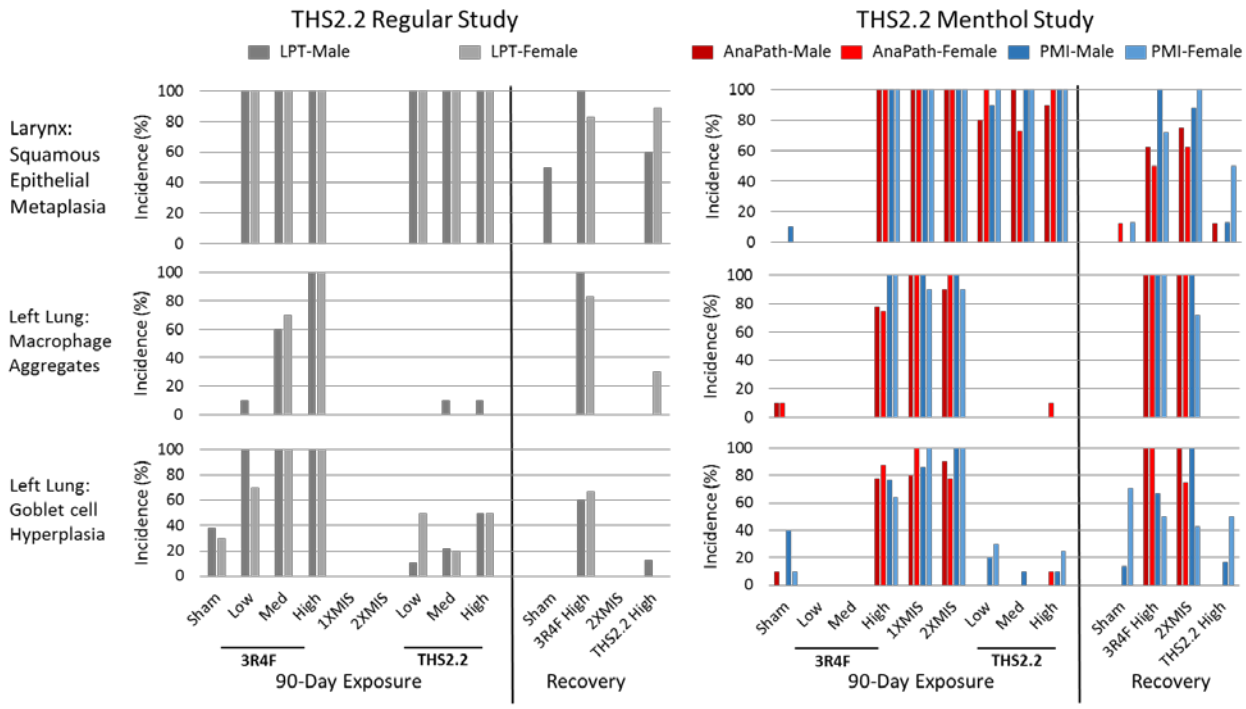

Figure 3: Incidence of Respiratory Tract Histopathological Findings from the 90-Day Nose-Only Inhalation Study* (Data Source: Section 7.2 of MRTPAs)

* Incidence or percent of animals (n=6-10) with squamous epithelial metaplasia at the base of epiglottis in the larynx and macrophage aggregates and goblet cell hyperplasia in the left lung after exposure to THS regular (left panel) or THS menthol (right panel) for 90 days and after a 42-day recovery period. Gray bars represent findings from LPT, red bars from AnaPath, and blue bars from the PMI in-house pathology report. Note: 3R4F is a reference cigarette made by the University of Kentucky. 1XMIS and 2XMIS are reference cigarettes made by PMP S.A. and are designed to produce similar smoke yields as the 3R4F cigarette but with either 1.2 mg (1XMIS) or 2.4 mg (2XMIS) of menthol in the mainstream smoke. The 1XMIS and 2XMIS cigarettes were not tested in the THS regular study, and the low and medium 3R4F cigarette smoke exposure groups were not included in the THS menthol study.

18-Month Carcinogenicity Study in A/J Mice (Preliminary Findings at 10 Months)

The applicant submitted preliminary data from an 18-month carcinogenicity study where A/J mice were exposed via whole-body inhalation (in cages containing up to eight mice for 6 hours/day, 5 days/week) to aerosol generated from *IQOS* regular *HeatSticks*, mainstream smoke generated from 3R4F cigarettes, or filtered air (sham control). Target atmosphere (inhalation chamber) nicotine concentrations for *IQOS* regular aerosol were 7, 13, and 23 µg/L and 13 µg/L for the 3R4F cigarette smoke. The applicant submitted a preliminary report covering findings from the first 10 months of the study. A final report for the full 18-month study is not expected to be submitted to FDA until mid-2018. At 10 months, the incidence of pre-neoplastic lesions (nodular hyperplasia of the alveolar epithelium and

bronchioloalveolar adenoma) in the lung of female mice (n=10) exposed to *IQOS* aerosol was similar to those exposed to cigarette smoke (Figure 4). No neoplasms were observed at 10 months, which is expected, as it takes longer for carcinomas to develop in A/J mice. *IQOS* aerosol exposures in male mice were terminated at 15 months, instead of 18 months as originally planned, due to a high number of deaths. All female exposure groups, including *IQOS*-exposed groups, completed the 18-month exposure period. The full study report, which is not expected to become available until 2018, is necessary to evaluate the carcinogenic potential of *IQOS* based on this study.

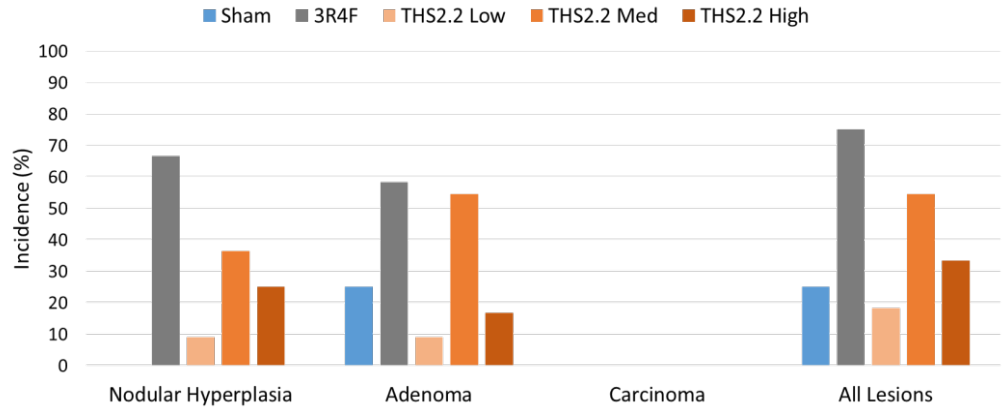

Figure 4: Incidence of Preneoplastic and Neoplastic Lesions in the Respiratory Tract of Female Mice* after 10-Month Exposure to THS and Cigarette Smoke (Data Source: Section 7.2 of MRTPAs**)**
*(n=10 females per group; no carcinomas were identified)

8-Month Switching Study in ApoE$^{-/-}$ Mice to Assess Cardiovascular and Respiratory Disease Endpoints

Female ApoE-null (ApoE$^{-/-}$) mice were exposed to either mainstream smoke from 3R4F cigarettes or aerosol from *IQOS* regular *HeatSticks* at a target atmosphere (inhalation chamber) nicotine concentration of 29 µg/L or filtered air (sham control) for 3 hours/day, 5 days/week for eight months. To assess switching from cigarettes to *IQOS* or cessation, mice were first exposed to mainstream smoke from 3R4F cigarettes for two months, then switched to either aerosol from *IQOS* regular *HeatSticks* with an atmosphere nicotine concentration of 29 µg/L or fresh air for the remaining six months of the study. The ApoE$^{-/-}$ mouse model is well-established for studying atherosclerosis, as mice develop hypercholesterolemia on a standard chow diet. However, it is not used widely as a model for lung disease. Furthermore, mice in this study were grouped 8/box within the inhalation chambers, which is not recommended in the OECD 413 guideline as the animals will filter the test aerosol through the fur of their cage mates. Since the study was exploratory and no hypothesis was specified, it was not designed with enough power to appropriately determine statistical significance between exposure groups.

The applicant noted a previously conducted study with a different product (described on pg. 13 of the ApoE Switching Study Report entitled "15015_CVD_Resp_ApoE_SW_SR_Part 3.pdf"). The applicant reported that in this previously conducted study, mice exposed to cigarette smoke for three months do not fully recover from smoke-induced toxicities after a three-month cessation (or recovery) period. This suggests that there is a threshold point, even in rodents, after which adverse effects induced by cigarette smoke are not reversible. In the submitted study for these applications, the applicant used the findings from the previous study described in 15015_CVD_Resp_ApoE_SW_SR_Part 3 as a basis to design a two-month cigarette smoke and six-month cessation protocol. However, it is unclear how results from the previous study (i.e., 3 month exposure & 3 month recovery) informs the methodology of the submitted study because they differ in both exposure and recovery duration.

Despite these study limitations, HbCO and urine BoE for NNK (total NNAL), acrolein (HPMA), benzene (SPMA), and acrylonitrile (CMEA), as well as some biomarkers for oxidative stress and inflammation (4-HNE and MDA, but not 8-OH-dG or any eicosanoids) in the *IQOS*-exposed group were similar to the sham control, while all analytes were elevated in the 3R4F cigarette smoke-exposed group. Plasma nicotine and urine cotinine were similar in the *IQOS* aerosol and cigarette smoke-exposed groups. Initially, cigarette smoke adversely impacted lung function; however, by eight months lung function was similar in all groups. Markers of lung inflammation (MMP, Timp1, immune cell infiltration) and aortic plaque size were increased in cigarette smoke-exposed animals and returned to normal levels upon switching to *IQOS* or undergoing cessation. The histopathological assessment indicated that mean cord length, destructive index, and alveolar emphysema score were elevated only in the cigarette smoke-exposed group while the number of bronchiolar attachments was decreased with no difference in lung volume; *IQOS* switching and cessation groups were similar to sham controls (Figure 5).

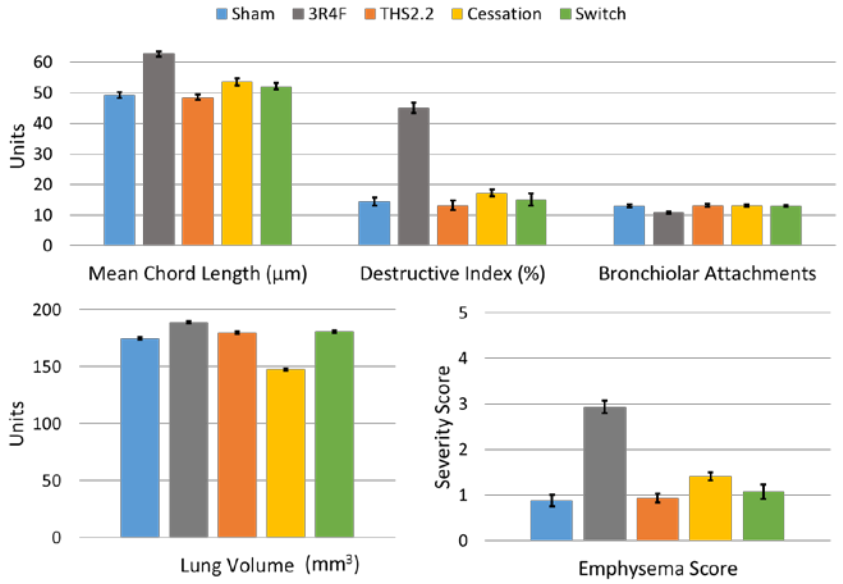

Figure 5: Histopathological Findings in ApoE$^{-/-}$ Mice* (Data Source: Section 7.5 of MRTPAs)
*(n=9-10 females)

Omics Analysis

The applicant conducted omics analyses (transcriptomics, genomics, proteomics, or lipidomics) for the five organotypic studies, in respiratory nasal epithelium, lung and liver tissues of animals in the 90-day nose-only inhalation studies and in the blood, nasal epithelia, lungs, liver, thoracic aorta, heart and kidney of ApoE$^{-/-}$ mice exposed to *IQOS* regular or menthol aerosol and cigarette smoke. Differences in gene and protein expression levels in all tissues from animals exposed to 3R4F cigarette smoke were generally higher compared to tissues from animals exposed to *IQOS* aerosols. Pathway analyses of the measured data indicated that cigarette smoke exposure caused increased theoretical perturbation of inflammatory, cell stress, cell fate, tissue repair and angiogenesis, and cellular proliferation processes in both respiratory nasal epithelium and lung tissue compared to *IQOS* aerosols, which produced only minimal changes. A similar trend was determined for the proteomic analyses, where the tissues from animals exposed to *IQOS* aerosol indicated fewer differentially abundant proteins. Lipid data was inconclusive. There are also a number of limitations for these analyses including a lack of genetic diversity, as all organotypic tissue came from a single donor, a small number of animals (4-6), and

sometimes only a single sex. Sections of whole organs (which can contain connective tissues) were analyzed rather than isolating areas or cell layers exhibiting histopathological changes, and several samples were reported as having poor RNA quality. The pathway analyses represent predicted biological outcomes; genes and proteins associated with inflammatory, cell stress, cell fate, tissue repair, angiogenesis and cellular proliferation processes that were found to be altered by pathway analyses were not validated using standard molecular and biochemical approaches.

Summary and Conclusions

HPHCs in aerosols produced by *HeatSticks* are reduced compared to 3R4F cigarette smoke. Furthermore, apart from nicotine, biomarkers of exposure are considerably reduced to levels comparable to those not exposed to cigarette smoke in both rodents and humans. The in vitro data submitted by the applicant indicate that *IQOS* aerosol can be cytotoxic and mutagenic, and can produce pathophysiological changes in human tissues. These effects are generally less severe and observed at much higher concentrations compared to 3R4F cigarette smoke. Data from the non-chronic nose-only inhalation studies and the eight-month switching study indicate that for some respiratory and cardiovascular endpoints, *IQOS* aerosol exposure produced fewer adverse changes compared with cigarette smoke exposure. Yet for other endpoints, specifically for potentially precancerous lesions such as hyperplasia and squamous metaplasia in the respiratory tract epithelium, the response produced by *IQOS* aerosol was similar to that produced by cigarette smoke. Results from the carcinogenicity study would provide information about the carcinogenic potential of *IQOS*, however, the study results are not expected to become available until later in 2018. Overall, data from the nonclinical studies submitted by the applicant suggest that *IQOS* aerosol has lower toxic potential than cigarette smoke under the conditions used in the assays and for the non-cancer endpoints measured. Furthermore, *IQOS* aerosol did not produce any additional adverse effects beyond those observed in test groups exposed to cigarette smoke. To be clear, *IQOS* aerosols did induce toxicity in the in vitro and in vivo studies, but only at higher concentrations when compared to reference cigarette smoke. Based on the studies submitted, it is unclear how the effects observed in treatment groups exposed to *IQOS* aerosols translate to a potential risk reduction for noncancer-related effects when chronically used by humans.

C. Clinical Studies

The applicant's modified risk hypothesis can be graphically depicted as follows:

To provide support for this framework and explore the potential of the *IQOS* system to reduce the risk of smoking-related diseases, the applicant conducted eight randomized clinical studies of the product. Four of the studies were single-use pharmacokinetic/pharmacodynamic (PK/PD) studies designed to assess and compare the rate and extent of nicotine uptake in participants switching to the *IQOS* system compared with those using combusted cigarettes and in participants who switched to *IQOS* compared to nicotine replacement therapy products. Subjective effects, such as urge to smoke (QSU-Brief) and measures related to reinforcing or aversive effects (MCEQ), were part of the PD assessment. These studies are described in more detail in the behavioral and clinical pharmacology section that follows. Four reduced exposure clinical studies were designed to evaluate systemic exposure to HPHCs among

cigarette smokers who switched to the *IQOS* system, as compared to continuing to smoke combusted cigarettes or abstaining from smoking.

All four reduced exposure studies enrolled healthy, adult-age males and females who were current smokers of at least 10 cigarettes daily for the past month and had at least a three-consecutive-year smoking history. Prior to randomization to *IQOS*, own-brand cigarette, or smoking abstinence groups, all participants tried the *IQOS* system and reported being willing to use it. Participants had no intent to quit smoking in the next three months, but were willing to be randomized to smoking abstinence. All four studies included a five-day confinement period, where tobacco products could be used without restriction (*ad libitum*) from 6:30 am to 11:00 pm. Participants in the *IQOS* arm received products at no cost, those in the combusted cigarette arm brought in their preferred products, and participants in the smoking abstinence arm did not receive nicotine replacement therapy (NRT) or supportive medication during confinement. Two of the four studies followed participants for a prolonged period (85 days) in an ambulatory setting (i.e., home environment; near to real-world conditions) following the five-day confinement period. For the ambulatory period, participants were instructed to continue using their assigned product exclusively (*IQOS*, own-brand cigarettes, or not smoking); however, participants were informed that use of "nicotine/tobacco-containing products other than the assigned product/regimen" would not result in removal from the study. *IQOS* was provided to participants at no cost, and participants in the cigarette arm continued to purchase their preferred products as usual. Participants in the smoking abstinence group could purchase and use NRT "if considered necessary by the Investigator or if requested by the subject." The studies were conducted in Poland, Japan, and the U.S. Reduced exposure studies measured systemic exposures to multiple HPHCs and their metabolites (biomarkers of exposure, BOE), select biomarkers of potential harm (characterized by the applicant as clinical risk endpoints), nicotine exposure, tobacco product consumption, various exploratory endpoints (e.g., topography, subjective effects), and monitored participant safety. Table 3 summarizes key aspects of the study design and main applicant conclusions for the four reduced exposure clinical studies.

Table 3: Summary of Reduced Exposure Clinical Studies

Clinical Study	Overview of Study Design	Population	Applicant Conclusions about Exposure
ZRHR-REXC-03-EU (Poland)	Single-center, open-label randomized, controlled, parallel group 3-arm study: • THS 2.2 (*IQOS*) arm: 80 subjects, 5 days *ad libitum* use • Combusted Cigarette (CC) arm: 40 subjects, 5 days *ad libitum* use of their preferred CC brand • Smoking Abstinence (SA) arm: 40 subjects, 5 days smoking abstinence **Study duration = 5-day confinement**	• Healthy, 21-65 yrs, Caucasian M and F, current smoker with average daily CC consumption ≥10 cc per day and had been smoking for the last 3 consecutive years with no intention to quit in the next 3 months, willing to accept 5 days of smoking abstinence • Enrolled n = 169 • Randomized N = 160	• Switching from CC smoking to THS use resulted in substantial reductions in exposure to 15 selected HPHCs (decrease by 56 - 94%). The kinetics and the magnitude of decrease of BOE levels observed in the THS arm were approaching the levels observed in the SA arm. • The exposure to nicotine was lower in THS than in CC arms
ZRHR-REXC-04-JP (Japan)	Single-center, open-label randomized, controlled, PK/PD, parallel group 3-arm study: • THS 2.2 (*IQOS*) arm: 80 subjects, 5 days *ad libitum* use	• Healthy, 23-65 yrs, Japanese M and F, current smoker of ≥ 10 non-menthol CC per day for the last 4 weeks with a max yield of 1 mg nicotine	• Switching from CC smoking to THS use resulted in substantial reductions in exposure to 15 selected HPHCs (decrease by

	• CC arm: 40 subjects, 5 days *ad libitum* use of their preferred CC brand • SA arm: 40 subjects, 5 days smoking abstinence **Study duration = 5-day confinement**	ISO per cigarette, average daily CC consumption ≥10 cc per day), at least 3 years of consecutive smoking with no intention to quit in the next 3 months, willing to accept 5 days of smoking abstinence • Enrolled n = 166 • Randomized N = 160	47 - 96%). The kinetics and the magnitude of decrease of BOE levels observed in the THS arm were approaching the levels observed in the SA arm. • Exposure to nicotine was similar between the THS and CC arms.
ZRHM-REXA-07-JP (Japan)	Multi-center, open-label, randomized, controlled, parallel group, 3-arm study: • Menthol THS 2.2 (mTHS; *IQOS*): 80 subjects, 5 days *ad libitum* use • Menthol CC (mCC): 40 subjects, 5 days *ad libitum* use • SA: 40 subjects, 5 days smoking abstinence **Study duration = 90 days**	• Healthy, 23-65 yrs, Japanese M and F, current smoker ≥ 10 commercially available mCCs per day with a maximum yield of 1 mg nicotine (ISO)/mCC, for the last 4 weeks; smoking history last 3 consecutive years with no intent to quit in the next 3 months, willing to accept 90 days of smoking abstinence • Enrolled: n = 216 • Randomized N = 216	• Switching from mCC smoking to mTHS use resulted in substantial reductions in systemic exposure to 15 HPHCs compared with mCC use. On Day 5 range of reduction was 49 - 94%, on Day 90, it was 41 - 94%. The kinetics and the magnitude of decrease of BOE in the mTHS arm were approaching the levels observed in the SA arm. S-BMA levels did not show any difference in levels across all study arms. • Comparable levels of nicotine exposure were achieved in both the mTHS and mCC arms following 90 days of product use.
ZRHM-REXA-08-US (USA)	Multi-center, open-label randomized, controlled, parallel group, 3-arm study: • mTHS 2.2 (*IQOS*): 80 subjects, *ad libitum* use • mCC: 80 subjects, *ad libitum* use • SA: 40 subjects, 5 days smoking abstinence **Study duration: 90 days**	• Healthy, ≥22 yrs old, M and F, current smoker ≥10 mCCs per day for the last 4 weeks; Smoking history of at least the last 3 consecutive years with no intent to quit in the next 3 months, willing to accept 90 days of smoking abstinence • Enrolled n = 164 • Randomized N = 164	• Switching from mCC smoking to mTHS use resulted in substantial reductions in systemic exposure to 15 selected HPHCs. On Day 5 range of reduction was 51 - 96%, on Day 90, it was 34 - 86% • Somewhat lower levels of nicotine exposure were achieved in the mTHS than mCC arms during 90 days of product use.

- **Primary Endpoint Biomarkers of Exposure**: monohydroxybutenyl mercapturic acid (MHBMA), 3-hydroxypropylmercapturic acid (3-HPMA), S-phenylmercpaturic acid (S-PMA), COHb on day 5 (plus, for REXA-07 and 08 only: Total NNAL level (concentration adjusted for creatinine) in 24-hour urine fraction as measured on Day 90 Visit)
- **Secondary Endpoint Biomarkers of Exposure**: As above plus: 1-OH, N-nitrosonornicotine (total NNN), 4-aminobiphenyl (4-ABP), aminonaphthalene (1-NA), 2-aminonaphthalene (2-NA), o-toluidine, CEMA (2-cyanoethylmercapturic acid), 2-hydroxyethyl mercapturic acid (HEMA), 3-hydroxy[a]benzopyrene (BaP), 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA), S-benzylmercapturic acid (S-BMA), nicotine equivalents (NEQ), nicotine and cotinine concentrations in plasma, and exhaled CO
- **Exploratory Endpoints**:
  - REXC-03: Urine mutagenicity (Ames test); Xenobiotic metabolism (CYP1A2 activity); CYP2A6 activity, 8-epi-prostaglandin F2α (8-epi-PGF2α), 11-dehydrothromboxane B2 (11-DTXB2), and relationship of 8-epi-PGF2-a and 11-DTXB2 to nicotine

equivalents
- REXC-04: as above
- REXA-07: as above plus: blood pressure, hs-CRP, fibrinogen, homocysteine, fasting blood glucose, LDL cholesterol, HDL cholesterol, TGs, TC, HbA1c, waist circumference, sICAM-1, WBC, 8-epi-PGF2, Body weight
- REXA-08: as above plus: Apo A1, Apo B, Oxysterol, and Lung function including DLCO, FEV1, FVC, VC, TLC, FRV, IC, and MEF 25-75

- **Abbreviations:** CC= combusted cigarette, ISO = International Organization for Standardization, SA = smoking abstinence

Biomarkers of Exposure (BOE)

The applicant assessed 16 biomarkers of exposure (BOEs) in the four exposure clinical studies, some of which were primary endpoints; others were secondary. Section 6.1.3.1 of the applications summarizes the selection of exposure biomarker endpoints for comparing exposures from *IQOS* to smoking combusted cigarettes. Biomarker endpoints selected by the applicant were based on the following: the HPHCs were representative of a variety of chemical classes and organ toxicity classes as defined by the FDA; the HPHC reflects a specific toxic exposure or is a reliable surrogate of exposure to HPHCs; the HPHCs cover a broad range of formation temperatures; the HPHC is specific to cigarette smoking with other sources being minor or non-existent; the BOE for each HPHC is reliably detectable using validated, reproducible, precise analytical methods; the BOE for each HPHC has a half-life that is suitable with the schedule of assessments.

In the applicant's Executive Summary (Section 2.7 of MRTPAs), the applicant stated that *IQOS* was designed to "generate an aerosol that has substantially fewer toxicants than combusted cigarette smoke" and, at the same time, "deliver tobacco taste, nicotine satisfaction and an acceptable ritual, which is important to providing an acceptable substitute for cigarettes to facilitate switching by current adult smokers."

In general, the four reduced exposure studies found that BOEs to HPHCs or HPHC metabolites were reduced among smokers completely switching to *IQOS* and that reductions were similar in magnitude to those reductions in biomarkers among smokers in the smoking abstinence arm. At the end of the five-day controlled (in confinement) switching from cigarettes to *IQOS* use, systemic exposure to 15 of 16 selected BOEs decreased by 47-96%. The pattern of reduction of the biomarker systemic exposures observed in the *IQOS* arm was similar to that observed in the smoking abstinence arm. The comparison of mean changes in HPHC exposures measured between *IQOS* and smoking abstinence (SA) arms on Day 5 for studies ZRHR-REXC-03-EU and ZRHR-REXC-04-JP is shown in Figure 6.

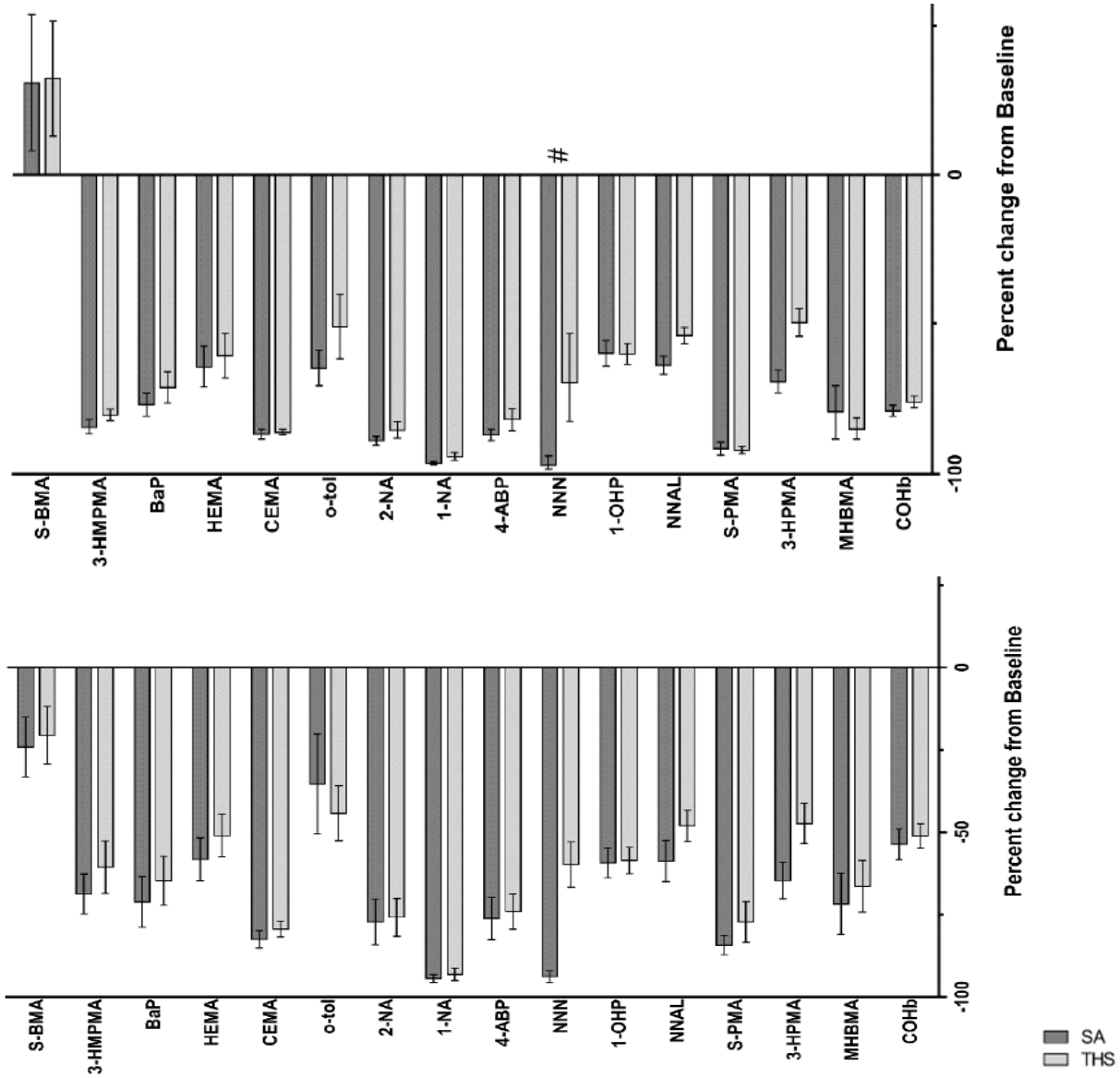

Figure 6. Percent Change in BOE Levels from Baseline of Geometric Mean Levels and 95% CIs at Day 5 in ZRHR-REXC-03-EU (upper panel) and ZRHR-REXC-04-JP (lower panel) (Source: Section 6.1.3.2 of MRTPAs) SA = Smoking abstinence. THS = Tobacco Heating System (*IQOS*)

At the end of the 90-day ambulatory period, for mentholated products, the decreases in systemic levels of BOEs were less pronounced, ranging from 34% to 86% (REXA-07-JP) and from 46% to 86% (REXA-08-US), most likely due to decreased compliance (dual use), but they remained statistically significant.

The comparison of mean changes in HPHC exposures between the Baseline and Day 90 in the *IQOS* arm in studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US is shown in Figure 7.

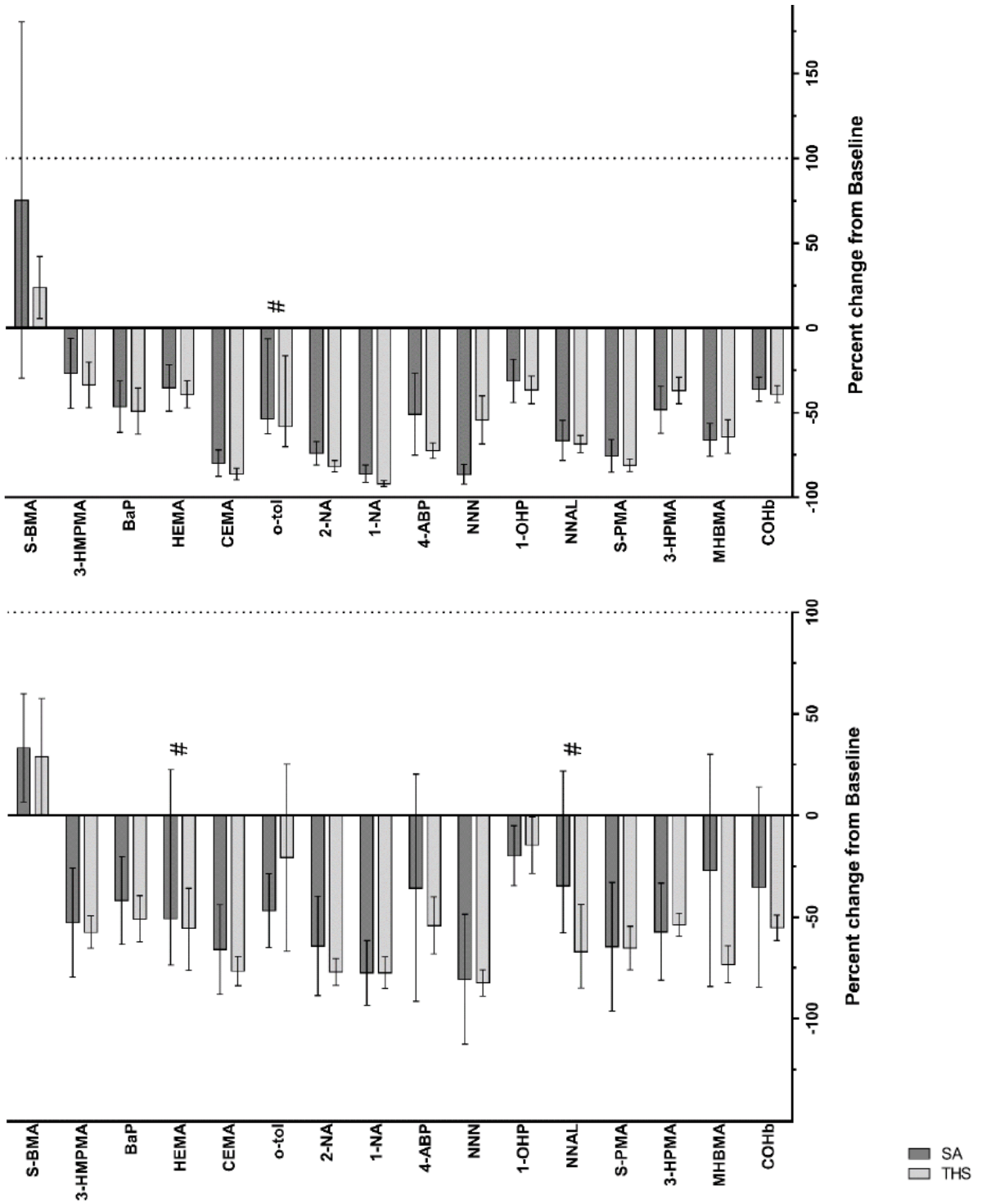

Figure 7: Percent Change from Baseline of Geometric Mean Levels and 95% CIs at Day 90 in ZRHM-REXA-07-JP (upper panel) and ZRHM-REXA-08-US (lower panel) (Source: Section 6.1.3.2 of MRTPAs) SA = Smoking abstinence. THS = Tobacco Heating System (*IQOS*). *Note*. Because of the limited number of subjects in the SA arm and outliers, percent change from Baseline values for total NNAL and HEMA are reported as median (and Q1; Q3) for both for the THS and SA arms.

The biomarkers of nicotine exposure (nicotine equivalents [NEQ]) remained similar to baseline levels among smokers switching to *IQOS* in four reduced exposure studies. After five days of *ad libitum* use, nicotine PK parameters were similar between *IQOS* and combusted cigarette arms for both the mentholated and regular products in Japanese studies, while NEQ values were lower in the *IQOS* arm in studies performed in Poland and the U.S. The differences in nicotine plasma kinetics may be related to the differences in the studied populations.

Several critical factors may impact interpretation of the findings. First, the studies were not designed to be representative of all smokers in the U.S. For example, light (i.e., less than 10 cigarettes per day) or non-daily smokers were not recruited into the studies. Second, the two 90-day studies focused on menthol cigarette smokers switching to mentholated *IQOS*. These data may not represent the exposure reduction associated with non-menthol *IQOS* after 90 days. A six-month U.S. study of non-menthol *Marlboro HeatStick*s is not yet complete (NCT02396381). Further, while the applicant selected BOEs that represent most of the main classes of HPHCs in cigarette smoke or filler identified by FDA, including tobacco alkaloids, VOCs, PAHs, aromatic amines, TSNAs, and variable gases, it is unclear if there are potentially harmful compounds present in *IQOS*, but not in cigarettes.

The purpose of the confinement period was to assess reductions in exposure that could be observed under optimal conditions, in which cigarette smokers completely switched to *IQOS*. For the ambulatory phase of the 90-day exposure studies, the applicant's primary analysis focused on the per protocol (PP) population rather than the full analysis set (FAS). While the FAS includes all randomized participants, the PP participants include only the subset defined as those who were (1) "correctly randomized and assigned study product"; (2) "with at least one post-randomization product use"; (3) "with at least one valid post-randomization BOE measurement"; (4) "that were adherent with their assigned study product"; (5) "without major protocol deviations that impacted the validity of the evaluation of the study results." In Section 6.1.3.4 of the applications, the applicant acknowledged that focusing on the PP population would achieve the optimal effect of the exposure reduction, but that the "optimal effect may be a somewhat ideal scenario, which differs from the real-world effect (effect under actual use setting) mainly by reducing the impact of non-compliance on the estimate." To illustrate, in the U.S. 90-day study (ZRHM-REXA-08-US), the average percent reduction in NNAL at Day 90 vs. baseline in the *IQOS* study arm (n=47) was 67% based on the PP population (see Table 15.2.4.5.1). When examining the FAS, the magnitude of the reduction in the *IQOS* study arm (n=80) was smaller at 53% (see Table 15.2.4.5.2). Although both sets of results show reductions, the FAS results suggest that the magnitude of the reduction would be smaller in a real-world setting. Additionally, the impact incomplete switching had on systemic exposure to HPHCs in these studies is unclear from these findings. For the 90-day studies, the applicant did not stratify FAS results by complete vs. incomplete switching, limiting the ability to assess exposures among dual users of *IQOS* and cigarettes. Therefore, it is unclear whether dual users would also achieve reduced exposure when compared to participants who continue to smoke cigarettes exclusively.

It is critical to evaluate these clinical study exposure reduction results in the context of the actual use study (PBA-07; see Section II.B "Epidemiology of *IQOS* Use" for further detail on the actual use study). Participants in the 90-day reduced exposure studies were more likely to switch completely to *IQOS* during the last month of the ambulatory period (84.6% REXA-07-JP, 55.0% REXA-08-US) compared to participants in the actual use study (only 7.5% of cigarette smokers were using *IQOS* >95% of the time at the end of the study). The higher rates of complete switching in the exposure studies may have occurred because participants were instructed to use the *IQOS* product exclusively and were confined and monitored to ensure compliance during the first five days of the study. As a result, participants across

studies differ drastically in rates of exclusive vs. dual use of *IQOS* and cigarettes, and therefore may experience different levels of exposure.

Several aspects of the reduced exposure studies may have impacted participants' use behavior, and therefore, reduced exposure outcomes. Participants in the *IQOS* arm received the product for free, whereas those in the smoking arm continued to pay for their cigarettes. Free access to the *IQOS* product may inflate use rates and encourage the use of *IQOS* over combusted cigarettes. Additionally, information about the *IQOS* product may influence perceptions of product safety profiles, thereby contributing to differences in use behavior and exposure. In addition to differences in labeling and warnings on combusted cigarettes compared to *IQOS* packages, participants in different reduced exposure studies were exposed to different information in the informed consent forms. For example, the informed consent form from study REXC-04-JP study suggests the investigational product is less harmful than combusted cigarettes, stating, "a number of clinical studies have been conducted… with the previous version of the device (THS 1.0 and THS 2.1)… showed reductions in exposure to selected smoke constituents in subjects who used the THS 1.0 or THS 2.1, as compared to subjects continuing smoking conventional cigarettes," whereas the informed consent of study REXA-08-US stated that "THS 2.2 Menthol has not been shown to reduce tobacco-related diseases and you should not assume that the risks associated with THS 2.2 Menthol use are different than smoking normal cigarettes."

Biomarkers of Potential Harm (BOPH)

The applicant measured several biomarkers of potential harm (BOPH) as secondary or exploratory study endpoints, aiming to determine if the reported reduced exposure from *IQOS* use in the clinical studies resulted in biological changes that might indicate a change in long-term disease risk, particularly for cardiovascular disease, COPD, and lung cancer. These biomarkers were chosen based on changes shown in smoking cessation studies, as well as their believed association with health risks. Detailed in Table 4, the applicant specified six of the BOPHs as representative of mechanisms underlying the diseases of interest. Two markers were measured in all four reduced exposure studies (8-epi-PGF2α, 11-DTX-B2) and another four markers were measured in the 90-day studies (HDL-C, WBC, sICAM, and FEV1). Table 5 provides a summary of the main findings of these biomarkers in the two 90-day clinical studies.

Table 4: Biomarkers of Potential Harm Literature Review Summary

Biomarkers of Potential Harm (BOPH)	Physiologic Mechanism	Associated Disease(s) of Interest	Purported Relationship to Disease(s) from Applicant Monograph	Summary of Applicant's Literature Review
sICAM	Endothelial Dysfunction	CVD, COPD	• Enables leukocyte binding then sub-endothelial migration in response to inflammation • Abundant in atherosclerotic plaques	• Possibly early marker of ASCVD; elevated in COPD • Higher in smokers v. non-/former smokers; preliminary evidence for rapid and durable decline with cessation
8-epi-PGF2a	Oxidative Stress	CVD, COPD	• A non-enzymatic free radical-catalyzed peroxidation product of arachidonic acid • Since LDL oxidation leads to CHD, could show causative link between smoking and CHD	• Elevated in heavy smokers, resistant HTN v. HTN, CAD v. no CAD, NYHA CHF Class III/IV v. no CHF/NYHA I/II; no published data for COPD or for products similar to the proposed product • No clear link between cessation and decrease in marker
HDL-C	Lipid Metabolism	CVD, COPD, Lung CA	• May be anti-inflammatory, anti-oxidative, anti-apoptotic, and vasodilatory • May inhibit platelet aggregation	• Widely accepted inverse relationship between HDL-C and CVD; however, strength of association varies • Mixed results in COPD, but HDL-C may be directly related • Weak direct relationship between lung CA and HDL or HDL-C • Dose-dependent reduction in smokers: increases by <10 mg/dL within 4-8 weeks of switch to THS
WBC	Inflammation	CVD, COPD, Lung CA	• Association between increased WBC and coronary atherosclerosis, AF and PAD appears to be independent of smoking • Clear association between WBC count and COPD and an inverse association with FEV1	• Higher with more CPD; correlates to lifetime exposure and smoking intensity • Elevation predicts MI/CVA mortality independent of other risk factors; • Smoking cessation leads to decline in 2 weeks or up to 6-12 months. • Studies support an association of WBC count and either incident lung cancer cases or lung cancer mortality
FEV1	Lung function	COPD	• Reflects physiologic state of lungs/airways and severity of COPD Drops with age, even in non-smokers	• FEV1 correlates poorly with smoking and with smoking cessation • Rate of decline in FEV1 (Beta) can indicate progression of

Biomarkers of Potential Harm (BOPH)	Physiologic Mechanism	Associated Disease(s) of Interest	Purported Relationship to Disease(s) from Applicant Monograph	Summary of Applicant's Literature Review
				COPD • Poor correlation between FEV1, symptoms, QOL, functional outcomes and biomarkers
11-DTX-B2	Platelet Activation	CVD	• Degradation product of and surrogate marker for, Thromboxane A2, a potent activator of platelet aggregation	• High levels in CVD and current smoking • Consistent elevation in smokers v. non-smokers • Study showed decrease in marker with quitting, but no decrease in those using NRT • 3 published studies of potentially reduced risk products had conflicting results

Abbreviations: sICAM=soluble intercellular adhesion molecule, CVD=cardiovascular disease, COPD=chronic obstructive pulmonary disease, ASCVD=atherosclerotic cardiovascular disease, 8-epi-PGF2α=8-epi-Prostaglandin F2-α, LDL=low density lipoprotein), CHD=coronary heart disease, HTN=hypertension, CAD=coronary artery disease, NYHA CHF=New York Heart Association Congestive Heart Failure, RRTP=reduced risk tobacco product, HDL-C=high density lipoprotein-cholesterol, lung CA=lung cancer, THS=tobacco heating system, WBC=white blood cells, AF=atrial fibrillation, PAD=peripheral arterial disease, FEV1=forced expiratory volume in one second, CPD=cigarettes per day, MI=myocardial infarction, CVA=cerebrovascular accident, QOL=quality of life, 11-DTX-B2=11-deyhdrothromboxane-B2, NRT=nicotine replacement therapy

Table 5: Exploratory BOPH findings in ZRHM-REXA-07-JP and ZRHM-REXA-08-US

Study	BOPH	Applicant Findings and Conclusions
ZRHM-REXA-07-JP	8-epi-PGF2a	The levels of 8-epi-PGF2α in subjects who switched to THS 2.2[a] Menthol were 12.7% (95% CI: 2.55, 21.81) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (92.8% ratio; 95% CI: 82.80, 103.96).
	11-DTX-B2	The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 9.0% (95% CI: -2.94, 19.52) lower than that observed in subjects who continued to smoke mCC. The levels of 11-DTX-B2 in subjects who switched to THS 2.2 Menthol were 13% (95% CI: -0.53, 28.12) higher than that observed in subjects who abstained from smoking.
	sICAM	The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol use were 8.7% (95% CI: 2.05, 14.94) lower than that observed in subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (102.4% ratio; 95% CI: 95.24, 110.12).
	HDL-C	The HDL cholesterol levels were increased by approximately 4.5 mg/dL (95% CI: 1.17, 7.88) in subjects who switched to THS 2.2 Menthol use compared to subjects who continued to smoke mCC. There was no notable difference between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-1.8 mg/dL difference; 95% CI: -5.28, 1.61).
	WBC	Total WBC (leukocytes) counts in subjects who switched to THS 2.2 Menthol use were 0.6 GI/L (95% CI: 0.10, 1.04) lower than that observed in subjects who continued to smoke mCC. There were no notable differences observed in the leukocyte counts between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (-0.2 difference; 95% CI: -0.65, 0.33)
ZRHM-REXA-08-US	8-epi-PGF2a	The levels of 8-epi-PGF2α in subjects who switched to THS 2.2 Menthol were 14% (95% CI: 2.0, 23.6) lower than that observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (geometric mean ratio: 95%; 95% CI: 77.7, 115.1).
	11-DTX-B2	There were no notable differences in levels of 11-DTX-B2 between subjects who switched to THS 2.2 Menthol and those who continued to smoke mCC (96% ratio; 95% CI: 75.4, 123.3) and no notable differences between subjects who switched to THS 2.2 Menthol and subjects who abstained from smoking (geometric mean ratio 104%; 95% CI: 70.4, 153.2).
	sICAM	The levels of sICAM-1 in subjects who switched to THS 2.2 Menthol were 11% (95% CI: 4.0, 16.7) lower than those observed in subjects who continued to smoke mCC. There were no notable differences between subjects who switched to THS 2.2 Menthol use and subjects who abstained from smoking (geometric mean ratio 99%; 95% CI: 88.7, 111.1).
	HDL-C	There were no notable differences observed in the levels of HDL-C (1.37 difference; 95% CI: -2.26, 5.00), between subjects who switched to THS 2.2 Menthol use, subjects who continued to smoke mCC, and to subjects who abstained from smoking.
	WBC	There were no notable differences observed in the total WBC (leukocytes) counts between subjects who switched to THS 2.2 Menthol use and subjects who continued to smoke mCC (0.2 GI/L increase with THS 2.2 Menthol compared to mCC; 95% CI: -0.5, 0.8). Total WBC (leukocytes) count was higher by 1.1 GI/L for subjects who switched to THS 2.2 Menthol use compared to subjects who abstained from smoking (95% CI: 0.1, 2.2).
	FEV_1	In the Per -Protocol (PP) *Set (Period 4-, i.e. 60-90-day visit), there were no notable differences on Day 91/Discharge Ambulatory in FEV1 between subjects who switched to THS 2.2 Menthol and subjects who continued to smoke mCC. (08) *The PP Set was a subset of the Full Analysis Set (FAS) and included all randomized subjects who had no major protocol deviations impacting evaluability of the study's primary objectives

[a] In a March 2017 amendment to the applications, the applicant stated that THS2.2 is the investigational product name for the product they plan to market as the *IQOS* system.

With respect to these biomarkers, the applicant asserted that the changes observed were in a favorable direction, consistent with reduced exposure to HPHCs, and comparable to the changes seen in the smoking abstinence groups. They interpret this to mean that cigarette smoking exposure effects are reversible, and the changes seen in those switching to *IQOS* are what they would expect with a reduced risk tobacco product (Section 6.1.6.6 of MRTPAs, page 8). While there were reductions in some of the BOPHs, in general, these biomarkers (related to oxidative stress, inflammation, platelet activation, cardiovascular risk, etc.) did not show substantial improvements for *IQOS* users compared to cigarette users during the 90 days of exposure. For example, the differences in BOPH levels between the mentholated *IQOS* and continued cigarette smoking arms were generally below 20%.

The considerably smaller reductions observed in BOPHs, compared with the changes in BOEs, may be because BOPHs are not tobacco-specific. In addition, the duration of the ambulatory studies may limit the interpretation of results related to the effects of long-term exposures. The applicant acknowledges that the 90-day duration of the clinical studies may not be enough time for changes in the observed BOPHs to manifest. For example, the applicant states that change in CRP "takes longer than a year"; "WBC reductions following smoking cessation are optimally detected after 6-12 months"; lung function "studies of longer duration (at least 6 to 12 months) will be required to fully assess the impact of the exposures on FEV1"; and "blood pressure was measured as part of the safety procedures and no significant changes were expected as a result of changes in product exposure for only 3 months." Therefore, these results should be treated with caution when interpreting the long-term effects of using *IQOS*.

In general, there are questions about the credibility of BOPHs as surrogate endpoints or substitutes for disease endpoints (Institute of Medicine, 2001; Institute of Medicine, 2012). In other settings, biomarkers used as validated surrogate endpoints often fail to predict the clinical outcome of interest (Temple, 1999; Temple, 2016). As described by Fleming and DeMets, potential surrogate endpoints often fail to predict clinical outcomes for the following reasons: (1) the biomarker under study is not found on the pathophysiologic pathway that leads to the clinical outcome of interest; (2) the biomarker is used to test an intervention associated with only one pathway when multiple causal pathways to a particular clinical outcome exist; (3) the biomarker is insensitive to or is not a part of the causal pathway of the intervention's effect or is insensitive to this effect; or (4) the intervention results in additional mechanisms of action (including other harmful effects) independent of the disease process (Fleming & DeMets, 1996). Any biomarker or set of biomarkers serving as a surrogate would ideally "be simultaneously, prospectively, and directly assessed against the desired clinical endpoint" (Institute of Medicine, 2012). Nevertheless, besides serving as surrogates for disease, BOPHs in studies assessing tobacco products are still informative for other purposes, particularly for enhancing "confidence that there is no worsening risk, in the least" (Institute of Medicine, 2001).

Summary and Conclusions

The four reduced exposure studies demonstrated that switching from combusted cigarette smoking to *IQOS* use (with regular and mentholated products) resulted in substantial reduction in systemic exposure to selected BOEs from Baseline to Day 5, ranging from 47% to 96%. The kinetics and the magnitude of decrease of BOE levels observed in the *IQOS* arm approached the levels observed in the smoking abstinence arm. However, the observed reductions were attenuated through the ambulatory period (studies using mentholated *IQOS*); at Day 90, reductions ranged from 34% to 86% (REXA-07-JP) and from 46% to 86% (REXA-08-US). In these studies, systemic exposures to nicotine were similar in the *IQOS* and combusted cigarette arms.

The reduced exposure studies demonstrated minor improvements in some of the BOPHs in the *IQOS* arm, relative to continued smokers; however, the significance of the changes is uncertain. As described above, substantial differences were not observed during the 90 days of exposure. This may be because the chosen markers were not observed long enough, were not tobacco-specific, or were not adequately sensitive to detect changes in physiology. It is not clear how predictive the chosen biomarkers are of long-term tobacco-related disease risk.

II. EVIDENCE RELATED TO THE IMPACT ON TOBACCO USERS

A. Clinical and Behavioral Pharmacology

To inform the abuse liability of the *IQOS* system with *HeatSticks*, the applicant submitted a range of studies, including PK/PD and actual use studies with clinical and behavioral pharmacology outcomes. The studies are summarized in Table 6 below, along with a preliminary evaluation of the clinical and behavioral pharmacology evidence to inform the TPSAC discussion.

Table 6: Summary of Studies with Behavioral and Clinical Pharmacology Outcomes

Study ID	Study Location	Tobacco Product Flavor	Study Design	Study Outcomes	
				Behavioral Pharmacology	Clinical Pharmacology
ZRHR-PK-01-EU	Ireland	Regular	Single use, PK/PD randomized 2-period, 4-sequence cross-over study	Abuse liability: dependence (QSU-Brief), reward (MCEQ)	Nicotine: plasma nicotine PK
ZRHR-PK-02-JP	Japan	Regular	Single use, PK/PD randomized 2-period, 4-sequence cross-over study	Abuse liability: dependence (QSU-Brief), reward (MCEQ)	Nicotine: plasma nicotine PK
ZRHM-PK-05-JP	Japan	Menthol	Single use, PK/PD randomized 2-period, 4-sequence cross-over study	Abuse liability: dependence (QSU-Brief), reward (MCEQ)	Nicotine: plasma nicotine PK
ZRHM-PK-06-US	U.S.	Menthol	Single use, PK/PD randomized 2-period, 4-sequence cross-over study	Abuse liability: dependence (QSU-Brief), reward (MCEQ)	Nicotine: plasma nicotine PK
ZRHR-REXC-03-EU	Poland	Regular	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined)	Use behavior: daily use/consumption, topography Abuse liability: dependence (QSU-Brief, MNWS), reward (MCEQ)	Nicotine: plasma nicotine PK on Day 5, urinary NEQ daily
ZRHR-REXC-04-JP	Japan	Regular	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined)	Use behavior: daily use/consumption, topography Abuse liability: dependence (QSU-Brief, MNWS), reward (MCEQ)	Nicotine: plasma nicotine PK on Day 5, urinary NEQ daily.

ZRHM-REXA-07-JP	Japan	Menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined, 85 days ambulatory)	Use behavior: daily use/consumption, topography Abuse liability: dependence (QSU-Brief, MNWS, FTND), reward (MCEQ)	Nicotine: plasma nicotine PK on Day 5, urinary NEQ and weighted C_{avg} through 90 days
ZRHM-REXA-08-US	U.S.	Menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined, 85 days ambulatory)	Use behavior: daily use/consumption, topography Abuse liability: dependence (QSU-Brief, MNWS, FTND), reward (MCEQ)	Nicotine: plasma nicotine PK on Day 5, urinary NEQ and weighted C_{avg} through 90 days
THS-PBA-07-US	U.S.	Regular & Menthol	Prospective, observational study with single-group design (6 weeks)	Use behavior: daily use/consumption Abuse liability: hypothetical purchasing, misuse	N/A
ZRH-POP-PK-01	All Locations listed above	Regular & Menthol	Population PK modeling of nicotine based on the combined data of studies listed above	N/A	N/A

Note: Studies ZRHR-PK-01-EU, ZRHR-PK-02-JP, ZRHM-PK-05-JP, ZRHM-PK-06-US were randomized with each participant using two of the following three products*: IQOS* System with *HeatSticks* (THS), own-brand combusted cigarettes and NRT (nicotine replacement therapy: nasal spray or gum). The statistical comparisons were performed for populations (1) THS vs. combusted cigarettes and (2) THS vs. NRT. For studies ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US, participants were randomized to one of three arms: THS, combusted cigarettes, or smoking abstinence (SA). QSU-Brief = Questionnaire of Smoking Urges, brief version. MNWS = Minnesota Nicotine Withdrawal Scale. FTND = Fagerström Test for Nicotine Dependence. MCEQ = Modified Cigarette Evaluation Questionnaire. PK = pharmacokinetic. NEQ = urinary nicotine equivalents (sum of nicotine and its five major metabolites). C_{avg} = average plasma nicotine concentration.

Summary of Studies Relevant to Clinical and Behavioral Pharmacology

PK/PD Studies. Four single-use, randomized, 2-period, 4-sequence cross-over studies of PK/PD (ZRHR-PK-01-EU, ZRHR-PK-02-JP, ZRHM-PK-05-JP, ZRHM-PK-06-US) were conducted to assess and compare the rate and extent of nicotine uptake (PK in plasma evaluated by comparison of C_{max} and $AUC_{0\text{-last}}$)[10] in participants switching to *IQOS* compared to smoking combusted cigarettes and in participants who switched to *IQOS* compared to using nicotine replacement therapy products (nicotine nasal spray and nicotine gum). Subjective effects, such as urge to smoke (QSU-Brief) and measures related to reinforcing or aversive effects (MCEQ), were part of the PD assessment.

Reduced Exposure Studies. Four randomized, controlled, open-label, 3-arm parallel group studies (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US) were conducted with the primary aim to investigate systemic exposure to biomarkers of HPHCs following five days of combusted cigarette (or mentholated combusted cigarette) use, *IQOS* use (regular or mentholated), or smoking

[10] C_{max} is the observed maximum plasma nicotine concentration and reflects systemic exposure; $AUC_{0\text{-last}}$ is the area under the nicotine concentration vs. time curve from time 0 to last observation and reflects systemic exposure.

abstinence (SA). All participants tried and were willing to use *IQOS* prior to randomization. During the five-day confinement, participants used the product they were randomized to without restriction (*ad libitum*) from 6:30 am to 11:00 pm. Dual use of *IQOS*, combusted cigarettes, and other nicotine/tobacco products was not permitted. Two of the four studies followed participants for a prolonged period (90 days) in an ambulatory setting (i.e., home environment; near to real-world conditions) after the five-day confinement period, with a primary aim of demonstrating that exposure reduction under controlled conditions can be maintained. During the ambulatory period, participants were instructed to continue using the product they were randomized to at the beginning of the study (e.g., "exclusive use of THS 2.2 Menthol") but were informed that use of "nicotine/tobacco-containing products other than the assigned product/regimen" would not result in removal from the study. Data were collected daily during confinement and on days 30, 60, and 90 during the ambulatory period. Secondary endpoints included plasma nicotine PK on Day 5, daily urinary nicotine equivalents (NEQ), and tobacco product consumption. The nicotine exposure assessment was well designed and performed satisfactorily. However, because of dual tobacco use during the ambulatory period, it is difficult to discern whether the nicotine exposures in the *IQOS* (menthol) arm came from *IQOS* (menthol) only or from dual use. Exploratory endpoints included smoking topography and subjective effects (e.g., QSU-Brief, MCEQ, MNWS). Participants were healthy adults who were moderate-to-heavy smokers; therefore, generalization of results to light or non-daily smokers is not possible.

Actual Use Study. One single-group, prospective observational study was conducted with a primary aim to investigate how U.S. adult daily smokers of cigarettes used *IQOS* in near to real-world conditions (i.e., naturalistic setting). After participants completed a one-week baseline period where they smoked own-brand cigarettes and potentially used other nicotine/tobacco-containing products, they received *IQOS* free of charge and could consume *IQOS*, cigarettes, and other nicotine/tobacco-containing products *ad libitum* for a period of six weeks. Participants completed interviews prior to the baseline period, after the baseline period, and every two weeks during the six-week observational period. Secondary endpoints included product consumption and *IQOS* system misuse; data on hypothetical purchasing of the *IQOS* system were reported (not listed as an endpoint). Participants were healthy, daily smokers (≥1 CPD, ≥100 cigarettes lifetime, who smoked >30 days) with no intent to quit smoking in the next 30 days and positive intention to use *IQOS*. See the "Epidemiology of *IQOS* Use" section for further details about the study.

Nicotine Exposure

In the PK/PD studies in the U.S. and Europe, systemic exposure to nicotine after a single use of *IQOS* was lower than after a single use of cigarettes. For non-mentholated *IQOS* products, geometric mean (GM) values of C_{max} decreased by 24% and of $AUC_{0\text{-}last}$ decreased 25%. For the mentholated *IQOS* products, GM values of C_{max} decreased 43% and of $AUC_{0\text{-}last}$ decreased by 44%. T_{max}[11] values were similar in both arms. In two single-use Japanese studies, systemic exposure to nicotine after a single use of *IQOS* (mentholated and regular) was similar to a single use of mentholated and regular cigarettes (comparison of GM values of both C_{max}, $AUC_{0\text{-}last}$). T_{max} values were similar in both arms. The differences in the study populations may have contributed to these findings.

In two five-day reduced exposure studies in Europe and Japan, after five days of *ad libitum* use, *IQOS* use resulted in systemic nicotine exposures similar to five-day *ad libitum* use of combusted cigarettes for

[11] T_{max} is the time to reach C_{max} and reflects rate of absorption.

both the mentholated and nonmentholated products. There was some variability in nicotine PK parameters in the *IQOS* arm(s) between the studies. The standardization of product use by setting puff number and puff interval might have resulted in a decreased intra - and/or inter-subject variability, but the large sample size of 42 participants allowed for an adequate precision of the C_{max} and AUC between 15% and 26%. In the 90-day study in Japan, the GM nicotine plasma C_{max} values on Day 5 and weighed C_{avg}[12] values in the *IQOS* (menthol) arm were 31% and 27% higher relative to the mentholated cigarette arm, respectively, and the GM of urinary NEQ adjusted for creatinine were comparable between mentholated *IQOS* and mentholated cigarette arms over the 90-day study period. In the 90-day study in the US, the GM nicotine plasma C_{max} values on Day 5 and weighed C_{avg} values in the mentholated *IQOS* arm were 11% and 15% lower than in the mentholated cigarette arm, respectively. The GM of urinary NEQ adjusted for creatinine were slightly lower in the mentholated *IQOS* arm than in the mentholated cigarette arm over the 90-day study period, but due to high variability, the differences were not statistically significant.

The population PK model (ZRH-POP-PK-01) described nicotine PK using combined data of all individual studies to determine the cause of variability in PK parameters, calculated using the non-compartmental method. The model explained the variability in nicotine PK by the effects of the covariates (nicotine yield, sex, race, body weight, etc.). These variabilities are expected to be similar in future studies in other populations; therefore, the results of the population PK modeling may be generalizable.

In summary, it appears that nicotine delivery from *IQOS* is sufficient to serve as a replacement for combusted cigarettes.

Product Use (Consumption/Topography)

Level of consumption (secondary outcome) was measured as the number of combusted cigarettes or *HeatSticks* used per day. Consumption was recorded by study staff during confinement (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US) and by self-report in an e-diary during the ambulatory period (ZRHM-REXA-07-JP, ZRHM-REXA-08-US) or observational period (THS-PBA-07-US). Compliance to the study product was strictly controlled during confinement, but non-compliance was possible during the ambulatory period. Self-report data is susceptible to missing and inaccurate data.

In 5- and 90-day reduced exposure studies, both *IQOS* and cigarette arms showed small changes in product use over time. These results were consistent despite differences in environment (controlled vs. ambulatory), populations, dual/exclusive use, and flavor (menthol vs. regular). In the observational study (THS-PBA-07-US), the average number of products (cigarettes and *HeatSticks* combined) used per day was slightly lower during the observational period compared to baseline (9.3 products per day vs. 10.2 cigarettes per day) for the overall sample (n=987). This decrease was similar for participants who used >70% of the time (n=141); participants used 8.1 products per day during the observational period compared to 9.0 cigarettes per day at baseline. Findings were similar for menthol and regular products.

Dual use of *IQOS* and cigarettes was evident in the exposure studies and the observational study. During the last month of the ambulatory period, self-reported dual use was low in the Japanese study: at least 84.6% used *IQOS* exclusively, and at least 85.9% used *IQOS* >95% of the time. In contrast, self-reported dual use was high in the U.S. study: at least 55.0% used *IQOS* exclusively, and at least 63.8% used *IQOS*

[12] C_{avg} is average plasma nicotine concentration and reflects systemic exposure.

>95% of the time. At the end of the actual use study, 7.5% reported using IQOS >95% of the time (THS-PBA-07-US). The higher rates of complete switching in the reduced exposure studies may have occurred because participants were instructed to use *IQOS* exclusively and were confined and monitored to ensure compliance during the first five days of the study.

Topography (exploratory outcome) was measured in the exposure studies using the HPT SODIM® Device model SPA/M for *HeatSticks* and cigarettes that were compatible with the device. Data provided were descriptive; no significance testing was completed. Topography behavior for the *IQOS* is limited by intrinsic properties of the device, which limits the number of puffs to 14 and smoking duration to a maximum of six minutes of use. The *IQOS* holder calculates the number of puffs based on differences in temperature on the surface of the blade. In contrast, the HPT SODIM® device calculates puff number based on differences in air flow rate and "is more sensitive in puff detection than the THS puff sensor." The applicant states that *IQOS* users overcome the fourteen-puff limit by using a "multipuff technique (i.e., not stopping completely the inhalation between all puffs)," which may affect exposure. Overall, switching from cigarettes to *IQOS* resulted in differences across a variety of topography metrics and variability was found across studies (populations). For example, compared to the combusted cigarette arm, participants in the *IQOS* arm took more puffs (three of four studies), had a shorter smoking duration (two of four studies), and had a higher puff frequency (four of four studies); in the cigarette arms, topography was stable over time. The applicant attributes these differences as adaptation to the intrinsic properties of the novel product and compensation for differences in nicotine delivery. Findings were similar for menthol and regular products.

Abuse Liability (Subjective Effects, Purchase Intentions, Misuse)

Dependence was measured by self-report questionnaires assessing relief from craving (Questionnaire of Smoking Urges – Brief [QSU-Brief]) and relief from withdrawal symptoms (Minnesota Nicotine Withdrawal Scale [MNWS-R]). In the PK studies, QSU was administered prior to product use, and 15, 30, 45 minutes and 1, 2, 4, 6, 9, and 12 hours after use; for these studies, QSU-Brief was a secondary outcome measure. In the exposure studies, QSU-Brief was administered at the end of the day (8-11 pm), while MNWS was administered prior to product use and reflected the previous day's experience; for these exposure studies, data were exploratory and therefore descriptive. In the 90-day exposure studies, the Fagerström Test for Nicotine Dependence (FTND) was administered at baseline and at the end of the ambulatory period (Day 90). Interpretation of data based on these questionnaires is limited by the following: (1) in some studies, translated versions may lack validity and generalizability; (2) the QSU-Brief was not modified to replace references to cigarettes with *HeatSticks*/THS/*IQOS*, so it is not clear if participants were aware of which product was being asked about; (3) scoring of the MNWS differed between studies (e.g., sum vs. average score, including different items for total score).

In the PK/PD studies, relief from craving (QSU-Brief) showed a similar time curve following both *IQOS* and cigarette arms: highest prior to use, sharp decline following use, and continued decline to approach baseline over 12 hours. In 5- and 90-day exposure studies, relief from craving (QSU-Brief) and withdrawal (MNWS-R) were similar between *IQOS* and cigarette arms and remained stable throughout the study. Findings were similar for mentholated and regular products. At the end of the ambulatory period, no difference in dependence severity (FTND) was found between *IQOS* and cigarette arms; both arms showed no change in the Japanese sample or reduced severity of symptoms in the U.S. study.

Reward was measured using a self-report questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]) with subscales including smoking satisfaction, psychological reward, aversion, enjoyment of

respiratory tract sensations, and craving reduction. In the PK studies, MCEQ was administered after product use; for these studies, MCEQ was a secondary outcome measure. In the exposure studies, MCEQ was administered at the end of the day (8-11 pm); for exposure studies, data were exploratory and therefore descriptive. Interpretation of MCEQ data is limited by the following: (1) in some studies, translated versions may lack validity and generalizability; (2) there is no assessment of the relationship between significant differences on the MCEQ (e.g., 1 point) and behavioral change (e.g., consumption).

In the PK/PD studies, *IQOS* had significantly lower ratings on MCEQ measures of reward (0.5-1.3 point difference, 7-point scale) compared to own-brand cigarettes. Subscales that differed by at least one point included smoking satisfaction (all four studies) and respiratory track sensation (one study). In 5- and 90-day exposure studies, switching from cigarettes to *IQOS* resulted in minor reductions in smoking satisfaction, reward, enjoyment of sensation, and craving reduction (MCEQ) on Day 5 (end of confinement), and these differences were generally absent by day 90 (end of study). Findings were similar for menthol and regular products.

In the actual use study (THS-PBA-07-US), participants were asked at the end of the observational period (week 6) about their likelihood to purchase *IQOS*, "if the *IQOS* device were available for $79.99 and a pack of *Marlboro HeatSticks* were available at a price comparable to a pack of *Marlboro* cigarettes." Responses were based on a Likert scale. This hypothetical assessment provides some information on abuse liability from a behavioral economics perspective. In the overall sample (n=987), nearly 20% of participants reported that they probably, or definitely, would buy *IQOS*. Findings were similar based on menthol/non-menthol preference, across age groups, and across baseline smoking rates. In a subsample of participants who used *IQOS* >70% of the time (week 6, n=138), nearly 50% reported they probably, or definitely, would buy *IQOS*. Although descriptive data were provided, this measure was not listed as an outcome measure.

Misuse of a product (secondary outcome) may potentially increase the nicotine exposure and/or quantity of use, thereby increasing abuse potential. *IQOS* misuse was assessed in the actual use study (THS-PBA-07-US) and based on self-report. The misuse rate was low. Of 985 participants, 47 (4.8%) reported using *HeatSticks* without the *IQOS* device; the majority (97.9%) lit the *HeatSticks* like a cigarette; one participant chewed the *HeatStick*. Only two participants (0.2%) reported using the *IQOS* device without *HeatSticks*; one participant used the *IQOS* device with marijuana and the other used it with combusted cigarettes.

Summary and Conclusions

Nicotine systemic exposure was similar after single and multiple uses of *IQOS* and combusted cigarettes (both regular and mentholated). From a PK point of view, the nicotine exposures achieved with *IQOS* use appear sufficient to provide user satisfaction.

IQOS use rates were similar to combusted cigarettes. *IQOS* produces reinforcing effects and is expected to have an abuse potential that is similar to combusted cigarettes based on the following: (1) both *IQOS* and combusted cigarette use leads to similar systemic nicotine exposures; (2) they both reduce withdrawal/craving at similar rates and to a similar extent; (3) they produce similar reinforcing effects; and (4) some participants report being willing to spend nearly $80 upfront, plus the cost of *HeatSticks,* to use the *IQOS system*. Topography profiles differ between *IQOS* and cigarettes; these differences likely reflect adaptation to differences in product design, flavor, and nicotine yield. Few participants misused the *HeatSticks* or the *IQOS* device. Dual use of *IQOS* and cigarettes was common in the U.S. studies.

B. Epidemiology of *IQOS* Use

The applicant conducted several observational studies to assess product usage among cigarette smokers. Two main pre-market studies assessed the use of *IQOS* among current tobacco users in real world settings: (1) PBA-07 (Section 7.3.2 of MRTPAs), an actual use study conducted in the U.S.; and (2) the Whole Offer Test (WOT) (Section 7.3.3 of MRTPAs), conducted in five countries in Asia and Europe. The applicant also provided findings on *IQOS* use patterns from two post-marketing studies conducted in Japan.

Studies Assessing *IQOS* Use Patterns

PBA-07. The PBA-07 Actual Use Study was an observational study to assess near real-world use patterns of the *IQOS* system among adult daily cigarette smokers in the U.S. The study was conducted between September 2015 and January 2016 in eight U.S. cities. Participants were recruited from market research databases, which include qualified individuals who voluntarily participate in various research studies. Enrollment into these databases is done directly through the research agencies' websites, referrals from friends and family already in the databases, social media, word of mouth, and random digit dialing telephone recruiting. The databases consist of approximately 400,000 individuals nationwide in the U.S. Potential participants who were contacted by phone for screening were initially identified based on information available for age, gender, and smoking status. Eligibility criteria included being aged 18 years or older, having smoked at least 100 cigarettes in their lifetime, currently smoking at least one regular and/or one menthol cigarette per day with no intention of quitting in the next 30 days, and not having started smoking in the past 30 days. Potential candidates were initially contacted by telephone to complete a short questionnaire to assess their eligibility. Those who passed the initial screening were invited to a study site where they were exposed to the *IQOS* system label and marketing material that contained the following modified risk information: "The *IQOS* system heats tobacco but does not burn it."; "This significantly reduces the production of harmful and potentially harmful chemicals."; and "Scientific studies have shown that switching completely from combusted cigarettes to the *IQOS* system can reduce the risks of tobacco-related diseases." After reviewing the labeling material, candidate participants were asked, "If you try this product and like it, how likely or unlikely are you to use this product regularly?" Respondents were eligible to enroll in the study if they responded "definitely", "very likely", or "somewhat likely". A total of 10 people were excluded for responding "somewhat unlikely", "very unlikely" or "definitely not." A total of 1,336 participants were enrolled. After excluding 230 participants who did not consume at least one cigarette during the baseline period and at least one *HeatStick* during the six-week observational period, the final sample size was 1,106 participants. Of those, 119 (10.8%) prematurely discontinued the study. A total of 987 participants (89.2%) completed the study, defined as completing the interview conducted after Week 6 to collect information on *IQOS* misuse, occasions of use, and appeal of the product. Of the 987 participants, 969 reported data in the e-diary during Week 6.

Participants first completed a one-week baseline period to establish their regular cigarette smoking patterns by using an e-diary to record every cigarette smoked. At the beginning of the six-week observational period, participants received a free *IQOS* system kit and five packs of *HeatSticks* containing a total of 100 *HeatSticks* (participants could choose regular, menthol, or both). Participants could obtain additional *HeatSticks* by calling the study's toll-free telephone line or going to the study enrollment site. The *HeatStick* packages that participants took home were white and unbranded and did not include the modified risk information. Participants were instructed to use *HeatSticks*, cigarettes and any other tobacco products containing nicotine *ad libitum*, and record in their e-diary each time they used a cigarette or a *HeatStick*. Each day, participants also recorded (yes/no) if they used e-

cigarettes or other tobacco products. Participants were not specifically instructed to try to use *HeatSticks* instead of cigarettes. Data from the e-diary were submitted in real time (i.e., at the time of data entry). If more than two days had elapsed since data were recorded in the e-diary, participants received a reminder call. Compensation for participating in the study was up to $440, depending on the length of time in the study and return of the *IQOS* system, used and unused *HeatSticks*, and the e-diary device. The number of *HeatSticks* used or cigarettes smoked did not influence the amount of compensation.

Whole Offer Test. The Whole Offer Test (WOT) was an observational study designed to evaluate the likelihood that adult daily smokers will switch from cigarettes to *HeatSticks* in near real-world conditions. The study was conducted in five countries: Japan (2013), South Korea (2015), Italy (2013), Germany (2014), and Switzerland (2014). Similar to the PBA-07 study, participants were recruited from a market research database. Eligibility criteria included being aged 19 years or older, having resided at least one year in the study country, having smoked at least 100 cigarettes since reaching the legal smoking age, having smoked for at least six months (including at least once in the past seven days), and having smoked at least three cigarettes per day. In Italy and Germany, participants only included smokers of non-menthol cigarettes. In South Korea, only males were eligible to participate. Participants also had to indicate an interest in using *IQOS* after trying a single *HeatStick*. Participants were exposed to pack design and other branded materials; however, it is unclear from the protocol whether these materials included the modified risk information.

During the baseline interview, participants reported the average number of cigarettes smoked per day. They did not complete a one-week baseline period as in the PBA-07 study. Participants were then provided *IQOS* and *HeatSticks* free of charge (regular and/or menthol, except for Italy and Germany, which only provided regular), and were instructed to use *HeatSticks*, cigarettes and any other tobacco products containing nicotine *ad libitum*. The *HeatSticks* taken home were in plain, unbranded packaging. During the four-week observational period, participants recorded each time they used a cigarette or *HeatStick* in a paper-and-pencil diary. In Italy and Japan, participants also recorded whether they used e-cigarettes each day (yes/no), however information was not collected about the use of other tobacco products in any country. The primary aims of the study and definitions for the use pattern outcomes are the same as those in the PBA-07 study (described above). The final sample size by country was: Japan (n=638), South Korea (n=843), Italy (n=535), Germany (n=377), and Switzerland (n=416).

Japanese Post-Market Studies. Information on *IQOS* use patterns were reported from two post-market studies in Japan. The first was an online survey conducted in September 2016 that was completed by 2,000 adults aged 20 years and older who were recruited across Japan from an online panel. The study included both smokers and non-smokers. The aim of the study was to "assess the effects of *IQOS*" on the prevalence of tobacco product use in the Japanese adult population. Respondents self-reported whether they were current users of cigarettes, heat-not-burn products, and other tobacco products on a provided list. In a second post-market study conducted in Japan, data on self-reported use of *IQOS* and cigarettes were collected from approximately 11,000 adults who had purchased *IQOS* and registered their device in an online database. Additional information about the design and results of the ongoing post-market studies are being requested from the applicant.

Table 7 summarizes the methodology of the above-mentioned pre- and post-market studies that provided information about *IQOS* use patterns.

Table 7: Description of Pre- and Post-Market Studies of *IQOS* Use Patterns (Data Source: Sections 7.3.2, 7.3.3 of MRTPAs, March 16, 2017 amendment, and September 13, 2017 amendment)

	PBA-07	**Whole Offer Test**	**Post-Market Online Cross-Sectional Study**	**Post-Market *IQOS* Purchaser Study**
Study Design	Longitudinal	Longitudinal	Cross-sectional	Unknown*
Location, time period	United States, September 2015 - January 2016, 6-week observational period.	Japan, 2013 South Korea, 2015 Italy, 2013 Germany, 2014 Switzerland, 2014, 4-week observational period.	Japan, September 2016	Japan, 2015-2016
Sample size	1,106	Japan - 638 South Korea - 843 Italy - 535 Germany - 377 Switzerland – 416	2,000	~11,000*
Attrition rate	12.4% (n=137) of participants included in the analyses did not have week 6 data.	All participants included in the analyses had week 4 data.	N/A	Unknown*
Population source	Market research consumer-based databases from across the US.	Market research consumer-based databases from across the US.	Online panels that recruited from across Japan.	Adults from across Japan who purchased *IQOS* and registered their product in an online database.
Eligibility criteria	Aged ≥18 years; current daily smoker of regular and/or menthol cigarettes with no intention of quitting in the next 30 days (mean CPD = 10.2); expressed positive intention to use *IQOS* following exposure to labeling material that included modified risk information.	Aged ≥19 years; smoked ≥100 cigarettes in lifetime, smoke at least 3 cigarettes per day and smoked in past 7 days (mean CPD: Japan = 16.5; South Korea = 15.2; Italy = 12.7; Germany = 17.4; Switzerland = 17.3); expressed positive intention to use *IQOS* after trying one *HeatStick*. It is unclear if the labeling material included modified risk information.	Aged ≥20 years and resided in Japan. Included cigarette smokers and non-smokers.	Adults that purchased and registered their *IQOS* device. Proportion of cigarette smokers unknown.
How *IQOS* was obtained	*IQOS* system and *HeatSticks* were provided for free (regular and/or menthol).	*IQOS* system and *HeatSticks* were provided for free (regular and/or menthol; only regular was available in Italy and Germany).	Respondents were not provided *IQOS*. The device was purchased by the respondent or someone else.	Respondents were required to have purchased *IQOS*.
Assessment of IQOS and cigarette use	1-week baseline period to daily record cigarette	Self-report average number of cigarettes per day during enrollment	One-time online survey that asked if respondents were	Self-reported use of *IQOS* and combusted cigarettes in an online

	PBA-07	Whole Offer Test	Post-Market Online Cross-Sectional Study	Post-Market *IQOS* Purchaser Study
	smoking frequency in e-diary. 6-week observational period to record cigarette smoking and *IQOS* use in e-diary on a daily basis.	interview. 4-week observational period to record frequency of cigarette smoking and *IQOS* use in paper and pencil diary on a daily basis.	current daily or some day users of cigarettes, "heat not burn" products, and other tobacco products.	survey.

CPD = cigarettes per day.
*Additional information about the study design was requested from the applicant.

Study Findings

PBA-07 and WOT. Table 8 presents some of the findings from the PBA-07 and WOT studies for the prevalence of initiating *HeatStick* use and switching from cigarettes to *HeatSticks*. During the six-week observational period of the PBA-07 study, 33.8% of current smokers initiated use of *HeatSticks* (i.e., consumed ≥100 *HeatSticks*). In the last week of the study, 32.7% of participants who started using *HeatSticks* met the applicant's criteria for switching to *HeatSticks* (i.e., *HeatSticks* were ≥70% of total cigarettes plus number of *HeatSticks* consumed in a week). Among those who started using *HeatSticks*, 16.3% were exclusively using *HeatSticks* (≥95% *HeatStick* use) during Week 6. Of those who switched to *HeatSticks* at an earlier week, 15.5% had reverted back to predominantly using cigarettes (i.e., *HeatSticks* were ≤30% of total cigarettes plus number of *HeatSticks* consumed in a week) by the last week.

In the WOT, the prevalence of using *HeatSticks* varied by country, with the highest prevalence observed in Japan and South Korea. *HeatStick* initiation ranged from 36.1% in Italy to 76.3% in South Korea and the prevalence of switching to *HeatSticks* among those who initiated product use ranged from 29.0% in Italy to 47.4% in South Korea. Exclusive *HeatStick* use among those who had used at least 100 *HeatSticks* ranged from 7.8% in Switzerland to 21.5% in Japan. The proportion of *HeatStick* initiators who switched from *HeatSticks* back to cigarettes ranged from 0% in Japan to 10.3% in Italy.

Table 8: Prevalence of *HeatStick* Initiation and Switching at Study End, by Country (Data Source: Sections 7.3.2 and 7.3.3 of MRTPAs)

Country	Started Using *HeatSticks*[a]	Switched to *HeatSticks*, Among Those Who Started Using *HeatSticks*[b]	Exclusive *HeatStick* Use, Among Those Who Started Using *HeatSticks*[b]	Switched Back To Cigarettes, Among Those Who Previously Switched To *HeatSticks*[c]
PBA-07				
United States	33.8%	32.7%	16.3%	15.5%
Whole Offer Test				
Japan	61.3%	46.3%	21.5%	0.0%
South Korea	76.3%	47.4%	20.1%	6.4%
Italy	36.1%	29.0%	13.0%	10.3%
Germany	50.1%	37.0%	15.3%	7.5%
Switzerland	49.5%	18.0%	7.8%	8.5%

Note: Estimates are the proportion of participants who met the criteria for each use pattern during Week 6 for the PBA-07 study and during Week 4 for the Whole Offer Test.

[a]Denominator is all participants: United States (n=1,106), Japan (n=638), South Korea (n=843), Italy (n=535), Germany (n=377), Switzerland (n=416). Started using *HeatSticks* is defined as consuming ≥100 *HeatSticks* during the observational period.

[b] Denominator is all participants who started using *HeatSticks*: United States (n=374), Japan (n=391), South Korea (n=643), Italy (n=193), Germany (n=189), Switzerland (n=206). Switched to *HeatSticks* was defined as *HeatSticks* comprising ≥70% of total cigarette and HeatStick consumption during the last week of the observational period. Exclusive *HeatStick* use was defined as *HeatSticks* comprising ≥95% of total cigarette and *HeatStick* consumption during the last week of the observational period.

[c] Denominator is participants who switched to *HeatSticks* in a previous week: United States (n=195), Japan (n= 180), South Korea (n=328), Italy (n=58), Germany (n=67), Switzerland (n=47). Switched back to cigarettes was defined as *HeatSticks* comprising ≤30% of total cigarette and *HeatStick* consumption after having switched to *HeatSticks* during an earlier week.

Figure 8 presents the main *IQOS* use categories for all participants during the last week of the observational period in the PBA-07 and WOT studies. In the U.S., 7.5% of all participants had "exclusive *HeatStick* use", 7.0% were predominantly using *HeatSticks*, 22.4% had combined use of *HeatSticks* and cigarettes, and 62.7% were predominantly using cigarettes. In the WOT, the proportion of participants who completely switched to *HeatSticks* was higher in South Korea (15.7%) and Japan (13.6%) than Germany (8.5%), Italy (5.2%), and Switzerland (4.3%). Depending on the country, between 5.6% and 21.5% of adult daily smokers were predominantly using *HeatSticks* at the end of the observational period.

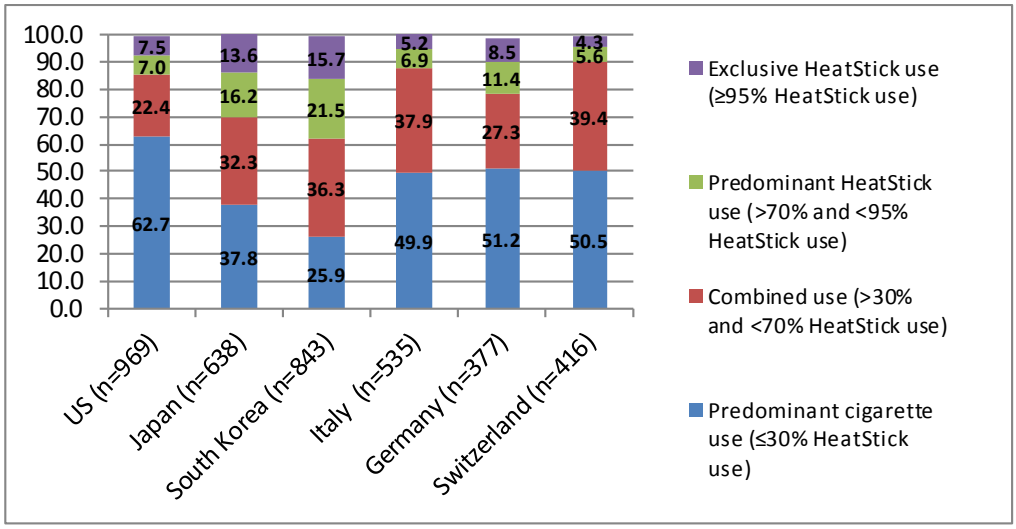

Figure 8: Percent of All Participants in Each Main IQOS Use Category at the End of the PBA-07 and Whole Offer Test Studies, by Country (Data Source: Sections 7.3.2 and 7.3.3 of MRTPAs). Some bars do not add up to 100% due to participants who did not report using any *HeatSticks* or cigarettes during the last week of each study, including 3 (0.3%) in the US, 1 (0.2%) in Japan, 6 (0.7%) in South Korea, 6 (1.6%) in Germany, and 1 (0.2%) in Switzerland. All participants in Italy reported using at least one *HeatStick* or cigarette during the last week.

PBA-07 also assessed the change from the mean number of cigarettes smoked per day at baseline to: (1) the mean total number of *HeatSticks* plus cigarettes used per day during Week 6; and (2) the mean number of CPD at Week 6 (Figure 9). Daily cigarette consumption decreased between baseline and Week 6 for all *HeatStick* use groups, with the largest decrease occurring in participants who were predominantly *HeatStick* users at Week 6 (a 7.6 decrease in average number of CPD). Across all groups, there was minimal change in total use of tobacco products (i.e., *HeatSticks* plus cigarettes) between baseline and the end of the observational period.

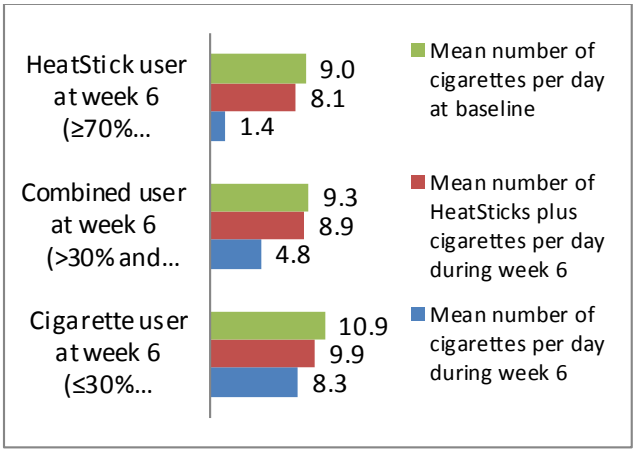

Figure 9: Change in Average Daily Cigarette Consumption and Total Tobacco Use (*HeatSticks* plus Cigarettes) from Baseline to Week 6 in the PBA-07 Study (Data Source: Section 7.3.2 of MRTPAs)

Post-Market Japanese Cross-Sectional Study. In the 2016 online cross-sectional survey from Japan, 3.7% of respondents reported using heat-not-burn tobacco products (2.3% used daily and 1.4% used less than daily). The prevalence of heat-not-burn product use was higher among those aged 20-29 (4.2%) and 30-39 (3.9%) than those aged 40-49 (1.5%) or ≥50 years (0.9%). Most current users of heat-not-burn products were using "*Marlboro HeatSticks* with *IQOS* device" (96.3%), while only 5.0% used "Ploom with Mevius/Pianissimo/Gold/Lugano/Orchard/Cooler Pods." The study indicated a high prevalence of dual use with cigarettes. Among respondents currently using heat-not-burn products, 84.9% also smoked cigarettes, most of them daily (Table 9). In total, 91.8% of heat-not-burn product users reported dual use with at least one other tobacco product. For most heat-not-burn product users, heat-not-burn products comprised less than 30% of their average total daily tobacco consumption (i.e., cigarettes plus heat-not-burn products). A total of 15.5% of heat-not-burn users were considered exclusive users (≥95% use). All respondents in the exclusive use group were not current cigarette smokers.

Table 9: Dual Use with Other Tobacco Products among Current Users of Heat-Not-Burn Products (n=71) (Data Source: March 16, 2017 amendment)

Tobacco Products Currently Used	% of Current Heat-Not-Burn Product Users That Use Each Product
Cigarettes (including roll-your-own) (daily or less than daily use)	84.9%
Cigarettes, use daily	79.4%
Cigarettes, use less than daily	5.5%
E-cigarettes	58.9%
Smokeless tobacco pipe	38.4%
Cigars/pipes/kiseru	24.7%
Chewing tobacco, snus, snuff	30.1%
Any of the above tobacco products	91.8%

Post-Market Study of IQOS Purchasers. Data on self-reported use of *IQOS* and cigarettes were also collected from approximately 11,000 adult *IQOS* purchasers in Japan who registered their device in an online market research database. The proportion of *IQOS* purchasers who were "exclusively" using IQOS (≥95%) increased from 52% in January 2016 to 65% in July 2016 (Figure 10). These estimates are much higher than the 7.5% of exclusive *IQOS* users observed in the U.S. PBA-07 actual use study, the 13.6% observed in Japan in the WOT study, or the 15.5% observed in the Japanese post-market cross-sectional study. The applicant suggests that these discrepancies between pre- and post-market studies are the result of increasing popularity and awareness of *IQOS* that occurred post-marketing through word of mouth or other forms of communication. It should also be considered that purchasing *IQOS* and registering the device was a requirement for inclusion in this study. Those who take the initiative to register their device are likely to be a non-representative sample of all users and may be more highly motivated to become exclusive *IQOS* users.

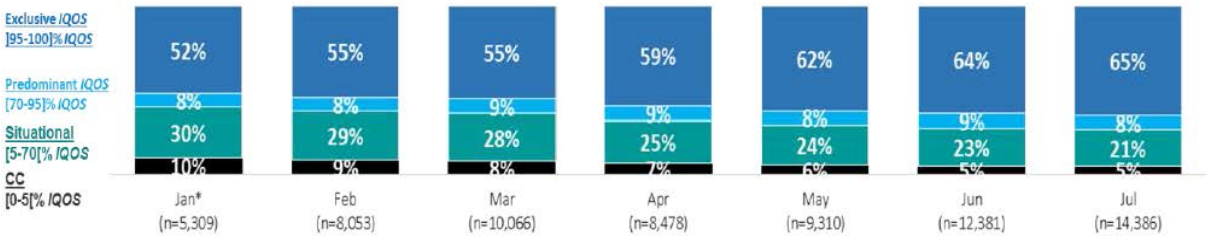

Figure 10: Percent of IQOS Use by Usage Category in the Japanese Post-Market *IQOS* Purchaser Study (Source: Section 2.7 of MRTPAs)

Summary and Conclusions

The prevalence of complete switching from cigarettes to *IQOS* was low in the U.S. Even using the applicant's definition for switching (i.e., ≥70% *HeatStick* use), less than 20% of participants in the U.S. PBA-07 study met the criteria for switching from cigarettes to *IQOS*. Although it is possible that with additional follow-up time some participants would have eventually become exclusive *IQOS* users, data from the PBA-07 study and the WOT study show that most smokers become dual users. A concern is what effect dual use of *IQOS* and cigarettes, compared to complete switching, will have on reducing health risks for tobacco-related diseases and reducing exposure to HPHCs. Despite incomplete switching, however, there was a reduction in daily cigarette consumption across all *IQOS* use groups in the PBA-07 study, even among the group of participants who were predominantly using cigarettes. These findings suggest that *IQOS* users are likely to reduce their cigarette consumption even if they continue to dual use.

However, the health benefit of reducing cigarette consumption instead of quitting completely is unclear. Epidemiological studies evaluating disease risk associated with reductions in smoking intensity have been inconsistent. For example, some studies have observed significant reductions in lung cancer risk associated with substantial (>50%) reductions in cigarettes smoked per day (Godtfredsen, Prescott, & Osler, 2005; Song, Sung, & Cho, 2008). However, other studies did not observe a change in disease or mortality risk with smoking intensity reduction (Godtfredsen, Holst, Prescott, Vestbo, & Osler, 2002; Godtfredsen, Osler, Vestbo, Andersen, & Prescott, 2003; Hart, Gruer, & Bauld, 2013; Tverdal & Bjartveit, 2006). The lack of consistent findings may be due, in part, to variations in definition of smoking reduction, differences in the dose-response relationship by disease endpoint, and the potential for smoking compensation among self-reported reducers.

Another concern is whether results from the U.S. and international actual use studies are generalizable to cigarette smokers in the general U.S. population. In the WOT study, results varied across countries, with a higher prevalence of complete switching in the Asian countries than the European countries. Post-marketing data from *IQOS* purchasers in Japan suggest that more than half of people who purchase *IQOS* will become exclusive users. However, it is unclear whether findings from the WOT and Japanese post-marketing studies are generalizable to U.S. smokers due to different cultural contexts and differences in the availability of e-cigarettes or other heat-not-burn products. It should also be noted that participants in the PBA-07 study came from a market research database that consisted of people who voluntarily joined through the research agencies' websites or referrals from friends and family; therefore, this population may not be representative of the general U.S. population.

Finally, some study design factors may have influenced the frequency with which participants used *IQOS*. Both the PBA-07 and WOT studies provided participants with a free *IQOS* system and *HeatSticks*.

There is concern that by receiving *IQOS* free of charge there may be participants who use *IQOS* during the study to save money on cigarettes, but who would not use *IQOS* if they had to purchase the product. The study was conducted with smokers who did not plan to quit in the next 30 days, and who reported that they would "somewhat likely," "very likely," or "definitely" use *IQOS* regularly if they tried it and liked it. We expect that this measure of intention to use *IQOS* would overestimate actual future purchase of *IQOS* (i.e., because people did not have to choose between *IQOS* and money, as they would have to do in the marketplace). Furthermore, the applicant's inclusion criteria for the study were more liberal than its criteria for defining use intentions in its other studies. That is, in its studies of smokers' responses to labeling and marketing materials, the applicant defined smokers as having a positive intention to use *IQOS* only if they reported that they would "definitely" or "very likely" use it, but not if they would "somewhat likely" use it. Indeed, when the applicant asked participants about their likelihood of purchasing *IQOS*, only 6% said they would "definitely" buy it, and 16% said they would "probably" buy it. These percentages were higher among participants whose tobacco product use was made up of 70-100% *HeatSticks* by the end of the study (16% of these would "definitely" buy *IQOS*, and 31% would "probably" buy it). Thus, as a caveat, we note that some proportion of the smokers in the applicant's PBA-07 study may not have purchased *IQOS* and, accordingly, may not have had the strong preferences for this type of product that would be expected to motivate complete switching from cigarettes. It is also unclear to what extent the modified risk information was communicated to and noticed by participants in the PBA-07 study. During enrollment, participants were exposed to *IQOS* labeling material with modified risk information, but it is unclear to what extent participants noticed the modified risk information or whether such information impacted behavior.

C. Impact of Proposed Labels, Labeling, and Advertising, Including Modified Risk Claims, on Tobacco Users

Evaluating an MRTP's population health impact includes assessing whether its labels, labeling, and advertising (LLA) materials impact tobacco use behavior and whether the LLA materials enable the public to understand the product's risks. To develop LLA materials and modified risk claims for *IQOS*, the applicant conducted several formative research studies. After developing a set of LLA materials and three claims, the applicant conducted four additional studies (described below) to assess people's intentions and perceptions regarding *IQOS* after viewing the materials.

LLA Materials

The applicant developed and tested LLA materials including a brochure, *HeatSticks* packs, and a direct mail communication. Also, the applicant stated that it will use other promotional channels to inform smokers about the product, including print and digital ads, age-restricted digital and social media channels, and package inserts and onserts on combusted cigarette packs. FDA notes that, in other countries, the applicant has also sold the product and provided information about the product in *IQOS* branded stores (Kim, 2017).

The LLA materials developed and tested in the applications (brochure, *HeatSticks* packs, and direct mail communication) stated that the product uses "real tobacco" and that *HeatSticks* have similar attributes to combusted cigarettes (i.e., paper, filter, real tobacco, a similar draw, an equal number of puffs). The applicant's qualitative research suggested that these product features resonated with smokers (e.g., "The real tobacco part is wonderful, that you're not sacrificing the enjoyment of having a cigarette…"). The brochure stated that the heat-not-burn technology has benefits, such as a lack of ashes, less odor and mess, and less disturbance to people in the user's vicinity, compared to combusted cigarettes. The

brochure also stated that the product is for smokers who want to continue using tobacco and is not for ex-smokers or smokers who want to quit. The *HeatSticks* in the applications would be marketed under the *Marlboro* brand, which CDC estimated was the most popular cigarette brand in the U.S. in 2016, with an estimated 41% market share (CDC, 2017). For current smokers, the branding, the LLA materials, and the product attributes may help communicate that *IQOS* is a tobacco product and perhaps that it is similar enough to combusted cigarettes to warrant trial among those who have not switched to currently-available electronic devices. This is consistent with the finding that a leading reason why some smokers have not tried e-cigarettes is because they are too dissimilar to cigarettes, which they enjoy using (Berg, 2016; Kong et al., 2015; McKegany & Dickenson, 2017).

The applicant's research on LLA materials informed participants that the *IQOS* device will be sold for $79.99. It also described the price of *HeatSticks*, which varied by study location to reflect differences in tobacco prices (i.e., across all studies, from $4.92 per pack in Missouri to $9.67 in Massachusetts). The high price of the *IQOS* device may discourage purchase by smokers, given that tobacco product prices have been shown to influence demand for the products (USDHHS, 2000).

Modified Risk Claims

In its LLA and claim assessment studies, the applicant proposed to use three sets of statements to disseminate modified risk information on its LLA materials. Table 10 shows these three modified risk claims. Briefly, modified risk claim 1 is about reducing risk of tobacco-related diseases; modified risk claim 2 is about reducing risk of harm; and modified risk claim 3 is only about reducing exposure to harmful and potentially harmful chemicals. Here, we refer to the first two modified risk claims as *reduced risk* claims, and we refer to the third modified risk claim as a *reduced exposure* claim.

Table 10: Modified Risk Claims in LLA and Claim Assessment Studies to Convey Information about Reduced Risk (1 and 2) and Reduced Exposure (3) to Consumers

Modified Risk Claim #1	Modified Risk Claim #2	Modified Risk Claim #3
"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 can reduce the risks of tobacco-related diseases."	"AVAILABLE EVIDENCE TO DATE Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes."	"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 and potentially harmful chemicals."

Stating that the potential benefits of *IQOS* are obtained by "switching completely" to the product is unambiguous and potentially informative to consumers, if supported by scientific evidence. However, consumers may be left to speculate about the potential benefits of *partial* switching, which is a more complex issue that could depend on the extent of switching and the disease endpoint.

The modified risk claims were not displayed prominently on the LLA materials and thus may not be noticeable to consumers, as proposed in the studies. The claims were displayed in rather small font and occupy a small percentage of space on the LLA materials. The brochure and direct mail communication also included multiple pages, and the modified risk claims did not appear on the first page. Given the claims' lack of prominence in the LLA materials used in the studies, the applicant's research may underestimate the claims' impact on perceptions and behavior if the modified risk claims were presented more prominently in other LLA materials. This is of concern given that the applicant's studies of people's responses to the LLA materials (discussed below) did not include a manipulation check to assess whether participants noticed and read the modified risk claims.

PMI Important Warnings

The applicant proposed three different PMI Important Warnings, with each version corresponding to one of its three modified risk claims. Table 11 shows the PMI Important Warnings. Each PMI Important Warning seems designed to qualify the modified risk claim that it would appear alongside. For LLA materials with the *reduced risk* modified risk claims, the PMI Important Warnings state that using *IQOS* still presents risks and that cessation is the best way for smokers to reduce their risks. For LLA materials with the *reduced exposure* modified risk claim, the PMI Important Warning states that switching to *IQOS* has not been shown to reduce disease risk. All three PMI Important Warnings also state that *HeatSticks* contain nicotine, which is addictive. The applicant proposes that these PMI Important Warnings would replace the Surgeon General (SG) Warnings currently mandated for cigarette products.

Table 11: Surgeon General (SG) Warnings and PMI Important Warnings

SG Warnings	One of the following displayed in rotating fashion: • "SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy." • "SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health." • "SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight." • "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide."		
PMI Important Warnings	PMI Important Warning proposed to accompany Modified Risk Claim #1:	PMI Important Warning proposed to accompany Modified Risk Claim #2:	PMI Important Warning proposed to accompany Modified Risk Claim #3:
	The following text displayed together: "IMPORTANT WARNING: • Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • HeatSticks™ contain nicotine, which is addictive. • Using the *iQOS* system can harm your health."	The following text displayed together: "IMPORTANT WARNING: • Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • HeatSticks™ contain nicotine, which is addictive."	The following text displayed together: "IMPORTANT WARNING: • It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes. • HeatSticks™ contain nicotine, which is addictive. • Using the *iQOS* system can harm your health."

Overview of LLA and Claim Assessment Studies

The applicant conducted four studies to assess people's intentions and perceptions regarding *IQOS* after viewing the LLA materials. Specifically, it conducted one study of people's responses after viewing materials with no modified risk claims, and three studies of people's responses after viewing materials with one of the three modified risk claims (see Table 10).

Table 12 summarizes the key design features of these four studies. These studies used the same recruitment strategies, design, procedures, and measures, and varied only in the stimuli presented to participants and the cities from which participants were recruited. Each study focused on four outcome variables: perceived risks of using *IQOS* and other tobacco and nicotine products, comprehension of the modified risk claims, intentions to use *IQOS*, and changes in smokers' intentions to quit smoking. The applicant examined these outcomes among current cigarette smokers, broken down based on whether or not they reported quit intentions in the near future. The applicant's rationale for examining outcomes separately based on smokers' quit intentions was to test whether the proposed MRTP (1) would be widely accepted among smokers and (2) would negatively influence smokers who are likely to quit smoking (Executive Summary, p. 19). However, we note that the applicant used a broad definition of quit intentions that includes up to two-thirds of current smokers in the U.S. (Persoskie & Nelson, 2013), even though only a fraction of these are likely to quit smoking within the next year (Babb et al., 2017).

Table 12: Key Design Features of the Applicant's Four LLA and Claim Assessment Studies

Modified Risk Claims	• No Claim Study (Study NOC): Participants viewed LLA materials without any of the three modified risk claims. • Study of Reduced Risk Claim 1 (Study RRC): Participants viewed LLA materials containing reduced risk claim 1. • Study of Reduced Risk Claim 2 (Study RRC2): Participants viewed LLA materials containing reduced risk claim 2. • Study of Reduced Exposure Claim (Study REC): Participants viewed LLA materials containing the reduced exposure claim.
LLA Material Stimuli	Participants in Study NOC were randomized to view one of the follow LLA materials: • *IQOS* Brochure with SG Warnings • *HeatSticks* pack with SG Warnings and "information planned to be used for commercialization" (statements about tobacco being heated, not burned) • *HeatSticks* pack with SG Warnings and no statements about tobacco being heated, not burned • Direct mail communication with SG Warnings Participants in studies RRC, RRC2, and REC were randomized to view one of the following LLA materials: • *IQOS* Brochure with SG Warnings • *IQOS* Brochure with PMI Important Warnings • *HeatSticks* pack with SG Warnings • *HeatSticks* pack with PMI Important Warnings • Direct mail communication with PMI Important Warnings Participants received a physical mock-up (i.e., hard copy) of the LLA material and kept it for viewing throughout the study.
Study Administration	Each study was administered in-person at research sites, using computer-assisted self-interviews.

Participants	Participants in each study were recruited from market research panels at research sites in each of the four U.S. census regions. Approximately equal numbers of participants were recruited in the following smoker status groups: • Adult current smokers who intend to quit • Adult current smokers who do not intend to quit • Adult former smokers • Adult never smokers • Oversample of young adult never smokers (i.e., minimum legal purchase age to 25 years of age).
Outcomes and Measures	Perceptions of Risk from Using *IQOS* and Other Tobacco and Nicotine Products: The applicant developed and validated its own multi-item measures of the perceived health and addiction risks of using different tobacco and nicotine products. The applicant provided numerous types of supportive evidence of the measures' validity, as well as evidence on item performance in test theory analyses. The measures included separate scales for health risk and addiction risk. Perceptions were assessed after participants were given LLA materials. Comprehension of Modified Risk Claims: The applicant asked multiple-choice questions about the risks presented by *IQOS*. These items varied across studies. The applicant submitted no information on the validity of these items for assessing comprehension, and it did not administer these items in Study NOC (no claim study). For these reasons, it is difficult to use these items to assess whether viewing the modified risk claims *improved* comprehension or whether participants would have responded similarly even without viewing claims (e.g., by guessing). These items were administered after participants were given LLA materials. Intentions to Use *IQOS* and Other Products: The applicant developed its own measures for assessing people's intentions to try and use *IQOS*. While the applicant did not assess the measures' predictive validity, these measures appear generally similar to those used by other tobacco researchers (e.g., Bunnell et al., 2015; Mays et al., 2016; Kaufman et al., 2014). Intentions to use *IQOS* were assessed after participants were given LLA materials. The applicant also assessed never and former smokers' intentions to try and use e-cigarettes, combusted cigarettes, and any nicotine-containing products. Changes in Smokers' Intentions to Quit Smoking: The applicant assessed whether smokers were either seriously considering quitting smoking in the next six months or planning to quit in the next 30 days. Smokers responding affirmatively to either question were classified as intending to quit. Intentions to quit were first assessed before participants were given LLA materials. Among those classified as intending to quit, intentions to quit were assessed again after participants were given LLA materials.
Analyses	The applicant conducted descriptive analyses (e.g., calculated means and percentages for outcome variables within each study, study condition, and smoker group) as well as inferential analyses of outcomes across studies (to provide evidence about whether the outcomes differed across the four studies in a way that would suggest effects of the modified risk claims). However, we note that the applicant did not provide inferential analyses of all effects that may be of interest. For example, it did not submit inferential statistical tests of whether viewing different LLA materials affected responses to its comprehension items.

Smokers' Perceptions of Risks

Modified Risk Claims' Effects on Smokers' Perceptions of Risk. Table 12 above provides information about the applicant's measures of perceived risk. The applicant presented graphs of mean perceived health and addiction risk with 95% confidence intervals. These graphs showed that, when smokers viewed LLA materials without any of the three modified risk claims, they tended (on average) to perceive the health and addiction risks of *IQOS* as lower than those of combusted cigarettes and similar to – or slightly higher than – those of e-cigarettes. In turn, they perceived all of these products as presenting greater health and addiction risks than nicotine replacement therapy (NRT) and cessation. This was true for smokers with and without an intention to quit smoking.

The applicant also conducted analyses comparing each outcome for people who had seen LLA materials with reduced risk or exposure claims to those who had seen the materials with no claim. Table 13 shows mean perceived risk score by study. Smokers' perceptions of the absolute health risks of *IQOS* (i.e., not compared to combusted cigarettes or any other product) tended to be lower when they viewed LLA materials with the modified risk claims. This occurred for smokers with and without quit intentions, but it only reached statistical significance for smokers with no intention to quit. When smokers viewed LLA materials containing one of the three claims (compared to none of the three modified risk claims), they perceived a significantly larger difference between *IQOS* and combusted cigarettes in terms of their health risks. Again, this was true for smokers with and without quit intentions.

Table 13: Results of the Applicant's Linear Regression Analyses Comparing Perceived Health Risk Scores for *IQOS* (and Combusted Cigarettes minus *IQOS*) in Studies in which LLA Materials Contained the Modified Risk Claims ("Claims studies") vs. None of the Three Modified Risk Claims ("No claim study"), Adjusting for Sociodemographic Factors (Source: September 13, 2017 amendment, pp 103)

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.
Note: "Adjusted mean score" refers to scores on the health risk subscale of the applicant's Perceived Risk Instrument. The Claim studies included Studies RRC, RRC2, and REC, described in Table 3. The No Claim study was Study NOC. Analyses adjusted for age, sex, race, education, employment status, and type of LLA material viewed. Abbreviations: THS = *IQOS*; CC = combusted cigarettes; SNIQ = smokers with no intention to quit; SIQ = smokers with an intention to quit; FS = former smokers; NS = never smokers; LA-25 NS = oversample of young adult never smokers (i.e., legal age to 25 years-old).

Several limitations apply to the above results. First, the applicant's studies did not randomize smokers to view LLA materials with or without the three modified risk claims. Rather, the applicant conducted a separate study for LLA materials with each of the three modified risk claims (and one study with none of

the three modified risk claims). Given the lack of participant randomization, factors such as the study's timing (i.e., history effects) or participants' characteristics may account for observed differences across studies. Relatedly, given that these studies were not designed to measure the effects of the modified risk claims, the applicant did not power the studies to detect such effects. However, we believe there is a low likelihood that these other factors account for the observed results (i.e., each study used a diverse set of study locations, had a large sample size, and was completed within 14 months of the other studies). Finally, the studies did not include a manipulation check to determine whether participants noticed and read the modified risk claims (e.g., a question at the end of the study to test whether participants could recognize or recall the claim).

Despite these limitations, comparisons among the claim and no-claim studies provide relevant information. The differences observed across studies are consistent with smokers perceiving larger differences in the health risks of *IQOS* and combusted cigarettes when exposed to the modified risk claims. Even without being provided with the modified risk claims, smokers perceive (on average) that *IQOS* presents lower risks of health effects and lower risks of addiction than combusted cigarettes. Providing smokers with the modified risk claims may lower their perceptions of *IQOS*'s health risks compared to combusted cigarettes. Also, the applicant examined the studies of LLA materials with the three modified risk claims and concluded that the three studies produced similar results (i.e., similar outcomes in studies of reduced risk claim 1, reduced risk claim 2, and the reduced exposure claim; September 13, 2017 amendment, p. 102).

The Effects of SG Warnings and PMI Important Warnings on Perceptions of Risk. In studies of LLA materials with the modified risk claims, the applicant also randomly assigned smokers to view materials with SG Warnings or with PMI Important Warnings. In each study, smokers who viewed materials with PMI Important Warnings tended to rate *IQOS* as slightly higher in health risks than did smokers who viewed the materials with SG Warnings. This occurred for smokers with and without an intention to quit. However, it is unknown whether these differences were statistically significant, as the applicant conducted no inferential statistical tests of the effects of viewing materials with SG Warnings vs. Important Warnings.

Smokers' Comprehension of Claims

In addition to analyzing perceptions of risk, the applicant also asked smokers targeted questions about the risks of using *IQOS* to probe their comprehension of the modified risk claims. One limitation is that the applicant submitted no information on the validity of these comprehension items. Also, the applicant did not administer these items (described below) in the No Claim Study. Thus, it is difficult to conclude whether viewing the modified risk claims *improved* comprehension or whether people would have responded similarly even without viewing those claims (e.g., by guessing). Finally, the applicant conducted no inferential statistical tests of whether various LLA formats or Warning Label variants may have improved comprehension.

Table 11 above lists the PMI Important Warnings that correspond with each modified risk claim. In studies of LLA materials with reduced risk claims 1 and 2, the applicant asked smokers a multiple-choice question about the health effects of completely switching from combusted cigarettes to *IQOS*. The exact questions and response options varied between the two studies, but there were options for *increased risk*, *reduced risk* (defined by the applicant as correct), *the same risk*, *elimination of risk*, and *don't know* (presented in that order). In both studies, the majority of people across all smoking status groups (i.e., including current, former, and never smokers) correctly responded that completely switching to *IQOS*

reduces a smoker's risk. The most common incorrect response was that it presents *the same* risk as continuing to smoke. Viewing PMI Important Warnings instead of SG Warnings appeared to very slightly increase the rate of correct responding.

In the study of the LLA materials with the reduced exposure claim, the applicant also asked smokers a multiple-choice question about the health effects of switching completely from combusted cigarettes to *IQOS*. Here, the response options included options for *greater risk*, *reduced risk*, *has not been demonstrated to reduce risk* (defined by the applicant as correct), *eliminates risk*, and *don't know*. When viewed across all participants (current, former, and never smokers), correct responding was higher when people viewed LLA materials with PMI Important Warnings rather than SG Warnings (e.g., brochure with PMI Important Warnings: 70%; brochure with SG Warnings: 41%). Although viewing PMI Important Warnings increased correct responding, approximately one quarter of participants who viewed PMI Important Warnings still incorrectly responded that *IQOS* reduces one's risk. These results reflect the difficulty of conveying that *IQOS* reduces exposure to harmful or potentially harmful chemicals but has not been shown to be less harmful or present less risk of disease. Confirming this, as mentioned above, smokers who viewed LLA materials with the reduced exposure claim tended to rate *IQOS* as lower in health risks (on average) than combusted cigarettes, regardless of whether the LLA materials contained PMI Important Warnings or SG Warnings.

Smokers' Intentions to Use *IQOS*

The applicant developed its own measures for assessing people's intentions to use *IQOS*. The measures included two items assessing intentions to try *IQOS* and two items assessing intentions to use *IQOS* regularly, if one tries it and likes it. The applicant analyzed each of the four items separately because pre-testing revealed poor psychometric performance when the items were combined into a multi-item scale. While the applicant did not assess the items' predictive validity, the items appear generally similar to those used by other tobacco researchers (e.g., Bunnell et al., 2015; Mays et al., 2016; Kaufman et al., 2014).

The applicant examined the percentages of participants who reported that they will "definitely" or "very likely" use *IQOS*, which were the top two categories on a six-point response scale ranging from "definitely not" to "definitely" (see rationale in September 13, 2017 amendment, p. 117).

Modified Risk Claims' Effects on Intentions to Use IQOS. Many current smokers expressed an intention to use *IQOS* even when LLA materials did not include any of the three modified risk claims. For example, among smokers with no intention to quit smoking, 40-44% reported that they would "definitely" or "very likely" try *IQOS* after they viewed the brochure, *HeatSticks* pack, or direct mail communication with none of the three modified risk claims. The analogous percentages for smokers with an intention to quit ranged from 38-43%. An additional 31-39% of smokers with no intention to quit reported that they were "somewhat likely" to try *IQOS*, as did an additional 38-43% of smokers with an intention to quit. Similarly, the applicant's qualitative research also suggested high interest in *IQOS* among smokers, including those with and without an intention to quit. However, the applicant acknowledged that self-reported intentions to use products are limited in terms of predicting behavior and can overestimate the likelihood of purchase, particularly when responses are unconstrained (i.e., when participants' responses have no consequences that motivate them to reveal their true preferences). Although participants viewed price information about *IQOS* and *HeatSticks*, they were not asked to actually make a choice between the product and money.

Considerable proportions of current smokers also reported that, if they tried *IQOS* and liked it, they would "definitely" or "very likely" use it regularly, on an ongoing basis. Depending on whether people viewed the *IQOS* brochure, *HeatSticks* pack, or direct mail communication, this ranged from 26-32% (smokers with no intention to quit) and 30-33% (smokers with an intention to quit).

The applicant found no evidence that adding the reduced risk or reduced exposure claims to the LLA materials increased smokers' intentions to use *IQOS*. In studies in which smokers viewed the LLA materials with one of the three modified risk claims, intentions to use *IQOS* regularly were slightly higher among smokers with no intention to quit, and intentions were slightly lower among smokers with an intention to quit. When compared with the "no-claim" study, neither of these differences was statistically significant. However, all of the same limitations described in the above section (Smokers' Perceptions of Risk) apply here. The applicant did not power the study to test for differences in responses to LLA materials based on whether they contained modified risk claims, and participants were not randomized to view materials with or without modified risk claims. Moreover, dichotomizing the intention items may have reduced statistical power by eliminating meaningful variation in the data (e.g., Altman & Royston, 2006; MacCallum et al., 2002; Royston, Altman, & Sauerbrei, 2006; Streiner, 2002). Specifically, the applicant's analyses treated participants as equally likely to use *IQOS* if they responded either "definitely not," "very unlikely," "somewhat unlikely," or "somewhat likely." Similarly, it treated participants as equally likely to use *IQOS* if they responded either "definitely" or "very likely." If adding the modified risk claims to the LLA materials caused changes *within* these ranges, the applicant's analyses would not have detected those effects.

Effects of the SG Warnings and PMI Important Warnings on Intentions to Use IQOS. Regarding the SG Warnings and PMI Important Warnings, the applicant found little evidence that smokers' intentions to use *IQOS* differed based on whether LLA materials included SG Warnings vs. PMI Important Warnings. Visual inspection of data tables identified no consistent pattern: smokers' intentions to try and use *IQOS* were sometimes higher with SG Warnings and sometimes higher with PMI Important Warnings. However, the applicant did not submit inferential statistical tests of whether intentions differed based on the warning label.

Smokers' Changes in Intentions to Quit Smoking

The applicant's research distinguished between smokers with and without an intention to quit smoking, as mentioned above. The applicant stated that this was done in order to evaluate whether marketing *IQOS* would have negative effects on smokers who intend to quit, such as causing them to delay their quit attempts. Indeed, among smokers who were identified as having an intention to quit, 1-14% no longer reported an intention to quit smoking after viewing LLA materials with none of the three modified risk claims. In studies in which smokers viewed LLA materials with the modified risk claims, similar percentages were observed (1-12% across studies and study arms). It is unknown whether the LLA materials caused reductions in quit intentions or whether these changes are attributable to low item reliability or testing effects. The applicant did not include a control condition in which, for example, it asked smokers twice about their quit intentions with a filler task in between. Furthermore, the applicant did not reassess intention to quit among smokers who first reported no intention to quit. It is possible that a similar number of participants would have newly reported an intention to quit after viewing the materials due to low item reliability or testing effects. Also, there may have been positive effects of LLA materials (either with or without the three modified risk claims) on quit intentions. For example, LLA materials (either with or without the three modified risk claims) may have stimulated quit intentions among smokers who initially were not classified as intending to quit smoking. Evaluating this possibility

would have been informative because some smokers who currently do not want to quit smoking may change their mind if an acceptable alternative is offered.

Smokers' Likelihood of Complete Switching

The applicant's Actual Use Study, described above, suggested a high potential for dual use of *IQOS* with combusted cigarettes. However, to our knowledge, participants in the Actual Use Study only had a single opportunity to view one of the reduced risk claims, and this was one week prior to their first opportunity to use *IQOS*. Specifically, participants viewed the *IQOS* brochure with reduced risk claim 1, then they completed one week of baseline reporting of their cigarette smoking, and then they were provided with the *IQOS* and *HeatSticks* for the start of their six-week observational period. Also, as in the applicant's other studies of its proposed MRTPs, there was no manipulation check to ensure that participants noticed and read the modified risk claim. This is noteworthy if the modified risk claim would have either (1) provided a reason to quit among smokers who were not previously considering quitting, or (2) provided extra motivation to those already considering quitting. Moreover, the applicant provided the *HeatSticks* to participants in unbranded packs with none of the three modified risk claims, missing an opportunity to re-expose and remind participants of the reduced risk information as it proposes to do in its marketing.

Summary and Conclusions

The applicant's LLA materials include information that may appeal to current smokers, such as statements that the product uses "real tobacco" and has similar attributes to combusted cigarettes. Together, the modified risk claims, LLA materials, and product attributes may help communicate to current smokers that *IQOS* is a tobacco product and perhaps that it is similar enough to combusted cigarettes to warrant trial among smokers who have not switched to currently-available electronic devices. One potential shortcoming of the modified risk claims is that they do not provide information about the health effects of *partially* switching from combusted cigarettes to *IQOS*, information that may affect how consumers use the product. Also, the applicant did not test smokers' comprehension of whether they could reduce their health risks by partially switching to *IQOS*.

In the applicant's research, many current smokers expressed an intention to use *IQOS* and, on average, perceived *IQOS* as presenting lower risks of health effects and addiction than combusted cigarettes. Adding the modified risk claims to the LLA materials did not appear to affect smokers' intentions to use *IQOS* (based on the applicant's analysis) but did seem to reinforce their perceptions of *IQOS* as lower in health risks than combusted cigarettes. All of these findings applied similarly to current smokers with and without an intention to quit smoking. We do note that there were limitations in the applicant's research, such as the lack of manipulation checks to ensure that smokers read the modified risk claims, and the analysis of intention items in a way that may have reduced statistical power to detect effects of viewing the modified risk claims.

Regarding SG Warnings and PMI Important Warnings, the applicant provided little evidence that displaying PMI Important Warnings, rather than SG Warnings, influenced smokers' intentions to use *IQOS* or their perceptions of risk. In some cases, viewing PMI Important Warnings improved performance on items purporting to assess claim comprehension. Most notably, when viewing LLA materials with the reduced exposure claim, viewing the PMI Important Warning increased the likelihood of selecting the response (defined by the applicant as correct) that scientific studies had not demonstrated a health benefit of switching from combusted cigarettes to *IQOS*. However, responses to

the applicant's perceived risk measure suggest that, on average, participants perceived *IQOS* as lower in health risk than combusted cigarettes even when viewing LLA materials with the PMI Important Warning. Compared to viewing SG Warnings, smokers who viewed the PMI Important Warning appeared to rate the risks of using *IQOS* only slightly higher, but still below the risks of combusted cigarettes. The applicant did not test LLA materials that included both the SG Warnings and PMI Important Warnings.

Several of the applicant's studies shed light on the likelihood that current smokers would dual use *IQOS* and combusted cigarettes. As mentioned above, intentions to try and use *IQOS* were high among current users both with and without an intention to quit smoking. Among smokers who originally expressed an intention to quit smoking, the applicant found that a subset (1-14%) no longer reported intending to quit smoking after viewing LLA materials. However, given the lack of a control group, it is unknown whether viewing the LLA materials *caused* this change. Also, the majority (86-99%) did continue to report an intention to quit smoking, in addition to their intention to use *IQOS*. Finally, the applicant did not examine whether smokers who initially did not report an intention to quit smoking did so after viewing the LLA materials. The applicant's Actual Use Study found high levels of dual use, but this was among participants who may not have been highly motivated to purchase *IQOS*, and the study did not appear to emphasize the modified risk claims to encourage complete switching. Understanding the population health impact of the *IQOS* system and *Heatsticks* entails considering, among other things, smokers with and without an intention to quit, and their likelihood of complete switching, significantly cutting down on smoking, or continuing to smoke at a level that does not reduce harm.

III. EVIDENCE RELATED TO THE IMPACT ON NON-USERS

Evaluating the population health impact of the proposed MRTPs as actually used by consumers requires assessing the potential for initiation by current non-users of tobacco products, including young people. Here, we review the impact of the proposed MRTPs on non-smokers, the population studied by the applicant. In particular, the applicant conducted research studies to assess responses to *IQOS* among young adult never smokers (aged 18-25 years), other adult never smokers, and adult former smokers. Examining outcomes separately for young adult never smokers is useful because young people are at higher risk of tobacco product trial and initiation than are older individuals. The applicant also conducted research on non-smokers' use of heat-not-burn products in Japan, where *IQOS* is on the market.

LLA Materials and Product Attributes

As mentioned above, the applicant developed LLA materials, including an *IQOS* brochure, *HeatSticks* pack, and direct mail communication. The brochure included a statement that the product is for smokers who want to continue using tobacco and is not for ex-smokers or non-smokers. The applicant stated that it will also use other channels to inform smokers about its product, such as print and digital ads, age-restricted digital and social media channels, and package inserts and onserts on combusted cigarette packs. FDA notes that, in other countries, the applicant has also sold the product and provided information about the product in *IQOS* branded stores (Kim, 2017).

The applicant's proposed LLA materials included information to distinguish *IQOS* from e-cigarettes. This includes statements about the product using "real tobacco" and having attributes similar to combusted cigarettes (e.g., a similar draw, the same number of puffs). *HeatSticks* also appear similar to combusted cigarettes insofar as they contain a filter and tobacco plug wrapped in paper, potentially further

distinguishing it from an e-cigarette. *HeatSticks* would be marketed under the Marlboro brand name, which consumers may associate with combusted cigarettes. As a cigarette product, *HeatSticks* cannot be marketed with characterizing flavors aside from menthol (e.g., fruit, vanilla, candy), which is a commonly-cited reason for never smokers' use of e-cigarettes (Berg, 2016; Kong et al., 2015). Such attributes of *IQOS*, along with its use of "real tobacco," may reduce its appeal to people who do not currently smoke.

In the applicant's research on LLA materials, it informed participants that the *IQOS* device will be sold for $79.99. It also described the price of *HeatSticks*, which varied by study location to reflect differences in tobacco prices (i.e., across all studies, from $4.92 per pack in Missouri to $9.67 in Massachusetts). The high price of the *IQOS* device may discourage purchase by non-users of tobacco, given that tobacco product prices have been shown to influence demand for the products (USDHHS, 2000).

Modified Risk Claims, PMI Important Warnings, and SG Warnings

Table 10 above shows the modified risk claims in the LLA and claim assessment studies. Table 11 shows the PMI Important Warnings and the currently mandated Surgeon General (SG) Warnings.

Non-Smokers' Perceptions of Risk

As noted above, the applicant developed and validated its own multi-item measures of the perceived health and addiction risks of using tobacco products (see Table 12). It presented graphs of mean perceived health and addiction risks with 95% confidence intervals.

The applicant found that, after former and never smokers viewed the LLA materials with none of the three modified risk claims, they tended (on average) to rate *IQOS* as presenting lower health risks than combusted cigarettes. They also tended to rate the addiction risk of *IQOS* as lower than that of combusted cigarettes. Former and never smokers appeared to rate the health and addiction risks of *IQOS* similarly to how they rated e-cigarettes or slightly higher. These patterns also all held for young adult never smokers.

The applicant also conducted analyses comparing people who viewed LLA materials with reduced risk or exposure claims to those who viewed the materials without those modified risk claims. Former and never smokers' perceptions of the absolute health risks of *IQOS* (i.e., not compared to combusted cigarettes) tended to be lower when they viewed LLA materials with the modified risk claims, although this difference did not reach statistical significance for young adult never smokers. Former and never smokers who viewed LLA materials with the modified risk claims also tended to rate *IQOS* as lower in *addictiveness* than did those who viewed the LLA materials with none of the three modified risk claims. When former and never smokers viewed LLA materials containing one of the three modified risk claims (compared to none of them), they perceived a significantly larger difference between *IQOS* and combusted cigarettes in terms of their health risks. This was also true for young adult never smokers.

As a caveat, we note that the applicant did not randomize former and never smokers to view LLA materials with or without modified risk claims. Rather, it conducted a separate study for LLA materials with each of the three modified risk claims (or none of the three modified risk claim). Given the lack of randomization, factors such as the study's timing (i.e., history effects) or participants' characteristics may account for observed differences. Also, given that the applicant did not design these studies to measure the effects of the claims, it did not power the studies to detect such effects. However, we

believe there is a low likelihood that these factors account for the observed results (i.e., each study used a diverse set of study locations, had a large sample size, and was completed within 14 months of the other studies).

Non-Smokers' Comprehension of Claims

In addition to asking questions about perceived risk, the applicant also assessed comprehension of its modified risk claims by using multiple-choice questions about the risks of using IQOS. One limitation is that the applicant did not administer these questions (described below) in the No Claim Study, and it did not submit information about how comprehension items were developed and validated, if at all. Thus, it is difficult to conclude whether viewing the modified risk claims *improved* comprehension or whether people would have responded similarly even without viewing claims (e.g., by guessing).

In the applicant's study of LLA materials with reduced risk claim 1 (see Table 10), participants were asked about the potential health effects of using *IQOS*, with response options including: "None – it is totally safe," "It is completely unknown," "It is more harmful than combusted cigarettes," "It can harm your health" (defined by the applicant as correct), and "Don't know". Among those who viewed the *IQOS* brochure with PMI Important Warnings, correct responding to this item was 90% among former smokers, 93% among never smokers, and 96% among young adult never smokers. Similarly, for those who viewed a *HeatSticks* pack with PMI Important Warnings, correct responding was 89% among former smokers, 92% among never smokers, and 94% among young adult never smokers. Finally, for those who viewed the direct mail communication with PMI Important Warnings, correct responding was 90% among former smokers, 92% among never smokers, and 90% among young adult never smokers. The applicant did not ask this question for participants who had viewed LLA materials with SG Warnings.

Non-Smokers' Intentions to Use IQOS

As noted above, the applicant developed its own measures for assessing people's intentions to try and use *IQOS*. The measures included two items assessing intentions to try *IQOS* and two items assessing intentions to use *IQOS* regularly, if one tries it and likes it. The applicant analyzed each of the four items separately because pre-testing revealed poor psychometric performance when the items were combined into a multi-item scale. The applicant examined the percentages of participants who reported that they will "definitely" or "very likely" use *IQOS*, which were the top two categories on a six-point response scale ranging from "definitely not" to "definitely" (see rationale in September 13, 2017 amendment, pp. 117-118).

Using this approach, the applicant found that few non-smokers expressed an intention to try *IQOS* among those who viewed the LLA materials without the modified risk claims. Also, it found no evidence that adding the reduced risk or reduced exposure modified risk claims increased the proportion of non-smokers' intending to try *IQOS*.

When never smokers viewed LLA materials with none of the three modified risk claims, 0-1% said they would "very likely" or "definitely" try *IQOS*. In the three studies in which never smokers viewed the modified risk claims, the comparable percentages were 0-1% (reduced risk claim 1), 0-1% (reduced risk claim 2), and 0-2% (reduced exposure claim). Intentions to try *IQOS* appear higher when including the percentages of never smokers who responded that they would "somewhat likely" try *IQOS*. However, these percentages do not appear to be any higher among people who viewed LLA materials with the modified risk claims rather than without those claims. When viewing LLA materials with none of the

three modified risk claims, 4-7% of never smokers said they would "somewhat likely" try *IQOS*. When viewing materials with modified risk claims, the percentages were 2-6% (reduced risk claim 1), 1-7% (reduced risk claim 2), and 2-5% (reduced exposure claim).

When young adult never smokers viewed LLA materials with none of the three modified risk claims, 0-1% said they would "very likely" or "definitely" try *IQOS*. This was similar to responses when LLA materials contained one of the three modified risk claims: 0-1% (reduced risk claim 1), 0-1% (reduced risk claim 2), and 0-2% (reduced exposure claim). Percentages responding "somewhat likely" were: 7-10% (no claim), 2-6% (reduced risk claim 1), 1-10% (reduced risk claim 2), and 3-5% (reduced exposure claim). Again, this suggests the modified risk claims did not increase young adult never smokers' intentions to try *IQOS*.

Intentions were somewhat higher among former smokers than never smokers. However, the applicant found no evidence that more former smokers intended to try *IQOS* when provided with the modified risk claims. When former smokers viewed LLA materials with none of the three modified risk claims, 5-7% said they would "very likely" or "definitely" try *IQOS*. When the LLA materials contained the modified risk claims, the comparable percentages were 3-10% (reduced risk claim 1), 2-8% (reduced risk claim 2), and 3-6% (reduced exposure claim). When examining the percentages of former smokers responding that they would "somewhat likely" try *IQOS*, there was also little evidence that the modified risk claims increased the proportion of former smokers' intending to use. Specifically, when LLA materials contained none of the three modified risk claims, 11-20% of former smokers said they would "somewhat likely" try *IQOS*, compared to 18-19% for reduced risk claim 1, 10-19% for reduced risk claim 2, and 9-15% for the reduced exposure claim.

The applicant conducted inferential statistical analyses comparing people who had seen LLA materials with reduced risk or exposure claims to those who had seen the materials with none of the three modified risk claims. The applicant conducted these analyses on intentions to try *IQOS* (discussed above), intentions to try *IQOS* if offered by a friend, and intentions to use *IQOS* regularly, if they try it and like it.[13] Table 14 presents the results. As shown, adjusted estimates of intentions to try and use *IQOS* were similar across studies in which people viewed LLA materials with one of the three modified risk claims vs. none of the three modified risk claims. The only significant difference was that young adult never smokers were significantly *less* likely to intend to use *IQOS* regularly in studies in which they viewed LLA materials with one of the three modified risk claims rather than with none of them.

Table 14 can also be used to examine intentions to try and use *IQOS* across each smoker group. As shown, intentions were much lower among non-smokers (i.e., former smokers, never smokers, young adult never smokers) than among current smokers with and without an intention to quit smoking.

For comparison, the applicant also asked former smokers about their intentions to use e-cigarettes regularly, and asked never smokers about their intentions to try e-cigarettes. Former smokers' intentions to use *IQOS* appeared to be similar to or somewhat lower than their intentions to use e-cigarettes, although the applicant provided no statistical tests of these differences. Never smokers' intentions to try *IQOS* appeared to be similar to their intentions to try e-cigarettes, although again the applicant provided no statistical tests of potential differences.

[13] The applicant did not submit inferential statistical analyses of its fourth intent to use variable, which asked participants how soon they will begin using *IQOS*, if they try it and like it.

Table 14: The Results of the Applicant's Statistical Analyses Comparing Intentions to Try and Use *IQOS* in Studies Exposing Participants to LLA Materials with Modified Risk Claims ("Claims studies") vs. None of the Modified Risk Claims ("No Claim study"), Adjusting for Sociodemographic Factors (except where noted) (Source: September 13, 2017 amendment, pp 104-105)

Object	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)
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).

Note: Adjusted percentages refer to the percentages of participants responding that they "definitely" or "very likely" will try or use *IQOS*. The Claim studies included Studies RRC, RRC2, and REC, described in Table 3. The No Claim study was Study NOC. Analyses adjusted for age, sex, race, education, employment status, and type of LLA material viewed. Abbreviations: THS = *IQOS*; SNIQ = smokers with no intention to quit; SIQ = smokers with an intention to quit; FS = former smokers; NS = never smokers; LA-25 NS = oversample of young adult never smokers (i.e., age 18-25 years).

These findings are subject to several limitations. As mentioned above, the applicant's studies were not designed or powered to compare intentions to use *IQOS* based on whether people did or did not view modified risk claims. People were not randomly assigned to view LLA materials with or without one of the three modified risk claims. Also, as mentioned, the modified risk claims were displayed in small font and the studies included no manipulation checks to ensure that participants read the claims. Moreover, dichotomizing the intention items (i.e., only examining changes in the top-two response categories) may have reduced statistical power by eliminating meaningful variation in the data (e.g., Streiner, 2002), although the applicant did provide reasons for preferring its dichotomization approach (September 13, 2017 amendment, p. 117-118). It is worth noting that the applicant conducted qualitative and quantitative claim development studies suggesting that non-smokers had low or no interest in *IQOS* when actively considering the modified risk claims. Also, the applicant's findings regarding levels of intent to use are generally consistent with national surveys of non-smokers' interest in hypothetical tobacco products advertised as less harmful than other products (O'Brien et al., 2017; Pearson et al., 2017).

Product Uptake among Non-Smokers

The applicant conducted two cross-sectional studies to monitor the prevalence of heat-not-burn product use by adult non-smokers (age 20 or older) in Japan, a country where *IQOS* is on the market. During the first one to two years after *IQOS* went on the Japanese market in 2014, the applicant reports that heat-not-burn product use by adult former and never smokers was low (1.5% among former smokers and 1.2% among never smokers). However, these findings are from an online panel that was not selected to be representative of Japan, let alone the U.S., which has a different tobacco product marketplace, tobacco use norms, and culture.

Given the applicant's finding that non-smokers in the U.S. viewed *IQOS* similarly to e-cigarettes in terms of health and addiction risks, and given that non-smokers had relatively similar intentions to use *IQOS* and e-cigarettes, it may be worth noting trends of e-cigarette use by adult and youth non-smokers in the U.S. An analysis of 2014 U.S. data found that it was very uncommon for adult never smokers and long-term quitters to report currently using e-cigarettes either some days or every day (never smokers: 0.4%; former smokers who had quit 4+ years ago: 0.8%; Delnevo et al., 2016). However, e-cigarettes are the type of tobacco product that was most commonly used in the past 30 days by middle and high school students in 2016 (4.3% among middle and 11.3% of high school students; Jamal et al., 2017).

IQOS has attributes that non-smokers may perceive differently than those of e-cigarettes. As noted above, the product is proposed to be labeled as "real tobacco," and the applicant's qualitative research suggested that this and other references to tobacco (e.g., "tobacco heating system") helped convey that using the product presents tobacco-related health risks. Also, *HeatSticks* have attributes similar to combusted cigarettes, such as a tobacco plug wrapped in paper. Given that the *Heatsticks* are cigarettes, the *HeatSticks* cannot contain a characterizing flavor aside from tobacco or menthol (e.g., fruit, vanilla, candy), which is a commonly-cited reason for non-smokers' use of e-cigarettes (Berg, 2016; Kong et al., 2015). The high price of the *IQOS* device also distinguishes it from e-cigarettes and may decrease the likelihood of young non-smokers using it (beyond a trial with friends), but price may decrease over time. Unlike some e-cigarette products, the *HeatSticks* in these applications all contain nicotine, and the applicant's studies suggest that *IQOS* may have an abuse potential that is similar to combusted cigarettes (see Section II.A, Clinical and Behavioral Pharmacology). These differences and other device attributes could influence non-smokers' likelihood of continuing to use the product following initial experimentation. Finally, we do not know whether people will view *IQOS* as similar to e-cigarettes in terms of social acceptability and other attributes that could lead to different patterns of use among former and never smokers.

Summary and Conclusions

The applicant provided evidence that few adult never and former smokers intended to try and use *IQOS* after viewing the LLA materials, although intentions were slightly higher among people who were former smokers. Also, the applicant found no evidence of more young adult never smokers intending to use, compared to never smokers overall. There was no evidence that adding modified risk claims to the LLA materials increased intentions to use the product among non-smokers – including adult former smokers, adult never smokers, and young adult never smokers – although it may have reduced their perceptions of the health risks of using *IQOS* compared to combusted cigarettes. Also, viewing the modified risk claims may have reduced former and never smokers' perceptions of the addictiveness of using *IQOS*. We note that there were some limitations in the applicant's research, such as the lack of manipulation checks to ensure that participants read the modified risk claims, and the analysis of

intention items in a way that may have reduced statistical power to detect effects of viewing the modified risk claims.

We would expect to observe some level of trial and experimentation with *IQOS* among non-smokers, including youth. This is based on public health surveillance of e-cigarette use, which adult non-smokers perceive similarly to *IQOS* in terms of health risks and addictiveness. However, comparisons with e-cigarette use are limited insofar as non-smokers may perceive *IQOS* differently in other respects (e.g., social acceptability) and may use it differently. We expect that some aspects of *IQOS* and its LLA materials may dissuade trial and initiation among non-smokers (e.g., its "tobacco" associations, limited characterizing flavors, high stated price). Among non-smokers who do experiment with *IQOS*, the likelihood of nicotine dependence may be elevated given that the *HeatSticks* all contain nicotine, unlike some e-cigarettes.

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Appendix A: Statutory Requirements for Modified Risk Tobacco Products (MRTPs) and Overview of FDA Review Process

The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines "modified risk tobacco product" (MRTP) as any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products [Section 911(b)(1)]. This means any tobacco product:

1) the label, labeling, or advertising of which represents, either implicitly or explicitly, that:
   a) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
   b) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
   c) the tobacco product or its smoke does not contain or is free of a substance;
2) the label, labeling, or advertising of which uses the descriptors "light", "mild", "low", or similar descriptors; or
3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [Section 911(b)(2)]

Before an MRTP can be introduced into interstate commerce, an order from FDA under Section 911(g) must be issued and in effect with respect to the tobacco product.

To request such an order from FDA, a person must file a modified risk tobacco product application (MRTPA) under Section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled "Modified Risk Tobacco Product Applications," which discusses the submission of applications for an MRTP under Section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (https://www.congress.gov/111/plaws/publ31/PLAW-111publ31.pdf).

Section 911(g) of the FD&C Act describes the demonstrations applicants must make to obtain an order from FDA. Sections 911(g)(1) and (2) of the FD&C Act set forth two alternative bases for FDA to issue an order.

Risk Modification Order: FDA shall issue an order under Section 911(g)(1) of the FD&C Act (risk modification order) only if it determines the applicant has demonstrated that the product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and

- 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.

FDA may require, with respect to tobacco products for which risk modification orders are issued, that the product comply with requirements relating to advertising and promotion of the tobacco product (Section 911(h)(5) of the FD&C Act).

Exposure Modification Order: Alternatively, for products that cannot receive a risk modification order from FDA under Section 911(g)(1) of the FD&C Act, FDA may issue an order under Section 911(g)(2) of the FD&C Act (exposure modification order) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances that are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to similar types of tobacco products on the market, unless such increases are minimal and the reasonably likely overall impact of product use remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful or presents or has been demonstrated to present less of a risk of disease than one or more other commercially-marketed tobacco products; and
- Issuance of the exposure modification order 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.

In evaluating the benefit to health of individuals and of the population as a whole under Sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the MRTP presents to individuals;

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the MRTP;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP;
- The risks and benefits to persons from the use of the MRTP compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and file it. In general, after filing an application, FDA begins substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee (TPSAC). FDA intends to review and act on a complete MRTPA within 360 days of FDA filing an application. An order authorizing an MRTP refers to a specific product, not an entire class of tobacco products (e.g. all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is for a fixed period of time that will be determined by FDA and specified in the order. To continue to market an MRTP after the set term, an applicant would need to seek renewal of the order and FDA would need to determine that the findings continue to be satisfied. Also, if at any time FDA determines that it can no longer make the determinations required for an MRTP order, FDA is required to withdraw the order. Before FDA withdraws an MRTP order, it will provide an opportunity for an informal hearing as required under the law.

Appendix B: Regulatory History for *IQOS* System with *HeatSticks* MRTPAs

On December 5, 2016, FDA received applications from Philip Morris Products S.A. (PMP S.A.). According to the applications, PMP S.A. is requesting modified risk tobacco product (MRTP) orders under Sections 911(g)(1) and 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for the following submissions listed by FDA Submission Tracking Numbers:

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

FDA also received the following amendments:

- January 25, 2017, containing clarification of product configurations, modified risk claims, and warnings
- February 8, 2017, containing clarification of product configurations
- March 16, 2017, containing responses to the March 2, 2017 Advice and Information Request letter
- May 5, 2017, containing re-submitted data previously provided in the March 16, 2017 amendment, with additional study reports and data
- June 8, 2017, containing manufacturing site details
- June 21, 2017, containing a letter of authorization for a tobacco product master file and re-submitted images for the *IQOS* device package
- June 30, 2017, containing revised manufacturing schedules
- August 10, 2017, containing confirmation of manufacturing facility inspection dates
- August 31, 2017, containing a request for additional time to respond to the August 4, 2017 Advice and Information Request letter, and confirmation of battery samples sent to the Winchester Engineering Analytical Center
- August 31, 2017, containing clarification of activities at (b) (4)
- September 6, 2017, containing responses to the August 4, 2017 Advice and Information Request letter
- September 13, 2017, containing responses to the August 4, 2017 Advice and Information Request letter
- November 1, 2017, containing withdrawal of certain case report forms and certain raw data files
- November 16, 2017, containing additional information for response to the August 4, 2017 Advice and Information Request letter
- December 8, 2017, containing additional information and data from recently completed studies

Pursuant to Section 911(e) of the FD&C Act, FDA is required to make PMP S.A.'s MRTPAs available to the public (except matters in the applications that are trade secrets or are otherwise confidential, commercial information) and to request comments by interested persons on the information contained in the applications and on the label, labeling, and advertising accompanying the applications. The notice of availability for these applications appeared in the Federal Register of June 15, 2017. In that notice, FDA announced the availability for public comment of the first batch of application documents and explained that it will post the application documents in batches on a rolling basis as they are redacted in

accordance with applicable laws.[14] On November 21, FDA issued a Federal Register notice extending the comment period; FDA intends to issue another notice in the Federal Register announcing when the comment period will close, which will be at least 30 days from the date the last batch of documents from the MRTPAs (including amendments) are posted. FDA has received comments and expects to continue receiving comments, and FDA is reviewing and will continue to review them.

[14] FDA anticipates making amendments received thus far and any amendments received in the future publicly available as they are redacted.

Appendix C: Comparison of *IQOS* HPHC Levels to the 3R4F Reference Cigarette and 31 Combusted Cigarettes on the U.S. market

HPHC	Unit	3R4F		31 US Brands		MR0000059					MR0000060					MR0000061				
		AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]
Weight	mg	1109				777					811					811				
Puff Count		10.6				12					12					12				
TPM	mg	42.3	23.2			50.8	39.08	↑68.1			55.7	45.7	↑96.4			53.6	45.8	↑97.1		
Tar	mg	25.5	14.0	30.6	15.3	21.3	16.38	↑16.4	↑7.1		20.1	16.5	↑17.6	↑7.7		16.9	14.4	↑3.1	↓5.6	
Nicotine	mg	1.82	1.00	2	1.00	1.3	1.00				1.22	1.00				1.17	1.00			
Glycerol	mg	2.16	1.19			4.95	3.81	↑221			4.41	3.61	↑205			4.37	3.74	↑215		
Water	mg	15.0	8.24	15.6	7.8	28.2	21.7	↑163	↑178		34.4	28.2	↑242	↑262		35.5	30.3	↑268	↑289	
Menthol	mg	ND				ND					1.77	1.45	Added			2.42	2.07	Added		
1,3-butadiene	µg	91.5	50.3	117	58.5	0.213	0.164	↓99.7	↓99.7	357	0.221	0.181	↓99.6	↓99.7	323	0.225	0.192	↓99.6	↓99.7	304
1-amino-naphthalene	ng	21.2	11.6	34.4	17.2	0.04	0.031	↓99.7	↓99.8	559	0.042	0.034	↓99.7	↓99.8	500	0.059	0.050	↓99.6	↓99.7	341
2-amino-naphthalene	ng	17.3	9.51	21.2	10.6	0.02	0.015	↓99.8	↓99.9	689	0.026	0.021	↓99.8	↓99.8	497	0.033	0.028	↓99.7	↓99.7	376
3-amino-biphenyl	ng	4.57	2.51			0.007	0.005	↓99.8			0.008	0.007	↓99.7			0.008	0.007	↓99.7		
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng	263	145	129	64.5	7.7	5.92	↓95.9	↓90.8	11	7.22	5.92	↓95.9	↓90.8	11	5.86	5.01	↓96.5	↓92.2	13
4-amino-biphenyl	ng	3.14	1.73	3.4	1.7	0.007	0.005	↓99.7	↓99.7	316	0.01	0.008	↓99.5	↓99.5	207	0.010	0.009	↓99.5	↓99.5	199
Acetaldehyde	µg	1637	899	1435	717.5	194	149	↓83.4	↓79.2	5	206	169	↓81.2	↓76.5	4	187	160	↓82.2	↓77.7	4
Acetamide	µg	13.7	7.53			2.95	2.27	↓69.9			3.07	2.52	↓66.6			3.08	2.63	↓65.0		
Acetone	µg	655	360			30.8	23.7	↓93.4			36	29.5	↓91.8			33.9	29.0	↓91.9		
Acrolein	µg	157	86.3	158	79	8.25	6.35	↓92.6	↓92.0	12	9.26	7.59	↓91.2	↓90.4	10	8.49	7.26	↓91.6	↓90.8	11
Acrylamide	µg	4.72	2.59			1.54	1.18	↓54.3			1.58	1.30	↓50.1			1.64	1.40	↓46.0		
Acrylonitrile	µg	22.3	12.3	24.1	12.05	0.135	0.104	↓99.2	↓99.1	116	0.129	0.106	↓99.1	↓99.1	114	0.127	0.109	↓99.1	↓99.1	111

HPHC	Unit	3R4F		31 US Brands		MR0000059					MR0000060					MR0000061				
		AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]
Ammonia	µg	30.9	17.0	32	16	11.4	8.77	↓48.3	↓45.2	2	10.9	8.93	↓47.4	↓44.2	2	10.1	8.63	↓49.2	↓46.0	2
Arsenic (As)	ng	ND	ND			ND	ND				ND	ND				ND	ND			
Benz[a]anthracene	ng	26.7	14.7			2.44	1.88	↓87.2			1.88	1.54	↓89.5			1.95	1.67	↓88.6		
Benzene	µg	76.5	42.0	86.2	43.1	0.474	0.365	↓99.1	↓99.2	118	0.453	0.371	↓99.1	↓99.1	116	0.429	0.367	↓99.1	↓99.1	118
Benzo[a]pyrene	ng	13.4	7.36	15	7.5	0.736	0.566	↓92.3	↓92.5	13	0.571	0.468	↓93.6	↓93.8	16	0.627	0.536	↓92.7	↓92.9	14
Butyraldehyde	µg	80.7	44.3			20.4	15.7	↓64.6			21.1	17.3	↓61.0			18.2	15.6	↓64.9		
Cadmium (Cd)	ng	94.1	51.7			ND	ND				ND	ND				0.291	0.249	↓99.5		
Carbon monoxide (CO)	mg	30.8	16.9	29	14.5	0.373	0.287	↓98.3	↓98.0	51	0.333	0.273	↓98.4	↓98.1	53	0.48	0.410	↓97.6	↓97.2	35
Catechol	µg	92.6	50.9		0	13.8	10.6	↓79.1			12.2	10	↓80.3			13.9	11.9	↓76.6		
Chromium (Cr)	ng	ND	ND		0	ND	ND				ND	ND				ND	ND			
Crotonaldehyde	µg	49.4	27.1	50.9	25.45	ND	ND				ND	ND				ND	ND			
Dibenz[a,h]anthracene	ng	ND	ND			ND	ND				ND	ND				ND	ND			
Ethylene Oxide	µg	16.7	9.18			ND	ND				ND	ND				0.138	0.118	↓98.7		
Formaldehyde	µg	85.2	46.8	98.8	49.4	13.9	10.7	↓77.2	↓78.4	5	14.7	12.0	↓74.3	↓75.6	4	9.07	7.75	↓83.4	↓84.3	6
Hydrogen cyanide (HCN)	µg	346	190			ND	ND				ND	ND				2.94	2.51	↓98.7		
Hydroquinone	µg	94.9	52.1			6.45	4.96	↓90.5			5.51	4.52	↓91.3			6.3	5.38	↓89.7		
Isoprene	µg	921	506	1032	516	1.6	1.23	↓99.8	↓99.8	419	1.52	1.25	↓99.8	↓99.8	414	1.32	1.13	↓99.8	↓99.8	457
Lead (Pb)	ng	30.9	17.0			2.12	1.63	↓90.4			1.92	1.57	↓90.7			ND	ND			
m-Cresol	µg	4.2	2.31			0.042	0.032	↓98.6			0.029	0.024	↓99.0			0.025	0.021	↓99.1		
Mercury (Hg)	ng	3.8	2.09			1.5	1.15	↓44.7			1.32	1.08	↓48.2			2.01	1.72	↓17.7		
Methyl-ethyl-ketone (MEK)	µg	173	95.1			10.2	7.85	↓91.7			13.7	11.2	↓88.2			7.04	6.02	↓93.7		
Nickel (Ni)	ng	ND	ND			ND	ND				ND	ND				ND	ND			
Nitric oxide (NO)	µg	485	266			12.2	9.38	↓96.5			12.1	9.92	↓96.3			12.3	10.5	↓96.1		
Nitrobenzene	µg	ND	ND			ND	ND				ND	ND				ND	ND			
Nitrogen oxides (NOx)	µg	538	296			13.8	10.6	↓96.4			13.6	11.1	↓96.2			13.5	11.5	↓96.1		
N-nitrosoanabasine	ng	31.6	17.4			2.24	1.72	↓90.1			2.23	1.83	↓89.5			2.35	2.01	↓88.4		

HPHC	Unit	3R4F		31 US Brands		MR0000059					MR0000060					MR0000061				
		AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]	AVG (/cig)	AVG (/mg nicotine)	% Δ 3R4F[a]	% Δ US brands[a]	# of heatsticks equal 1 US brand[a]
(NAB)																				
N-nitrosoanatabine (NAT)	ng	274	151			13.9	10.7	↓92.9			12.7	10.4	↓93.1			16.3	13.9	↓90.7		
N-Nitrosonornicotine (NNN)	ng	273	150	179	89.5	9.44	7.26	↓95.2	↓91.9	12	7.23	5.93	↓96.0	↓93.4	15	8.45	7.22	↓95.2	↓91.9	12
o-Cresol	µg	4.79	2.63			0.075	0.058	↓97.8			0.056	0.046	↓98.3			0.052	0.044	↓98.3		
o-Toluidine	ng	101	55.5			1.08	0.831	↓98.5			0.946	0.775	↓98.6			1.03	0.880	↓98.4		
p-Cresol	µg	9.83	5.40			0.072	0.055	↓99.0			0.052	0.043	↓99.2			0.043	0.037	↓99.3		
Phenol	µg	16.5	9.07			1.47	1.13	↓87.5			1.08	0.885	↓90.2			1.09	0.932	↓89.7		
Propionaldehyde	µg	114	62.6			10.9	8.38	↓86.6			11.8	9.67	↓84.6			11.3	9.66	↓84.6		
Propylene Oxide	ng	948	521			140	108	↓79.3			119	97.5	↓81.3			114	97.4	↓81.3		
Pyrene	ng	83	45.6			7.78	5.98	↓86.9			5.94	4.87	↓89.3			8.58	7.33	↓83.9		
Pyridine	µg	28.3	15.5			6.14	4.72	↓69.6			5.85	4.80	↓69.2			5.44	4.65	↓70.1		
Quinoline	µg	0.432	0.237			ND	ND				ND	ND				ND	ND			
Resorcinol	µg	1.84	1.01			ND	ND				ND	ND				ND	ND			
Selenium (Se)	ng	ND	ND			1.37	1.05				1.13	0.926				ND	ND			
Styrene	µg	12.7	6.98			0.58	0.446	↓93.6			0.448	0.367	↓94.7			0.475	0.406	↓94.2		
Toluene	µg	127	69.8	149	74.5	1.48	1.14	↓98.4	↓98.5	65	1.29	1.06	↓98.5	↓98.6	70	1.19	1.02	↓98.5	↓98.6	73
Vinyl chloride	ng	96	52.7			ND	ND				ND	ND				ND	ND			

ND – not detected

[a] comparison made using per mg nicotine values

Data Sources: NS308-H, NS309-H, and NS336-H in MR0000066 and SR1_Q08-A1_HPHC-MarketMap-Results.xls