U.S. Food & Drug Administration
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PMTA Coversheet: Technical Project Lead Review (TPL)

SUBMISSION INFORMATION			
Applicant	Philip Morris Products S.A.		
Product Manufacturer	Philip Morris Products S.A.		
Submission Date	05-15-2017	**FDA Receipt Date**	05-15-2017
Primary STN(s)	PM0000424	Marlboro Heatsticks[1]	
	PM0000425	Marlboro Smooth Menthol Heatsticks[1]	
	PM0000426	Marlboro Fresh Menthol Heatsticks[1]	
	PM0000479	IQOS System Holder and Charger[1]	
Cross-referenced Submission(s)	**Cross-referenced STN**	**Primary STN(s)**	
	MR0000059	APPLIES TO PM0000424-PM0000426, PM0000479	
	MR0000060		
	MR0000061		
	MR0000133		
	MF0000013		
	MF0000243		
	MF0000264		

[1] May be sold individually or as co-packaged product.

Amendments			
Amendment STN	**Primary STN**	**Description**	**FDA Receipt Date**
PM0000440	PM0000424-426, PM0000479	Resubmitted label images	06-21-2017
PM0000443	PM0000424-426, PM0000479	Request for A/I Request letter response extension; confirmed battery samples	08-31-2017
PM0000457	PM0000424-426, PM0000479	Response to 11/22/17 A/I Request letter	12-26-2017
PM0000458	PM0000424-426, PM0000479	Response to 11/22/17 A/I Request letter	12-22-2017
PM0000461	PM0000424-426, PM0000479	Ongoing study data	12-08-2017
PM0000464	PM0000424-426, PM0000479	Response to 3/2/18 EA A/I Request letter	03-29-2018
PM0000466	PM0000424-426, PM0000479	P1 Characterization study update	04-26-2018
PM0000467	PM0000424-426, PM0000479	Response to 4/23/18 A/I Request letter	05-23-2018
PM0000468	PM0000424-426, PM0000479	Response to 6/6/18 teleconference questions	06-13-2018
PM0000475	PM0000424-426, PM0000479	Response to 7/18/18 teleconference questions	08-03-2018
PM0000476	PM0000424-426, PM0000479	Response to 8/20/18 A/I Request	09-05-2018
PM0000478	PM0000424-426, PM0000479	Corrected versions of two study reports	09-25-2018

NEW TOBACCO PRODUCTS	
STN	PM0000424
Product Name	Marlboro Heatsticks[1]
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	20 Heatsticks
Characterizing Flavor	None
Length	45 mm
Diameter	7.42 mm
Ventilation	Not Applicable[2]
Source of Energy	Electric (rechargeable battery)[3]
STN	PM0000425
Product Name	Marlboro Smooth Menthol Heatsticks[1]
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	20 Heatsticks
Characterizing Flavor	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation	Not Applicable[2]
Source of Energy	Electric (rechargeable battery)[3]
STN	PM0000426
Product Name	Marlboro Fresh Menthol Heatsticks[1]
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	20 Heatsticks
Characterizing Flavor	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation	Not Applicable[2]
Source of Energy	Electric (rechargeable battery)[3]
STN	PM0000479
Product Name	IQOS System Holder and Charger[1]
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box

[2] For this product neither filter efficiency or ventilation are used to control aerosol deliveries.
[3] The components and assemblies control the delivery of energy. The critical items include the Heater Printed Circuit Board Assembly (PCBA) including the heating blade and the battery.

Package Quantity	1 Holder, 1 Charger
Characterizing Flavor	None
Length	93.60 mm (Holder)
Diameter	15.04 mm (Holder)
Length	112.50 mm (Charger)
Width	51.20 mm (Charger)
Ventilation	Not Applicable[2]
Source of Energy	Electric (rechargeable battery)[3]
Additional Properties	Depth: 21.86 mm (Charger)
	Battery Capacity: (b) (4) (Holder)
	Wattage: (b) (4) (Charger)[3]
	Battery Capacity: (b) (4) (Charger)

DISCIPLINES REVIEWED	**DATE OF REVIEW**
Behavioral and Clinical Pharmacology	March 8, 2019
Chemistry	March 11, 2019
Environmental Science	March 26, 2019
Engineering	March 11, 2019
Epidemiology	March 13, 2019
Medical	March 28, 2019
Microbiology	March 11, 2019
OCE – DEM	March 15, 2019
OCE – DPAL	March 13, 2019
OCE – BIMO	March 15, 2019
Social Science	March 13, 2019
Statistics	March 15, 2019
Toxicology	March 15, 2019

Recommendation

☒ Issue marketing order letters

☐ Issue denial letters

Technical Project Lead (TPL):

Digitally signed by Priscilla Callahan-lyon -S
Date: 2019.04.29 15:13:25 -04'00'

Priscilla Callahan-Lyon, M.D.
Deputy Director
Division of Individual Health Science

Signatory Decision:

X Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Digitally signed by Matthew R. Holman -S
Date: 2019.04.29 16:46:36 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science

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I. Executive Summary

On May 15, 2017, FDA received PMTAs for the IQOS Tobacco Heating System (THS)[4] with Marlboro Heatsticks, Smooth Menthol Heatsticks, and Fresh Menthol Heatsticks from Philip Morris Products S.A. (PMP S.A. or the applicant). PMP S.A.'s parent company, Philip Morris International Management S.A. (PMI) has entered into a distribution agreement with Altria Client Services LLC (ALCS) by which ALCS and an ALCS affiliate, Philip Morris USA Inc. (PM USA), will be licensed to distribute and sell the IQOS system and the Marlboro Heatsticks in the U.S. upon receipt of a marketing authorization.[5]

The THS consists of three main components:

1. The IQOS Heatstick: a tobacco plug consisting of crimped cast reconstituted tobacco sheet made from ground tobacco powder. Three different Heatsticks will be available - Regular, Smooth Menthol and Fresh Menthol. Heatsticks will be marketed under the Marlboro brand in packs of 20.
2. The IQOS Holder: an electrically powered and rechargeable unit designed to hold and heat the Heatsticks during consumer use to generate the nicotine-containing aerosol.
3. The IQOS Charger: used to recharge the Holder after each use. The Charger stores sufficient energy for the use of approximately 20 Heatsticks before requiring recharging itself. It can be recharged from household power.

A new tobacco product, including a tobacco product modified in any way ("including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient" after February 15, 2007 (section 910(a)(1)(B)), generally requires premarket review and an order from FDA authorizing the marketing of the product (section 910(a)(2)(A)).

A PMTA must be submitted to FDA under section 910(b) of the FD&C Act and a marketing authorization order must be received from FDA under section 910(c)(1)(A)(i) prior to marketing any new tobacco product, unless FDA has found that the new tobacco product is substantially equivalent to a tobacco product commercially marketed in the US as of February 15, 2007 (see section 910(a)(2)(A)(i)) or is exempt from a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii)).

FDA will deny a PMTA and issue a no marketing authorization order that the product may not be introduced or delivered for introduction into interstate commerce under section 910(c)(1)(A)(ii) where FDA finds that:

- there is a lack of a showing that permitting the product to be marketed would be appropriate for the protection of the public health;
- the methods, facilities, or controls used in manufacturing, processing, or packing do not conform to manufacturing regulations issued under section 906(e) (21 U.S.C. 387f(e));
- based on a fair evaluation of all material facts, the proposed labeling is false or misleading; or
- it is not shown that the product complies with any tobacco product standard in effect under section 907 (21 U.S.C. 387g), and there is not adequate information to justify deviation from the standard.

[4] Throughout the remainder of this review, the Tobacco Heating System will be referred to as either "THS" or "IQOS" and the tobacco sticks will be referred to as the "Heatsticks." Unless otherwise designated, the terms THS, THS 2.2, and IQOS refer to the same thing; mTHS 2.2 refers to mentholated Heatsticks.

[5] Altria Client Services LLC is a wholly-owned subsidiary of Altria Group, Inc. and provides certain services to the Altria family of companies. PM USA is not part of Philip Morris International group of companies.

The statute provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account –

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Scientific review of these applications has demonstrated the following:

- There are adequate process controls and quality assurance procedures to help ensure the IQOS Holder, IQOS Charger, Marlboro Heatsticks, Fresh Menthol Heatsticks, and Smooth Menthol Heatstick are manufactured consistently to meet the applicant's specifications.
- Marlboro, Smooth Menthol, and Fresh Menthol Heatstick aerosols contain some chemicals which are different from those found in combusted cigarettes (CC).[6] Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC (see below).
- The toxicological profiles of Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks are essentially identical except for the quantity of menthol. The available toxicological data indicates the potential for a relative benefit compared to CC for smokers who switch completely to IQOS.
- Smooth Menthol Heatsticks contain 6.98 mg menthol/Heatstick. Fresh Menthol Heatsticks contain 13.23 mg menthol/Heatstick. The applicant compared this to 23 mentholated cigarette brands in the U.S. which had 2.9-19.5 mg menthol/cigarette.
- PK studies show Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks have nicotine delivery, addiction potential, and abuse liability similar to CC. This is potentially beneficial for smokers trying to switch to IQOS as they are more likely to have satisfactory results and not resume CC smoking. The nicotine levels do pose an addiction risk for non-tobacco users who initiate use of these products; however, the risk is no higher than for other, currently available, tobacco products and initiation is expected to be low generally. (See also the discussion regarding the inclusion of a nicotine addiction warning below.)
- The 5-day studies demonstrate improved biomarkers of exposure (BOE) which indicates reduced HPHC exposures. These improvement trends persisted in the 90-day studies despite reduced compliance and use of other tobacco products. Additionally, the applicant recently submitted data from a six-month clinical trial which demonstrated reduction in eight BOE as well as NNAL and COHb for self-reported users of IQOS compared to CC users.
  Although the studies conducted by the applicant do not demonstrate reduction in long-term disease risks, the currently available evidence indicates CC smokers who switch completely to IQOS will have reduced toxic exposures and this is likely to lead to less risk of tobacco-related diseases. The data for CC smokers who use IQOS while continuing to smoke (dual use) is less clear but the available evidence shows no increase in HPHC exposures for those who dual use.
- There have been no specific, short-term health-related or product quality issues unique to IQOS in the clinical studies, the current world-wide markets, or the published literature.
- Misuse of IQOS is uncommon and the product design makes it unlikely users will have a satisfactory experience (e.g., no significant nicotine is delivered with reusing a Heatstick).
- Dual use of IQOS and CC was common in all countries in the pre- and post-market studies though the CC users in the U.S. actual use study who switched to exclusive IQOS use during the study remained

[6] For the purposes of this review CC=combusted cigarette(s) or conventional cigarette(s)

generally stable during the 6-week observational period. Individuals who initiate IQOS and maintain exclusive IQOS use over time can potentially replace their use of CC with Heatsticks long-term. The toxicological and clinical studies do not show an increase in HPHC exposures when consumers are using both IQOS and CC and, although the decreases are not statistically significant, some HPHC exposures appear to be decreased.

- Although the data for IQOS uptake by never smokers, former smokers, and youth is limited, there are some data from countries where IQOS is marketed - Italy and Japan - which show low uptake by youth and current nonsmokers. In these countries, the likelihood of uptake is slightly higher in former smokers, but still low. Appropriately, the population most likely to use IQOS are current CC smokers. The proposed marketing and advertising restrictions will help ensure lower youth exposure and access to the products. Additionally, the applicant will be required to monitor consumer use patterns and demographic information and provide FDA with regular reports.

As discussed in more detail in Sections III C, III D, and IV F of this review, I recommend the PMTAs be authorized subject to the following changes to the proposed product labeling and advertising for IQOS:

1. Inclusion of the warning: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on the package labels of all Heatsticks packs and of all kits containing Heatsticks packs as well as in all advertisements for such products and kits. Data shows that consumers do not accurately perceive the addiction risks of IQOS. Permitting IQOS to be marketed without this warning would not be appropriate for protection of public health.
2. Removal of the warning: "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide." from the required warnings to be displayed on the product package labels and advertisements under FCLAA. Based on a fair evaluation of all material facts, the warning is misleading with respect to these products which, although categorized as cigarettes, do not produce carbon monoxide above environmental levels and do not increase CO-related health risks.

In conclusion, none of the grounds specified in Section 910(c)(2) of the FD&C Act apply. Specifically, I find the following:

1. Permitting the marketing of the products is appropriate for the protection of the public health, as described in Section 910(c)(4) of the FD&C Act (subject to the labeling and advertising changes described above);
2. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in 906(e);[7]
3. Based on a fair evaluation of all material facts, the labeling (when subject to the changes described above) is not false or misleading in any particular; and
4. The products do not fail to conform to a tobacco product standard in effect under Section 907 of the FD&C Act.

[7] FDA has not yet promulgated any regulations under Section 906(e) of the FD&C Act.

I recommend FDA grant marketing authorization for the products described in the STNs, subject to the changes to the products' package labels and advertisements, as described above:

1. PM0000424: Marlboro Heatsticks
2. PM0000425: Marlboro Smooth Menthol Heatsticks
3. PM0000426: Marlboro Fresh Menthol Heatsticks
4. PM0000479: IQOS System Holder and Charger[8]

[8] Originally, FDA assigned the STNs as: PM0000424 - IQOS System with Marlboro Heatsticks, PM0000425 - IQOS System with Marlboro Smooth Menthol Heatsticks, and PM0000426 – IQOS System with Marlboro Fresh Menthol Heatsticks. For administrative convenience, a decision was made to change the STNs and assign the Heatsticks to PM0000424, PM0000425, and PM0000426 and the IQOS System Holder and Charger to a separate STN; PM0000479. (See memo dated February 19, 2019.)

II. Review of PMTA

A. Regulatory History

On May 15, 2017, FDA received PMTAs for the IQOS system including the IQOS Holder and Charger with three Heatsticks: Marlboro, Smooth Menthol, and Fresh Menthol from Philip Morris Products S.A. (PMP S.A. or the applicant). The applications were accepted and acknowledged June 14, 2017 and filed for scientific review on August 4, 2017. As per agreement with FDA, PMP S.A. included only PMTA-specific information in these submissions and cross-referenced other pertinent materials contained in the MRTPAs (MR000059-61) submitted for the products with modified risk information.

There have been several amendments submitted for the applications including applicant responses to FDA information requests, confirmation of laboratory samples, and responses to clarifying questions. In addition, amendments have been submitted to the MRTPAs that have been reviewed as part of the PMTA process, e.g., a safety update and a recently completed clinical study. All relevant information submitted to the agency, including information from the MRTPAs, the TPSAC meeting on the MRTPAs and the public comments to the MRTPAs, to the extent relevant to the PMTAs, has been considered in review of these applications.

The new tobacco products that are the subjects of the PMTAs include the IQOS Holder and Charger, and three different Heatstick packs: Marlboro Heatsticks (non-mentholated), Marlboro Smooth Menthol Heatsticks (1.35 mg menthol in smoke/ stick)[9] and Marlboro Fresh Menthol Heatsticks (2.3 mg menthol in smoke/ stick).[10] Throughout the remainder of this review, unless the products are specifically designated, the Marlboro Heatsticks and general discussion will refer to Heatsticks and mentholated Heatsticks includes both Smooth Menthol and Fresh Menthol Heatsticks.

Review Format

The applicant provided information on each new tobacco product included in this review. IQOS is the commercial name of the Tobacco Heating System (THS), which includes a tobacco heating device (THD) and tobacco sticks. Throughout the remainder of this review, the Tobacco Heating System will be referred to as either "THS" or "IQOS" and the tobacco sticks will be referred to as the "Heatsticks." Unless otherwise designated, the terms THS, THS 2.2, and IQOS refer to the same thing. Mentholated Heatsticks are designated mTHS 2.2. Section IV summarizes the technical project lead's conclusions and recommendations for these applications.

B. Product Description: Engineering, Chemistry, Stability, and Manufacturing

1. General

IQOS is the commercial name of the Tobacco Heating System (THS), which includes a THD with Holder and Charger and Heatsticks: Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks. In response to FDA's request for clarification, the applicant provided additional information about the product development history and the evolution of product naming. The applicant states ZRH, P1, and THS 2.2 all refer to the same tobacco heating system. THD 2.2 was the developmental device; the planned commercial device is THD 2.4. The proposed products, also known as IQOS or THS 2.2, uses THD 2.4. All products tested in the reduced exposure studies (REX) and most toxicology studies correspond to THS 2.2. The applicant made changes to the (b) (4) during product development and

[9] Target level in aerosol, using the Canadian Intense Smoking Regime.

[10] Target level in aerosol, using the Canadian Intense Smoking Regime.

(b) (4) . The applicant changed to (b) (4) and has provided bridging information to support that the products that are the subject of these applications are comparable to the study products.

The applicant confirmed that THD 2.4 (b) (4)), which reflects certain modifications as part of continuous product development (See Section II.B.3.c), is the device that is the subject of these applications. This device, including these modifications, has been evaluated by FDA.

The IQOS Tobacco Heating System (referred to in this document as IQOS or THS) consists of three main components (see Figure 1 below):

- The IQOS Heatstick, which contains a tobacco plug consisting of crimped cast reconstituted tobacco sheet made from ground tobacco powder. There are three different Heatsticks –Regular, Smooth Menthol and Fresh Menthol. Approximately half the length of a conventional cigarette, the Heatsticks will be marketed under the Marlboro brand in packs of 20. Heatsticks are designed to be electrically heated to release nicotine-containing aerosol and are not intended to be combusted. Heatsticks use reconstituted tobacco blended with glycerin to allow the generation of aerosol. HeatSticks are not designed or intended to be reused; the glycerin, which generates the aerosol, is depleted after one use. Heatsticks are filtered non-combusted cigarettes.
- The Holder is an electrically-powered and rechargeable unit designed to hold and heat the Heatsticks during consumer use to generate the nicotine-containing aerosol. (b) (4) This heating blade is inserted into a Heatstick to heat the tobacco. The user activates the Holder by pressing the activation button for a set period until the light begins to blink, signaling that the product may be used. It is designed to be used for a single Heatstick (a period of use of 6-7 minutes or 12-14 puffs) after which the Holder requires recharging and the used Heatstick is discarded. The Holder is electronically controlled to maintain a specific temperature range that allows generation of aerosol and prevents reaching temperatures where combustion can occur.
- The IQOS Charger is used to recharge the Holder after each use. The Charger stores sufficient energy for the use of approximately 20 Heatsticks before requiring recharging itself. It can be recharged from household power. The Charger is designed to initiate and control the automatic cleaning cycle of the Holder heating blade at regular intervals; (b) (4) (b) (4) Cleaning (b) (4) (b) (4) and can only be performed when the Holder is securely held in the Charger, preventing the user from using the cleaning mode to heat a tobacco stick. The Charger electronically monitors and manages the Holder battery as well as the Charger battery.

Figure 1: The IQOS Charger, Holder, and Heatstick

To operate the THS, the user inserts a Heatstick into the IQOS Holder and turns on the device, which initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The Heatstick is not designed or intended to ignite or burn. The applicant states the electronically controlled heating at a set temperature range, in combination with the uniquely processed tobacco, prevents combustion from occurring. The temperature of the heating blade is controlled and the energy supply to the blade is cut off if its operating temperature exceeds 350°C. The temperature measured in the tobacco plug is designed to not exceed 300 °C.

2. Heatsticks

Heatsticks consist of a tobacco plug and a non-tobacco component. Heatsticks do not contain tobacco cut-filler (tobacco leaf cut in small pieces found in CC); instead, the tobacco is ground and reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum and cellulose fibers. The Heatstick contains smaller amounts of tobacco than a CC. The weight of the tobacco plug in the Heatstick is approximately 320 mg compared with the 550-700 mg of cut-filler found in CC. The reconstituted tobacco cast-leaf is fashioned into a small plug through "crimping" that allows aerosol to flow through the tobacco plug during heating. The tobacco plug portion is composed of crimped cast tobacco sheet made from ground tobacco powder, humectants, and flavorings.

The non-tobacco component includes a hollow acetate tube (HAT), polylactic acid (PLA) filter, mouth piece filter (MPF), outer paper, and tipping paper. Unlike a conventional cigarette, the Heatstick contains two independent filters: (1) a polymer-film filter to cool the aerosol and (2) a low-density cellulose acetate filter that functions as a mouthpiece. In addition, a hollow acetate tube separates the tobacco plug and the polymer-film filter to prevent contact with the heating blade during use. Various papers are used to hold the Heatstick together. The plugs are individually wrapped with a plug wrap paper. The tobacco plug, the HAT and the PLA filter are held together with a cigarette paper and attached to the MPF using a tipping paper. Although typical cigarette papers and wraps are used in the construction of the Heatstick, they only serve as structural components and do not have any functionality as they would in a CC.

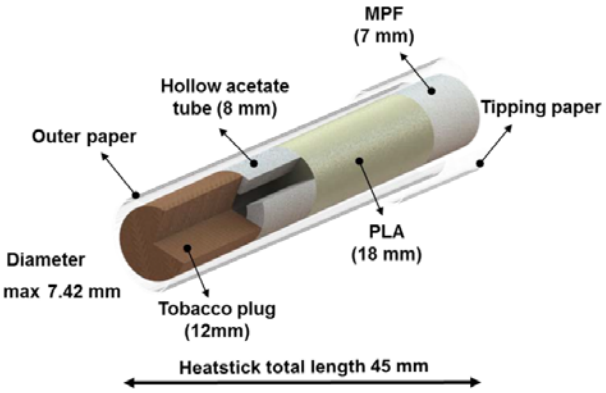

Figure 2: Heatstick Components
Source: MR0000059-61, Section 3.1, Figure 3

a. Tobacco Ingredients

The tobacco blend in the three Heatsticks includes (b) (4) (b) (4) blend types. In comparison, the Kentucky reference cigarette 3R4F includes flue-cured (35%), burley (22%), oriental (12%), Maryland (1%), and reconstituted (30%) tobacco blend types. The mainstream smoke of cigarettes made solely from reconstituted tobacco can produce high levels of carbon monoxide, nitrogen oxides, and tobacco-specific nitrosamines (TSNAs) during

combustion. The applicant included a description of the tobacco by (b) (4), (b) (4) of the tobacco in Section 3.2.2.3.2 of the MRTPAs.

To maintain the blend characteristics over time, each individual tobacco lot is analyzed (b) (4) (b) (4)) to ensure consistency and comparability. The total amount of tobacco in each of the three Heatsticks is (b) (4) mg. This is (b) (4) less than the mass of tobacco in the Kentucky reference cigarette 3R4F (760 mg/cigarette).

b. Non-tobacco Ingredients

Section 3.1.3 of the MRTPAs lists some of the non-tobacco ingredients included in the Heatsticks. Based on this information, the Heatsticks do not include any preservatives, which are frequently added to prevent undesirable microbial growth. This is discussed in Section II.B.2.e of this review. The applicant stated that the detailed list of ingredients and their quantities are commercially sensitive and were submitted via a TPMF (MF0000278) on November 30, 2017. The TPMF has been reviewed and found to include sufficient information regarding the tobacco blend in PM0000424 – PM0000426.

In the three Heatsticks, glycerol (52.3 mg/Heatstick) is 26% of the total weight of the tobacco in the Heatstick compared to levels of 1-5% typically added to tobacco in CC.[11] In the three Heatstick products, propylene glycol (~2 mg/Heatstick) constitutes 1% of the total tobacco weight. 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, which could increase acrolein generation by IQOS systems with Heatsticks compared to CC; however, the applicant provides data to show this does not occur. (See Section II.C.1.c).[12]

(b) (4) A study of 48 mentholated cigarette brands available in the U.S. market between 2002 and 2003 includes a menthol range of 1.61 to 4.38 mg/cigarette.[13] In addition, an Altria Client Sciences report submitted to the Tobacco Products Scientific Advisory Committee in 2010, includes a menthol range of 2.2 to 9.8 mg/cigarette.[14] The total amount of menthol in PM0000426 (13.23 mg/Heatstick) is 35% higher than the upper limit of menthol reported in the U.S. market for combusted cigarettes (9.8 mg/cigarette).

Triacetin is included in the hollow acetate tube (10.7 mg) and in the mouth piece filter (2.22 mg) of the three Heatsticks. In CC, triacetin can increase the menthol amounts captured in the filter due to a change in filter efficiency and smoke transfer, and thus, affect menthol yield in mainstream smoke.[15] The three Heatsticks

[11] Carmines, E. and Gaworski, C. Toxicological evaluation of glycerin as a cigarette ingredient. Food and Chem Toxicol. 2005, *43*, 1521-1539.

[12] Sleiman, M.; Logue, J.; Montesinos, V.; Russell, M. et al. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. Environ. Sci. Technol. 2016, *50*, 9644−9651.

[13] Celebucki, C.; Ferris Wayne, G.; Connolly, G.; Pankow, J; Chang, E. Nicotine & Tob. Res. 2005, 7 (4), 523–531.

[14] Altria Client Services. Background Information to Tobacco Products Scientific Advisory Committee, Menthol Discussion, 2010.

[15] Wilson SA. Theoretical aspect of menthol migration and transfer. Recent Advances in Tobacco Science. 1993; 19, 129-153.

include 7.85 mg/stick of guar gum in the tobacco blend. In CC guar gum produces formaldehyde, benzo[a]pyrene, benzene, acetaldehyde, and styrene.[16]

The three Heatsticks include cellulose in the tobacco (5.23 mg/Heatstick), wrap papers (4-45 mg/Heatstick), outer paper (14-23 mg/Heatstick), mouth piece filter (27 mg/Heatstick), tipping paper (12 mg/Heatstick), and cellulose acetate in the hollow acetate tube (56 mg/Heatstick). In addition, PM0000425 and PM0000426 include 20.9 mg of cellulose acetate in the polylactic acid filter. Thermal degradation of carbohydrates such as cellulose, pectins, starch, and sugars produce polyaromatic hydrocarbons (PAHs), phenols, aldehydes, and ketones.[17]

The three Heatsticks include 214.8 mg/Heatstick of polylactic resin in the polylactic acid filter. The polylactic acid is biodegradable and the main degradation product is lactic acid.[18] No harmful and potentially harmful constituents (HPHCs) are known to increase due to the presence of polylactic resin or lactic acid in the mainstream smoke of cigarettes.

The three Heatsticks include the copolymer ethylene-vinyl acetate in the outer paper adhesive (2.98 mg/Heatstick) and in the tipping paper adhesive (7.26 mg/Heatstick). Copolymer ethylene-vinyl acetate is also present at ~0.35 mg/Heatstick in the tobacco plug, polylactic acid filter, and mouth piece filter of the three Heatsticks. The copolymer ethylene-vinyl acetate decomposes at temperatures above 230°C[19] to produce straight-chain hydrocarbon products.[20] No HPHCs are known to increase due to the presence of straight-chain hydrocarbon products in the mainstream smoke of cigarettes.

The three Heatsticks include titanium dioxide in the tipping paper (1.34 mg/Heatstick). There is no significant difference in tar, nicotine and carbon monoxide (TNCO) between cigarettes using a filter with or without titanium dioxide.[21] The three Heatsticks also include kaolin (0.39-3.00 mg/Heatstick) in the tipping paper, polylactic acid filter plug wrap paper, and mouth piece filter plug wrap paper. No HPHCs are known to increase due to the presence of kaolin in the mainstream smoke of cigarettes.

The three Heatsticks include calcium carbonate (0.7-19 mg/Heatstick) in the tobacco plug wrap paper, outer paper, hollow acetate tube plug wrap paper, polylactic acid filter, and tipping paper. A search of tobacco industry documents and patents indicates that calcium carbonate is added to CC to reduce side-stream smoke visibility.[22] Calcium carbonate, in combination with alkali citrates, acetates or ammonium phosphates, regulates the porosity of the cigarette paper.[23] Higher permeability of the cigarette paper

[16] Nair, U. Fact sheet on the tobacco additive guar gum created by the German Cancer Research Center (DKFZ), 2012, Heidelberg, Germany.
[17] Rodgman, A. and Perfetti, T. The Chemicals Components of Tobacco and Tobacco Smoke, CRC Press, 2013, 1325.
[18] Jamshidian, M.; Tehrany, E.; Imran, M.; Jacquot, M. et al. Poly-Lactic Acid: Production, Applications, Nanocomposites, and Release Studies. Comprehensive Reviews in Food Science and Food Safety. 2010, 552 – 571.
[19] Beckman Sundh, U.; Binderup, M.-L.; Bolognesi, C.; Brimer, L.; Castle, L. et al. Scientific Opinion on the safety assessment of the substance ethylene-vinyl acetate copolymer wax, CAS No 24937-78-8 for use in food contact materials. EFSA Journal 2014, 12(2):3555.
[20] McGrattan, B. Decomposition of Ethylene—Vinyl Acetate Copolymers Examined by Combined Thermogravimetry, Gas Chromatography, and Infrared Spectroscopy. Chapter 8. Hyphenated Techniques in Polymer Characterization, 1994, 103-115.
[21] Wendeborn R.; Leutner T. Bull. Spec. CORESTA Symposium, Kallithea, 1990, 196, T09.
[22] Connolly, G.; Wayne, G.; Lymperis, D.; Doherty, M. How cigarette additives are used to mask environmental tobacco smoke. Tobacco Control, 2000, *9*:283–291.
[23] Klus, H.; Scherer, G.; Müller, L. Influence of Additives on Cigarette Related Health Risks. Beiträge zur Tabakforschung International/Contributions to Tobacco Research, 2012, 25, 3, 411-493.

facilitate ventilation with external air, reducing the TNCO yields.[24] In CC, calcium carbonate increases paper porosity and consequently increases burn rate, and decreases puff count and tar delivery.[25]

The three products include polyvinyl acetate (0.51-0.93 mg/Heatstick) as an adhesive in the hollow acetate tube, polylactic acid filter, and mouth piece filter. No HPHCs are known to increase in the mainstream smoke of cigarettes due to the presence of polyvinyl acetate.

In PM0000424, epichlorhydrin resin (1.66 mg/Heatstick) is included in the outer paper. Epichlorhydrin has not been identified as a HPHC but has been identified as a potentially toxic hemoglobin adduct formed by inhalation of cigarette smoke. This level is 3-5 times higher compared to levels in non-smokers,[26] but since the paper is not combusted during Heatstick use, FDA chemistry reviewers agree with the applicant's assessment that the use of epichlorhydrin in Heatstick paper does not raise toxic exposure concerns.

c. *Manufacturing, Process, and Controls*

Packaging materials are listed in Section 3.2.2.6 of the MRTPAs and in Amendment PM0000464. The packaging consists of a metalized/coated paper inner liner, cardboard inner frame, cardboard hinge lid blank, polypropylene wrapping film, and polypropylene tear tape.

The manufacturing process of the Heatstick consists of (b) (4)

The manufacturing process occurs in two different facilities. The blending and grinding of tobacco leaves is performed at the Neuchatel site in Switzerland and the Heatstick manufacturing and packaging are performed at the Bologna site in Italy. (b) (4)

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d. *Quality Assurance/Sample Testing*

The applicant's control strategy is a (b) (4)
(b) (4)

[24] Stephens, W. Dependence of tar, nicotine and carbon monoxide yields on physical parameters: implications for exposure, emissions control and monitoring. Tobacco Control, 2007, 16:170–176

[25] Baldwin, S.; Dwyer, R.; Newman, D.; Floyd, B. et al. Cigarette and Wrapper with Controlled Puff Count. United States Patent, 1993, Patent Number: 5,263,500.

[26] Landin, H.; Osterman-Golkar, S.; Zorcec, V.; Törnqvist, M. Biomonitoring of epichlorohydrin by hemoglobin adducts. Anal. Biochem, 1996, 240, 1–6.

To verify chemical and physical data submitted in the applications, analytical testing of tar, nicotine, acrolein, formaldehyde, and benzo[a]pyrene in mainstream aerosol and ammonia, NNN, and NNK in the tobacco filler was performed at FDA's Southeast Tobacco Laboratory (STL) in October 2017. Results are shown in Table 1 below. There are some key differences between the applicant's analytical methods and the methods used by STL to generate the data; e.g., the applicant used a 20-port linear smoking machine and STL used an e-cigarette smoking machine. The level of tar determined by STL is 20% lower than the level reported by the applicant. The level of nicotine determined by STL was similar to that reported by the applicant. In the tobacco filler, the level of ammonia reported by STL is 9-17% higher than the higher value reported by the applicant. The value reported by STL for NNK is 14-21% lower and NNN is 0-20% higher than the value reported by the applicant. The FDA chemistry reviewers believe the differences between the applicant's measures and STL results are related to methodological differences and are not significant. The level of acrolein reported by STL is comparable to the level reported by the applicant. The levels obtained by STL for formaldehyde (23-39%) and benzo[a]pyrene (80%) are higher than those reported by the applicant; however, the levels for acrolein, formaldehyde, and benzo[a]pyrene are still significantly (90% for acrolein and benzo[a]pyrene, 77% for formaldehyde) lower than the levels in the mainstream smoke of the Kentucky reference material 3R4F.

Table 1: Select HPHCs in Aerosol and Filler as Tested by Southeast Tobacco Laboratory (STL) (Modified Canadian Intense Smoking Regimen)

Regular Heatstick[a]	**PM0000424 (Mean ± SD)**	**STL Test Reports[◊] (Mean ± SD)**	**Difference (%)**
Nicotine (mg/stick)	1.29 ± 0.047	1.25 ± 0.02	↓3.1
Acrolein (µg/stick)	8.32 ± 0.755	12.32 ± 0.55	↑48.1
Formaldehyde (µg/stick)	14.1 ± 0.43	19.64 ± 0.78	↑39.3
NNN (ng/g)	384.0 ± 58.3	285.41 ± 3.54	↓25.7
NNK (ng/g)	185.1 ± 12.7	127.69 ± 3.45	↓31.0
Smooth Menthol Heatstick[a]	**PM0000425 (Mean ± SD)**	**STL Test Reports[◊] (Mean ± SD)**	**Difference (%)**
Acrolein (µg/stick)	9.79 ± 1.66	10.10 ± 0.83	↑3.1
Formaldehyde (µg/stick)	15.2 ± 0.0	18.73 ± 1.34	↑23.2
Fresh Menthol Heatstick[a]	**PM0000426 (Mean ± SD)**	**STL Test Reports[◊] (Mean ± SD)**	**Difference (%)**
B[a]P (ng/stick)	0.448 ± 0.073	0.99 ± 0.04	↑121.0
NNN (ng/g)	248.3 ± 19.5	271.59 ± 5.2	↑9.4
NNK (ng/g)	199.5 ± 10.5	133.44 ± 3.06	↓33.1

[a] Source: Section 7.1

[◊] Source: Final Laboratory Testing Report (Form FD-431) from Southeast Tobacco Laboratory

The chemistry reviewers conducted a search of peer-reviewed literature and identified eight additional studies reporting results of chemical analyses of "heat-not-burn" tobacco products. The individual studies are described in the chemistry PMTA review. Auer et al.[27] compared the concentrations of eight volatile organic compounds (VOCs), 16 PAHs, three inorganic compounds, and nicotine in mainstream aerosol generated at 330 °C in the IQOS system with Heatsticks and in mainstream cigarette smoke at 684 °C. Although the results indicated significantly elevated levels of acenaphthene and formaldehyde in the IQOS product, the chemists concluded the data published by Auer et al. are not considered adequate for comparing the levels of HPHCs between the IQOS products and CC due to analytical issues – specifically lack of testing reference samples, low number of replicates, and a lack of sensitivity on some analytical methods. Other studies and conclusions include:

- Farsalinos et al.[28] compared nicotine levels among IQOS, e-cigarettes (EC), and commercially available cigarettes and conclude that the "HnB[29] 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.[30] reported on a list of 205 compounds identified in the aerosol of Heatsticks, including flavor and fragrance agents, humectants, natural substances, and a plasticizer. The article lists 82 compounds that were not previously reported in cigarette smoke, including 43 compounds previously reported in tobacco leaves. Savareear et al. conclude the chemical composition of the aerosol of Heatsticks is significantly less complex compared to the smoke of a combustible product, although the aerosol is not fully characterized.
- Bekki et al.[31] compared nicotine, tar, carbon monoxide (CO), and TSNA levels in mainstream smoke and tobacco filler between the IQOS products and the reference cigarettes 1R5F and 3R4F. CO was found to be 99% lower in the Heatstick aerosol compared to mainstream cigarette smoke; NNN was reduced by 90-94% and NNK by 87-95%.
- Davis et al.[32] evaluated the performance of the IQOS system using two different cleaning protocols. This study found evidence of release of formaldehyde cyanohydrin (glycolonitrile) when the cleaning protocol described by the applicant (clean after every 20 Heatsticks) is followed. In amendment PM0000466, the applicant submitted a chromatographic study of PLA in response to the release of formaldehyde cyanohydrin reported by Davis et al. The applicant stated that, based on chromatographic data and literature,[33] the compound that Davis et al. identified as formaldehyde cyanohydrin is likely meso-lactide, a condensation product of lactic acid.

[27] Auer, R., Concha-Lozano, N., Jacot-Sadowski, et al. Heat-not-burn tobacco cigarettes: smoke by any other name. (2017). JAMA Internal Medicine, 177, 1050-1052.

[28] Farsalinos, K., Yannovits, N., Sarri, T., et al. (2017). Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. Nicotine Tob Res, 1-6.

[29] HnB = Heat not burn

[30] Savareear, B., Lizak, R., Brokl, M., et al. (2017). Headspace solid-phase microextraction coupled to comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry for the analysis of aerosol from tobacco heating product. J. Chromatogr, 1520, 135-142.

[31] Bekki, K., Inaba, Y., Uchiyama, S., & Kunugita, N. (2017). Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. J University of Occupational and Environmental Health (UOEH), Japan, 39(3), 201-207.

[32] Davis, B.; Williams, M.; Talbot, P. (2018). IQOS: evidence of pyrolysis and release of toxicants from plastic. Tob Control, 1-8.

[33] Arrieta, M.; Parres-Garcia, F.; Lopez-Martinez, J.; Navarro-Vidal, R.; Ferrandiz, S. (2012). Pyrolysis of biBplastics Waste: Obtained Products from Poly(lactic acid) (PLA). Dyna, 87 (4), 395-399.

- Stephens[34] compared the quantities published in the literature for 13 HPHCs in mainstream cigarette smoke, in mainstream aerosol of e-cigarettes, and in a prototype of "heat-not-burn" device (THS 2.2).[35] The quantities of the 13 HPHCs are 1-3 orders of magnitude lower in THS 2.2 compared to CC and the quantities of four HPHCs (acetaldehyde, formaldehyde, NNN, and NNK) are 1-2 orders of magnitude higher in THS 2.2 compared to e-cigarettes.
- Mallock et al.[36] compared the levels of nicotine, tar, TPM, water, four aldehydes (acetaldehyde, acrolein, formaldehyde, and crotonaldehyde) and five VOCs (1,3-butadiene, benzene, isoprene, styrene, and toluene) in the aerosol of the IQOS system with the three different Heatsticks with data from combustible cigarettes published in Counts et al.[37] The level of nicotine was comparable to combustible cigarettes, and lower for aldehydes (80-96%) and VOCs (97-99.8%) in the aerosol of the IQOS system with Heatsticks compared to mainstream cigarette smoke.
- Li et al.[38] compared the levels of TPM, water, tar, nicotine, propylene glycol, glycerin, carbon monoxide, and 25 HPHCs in the IQOS system with Heatsticks and the Kentucky reference cigarette 3R4F, under International Organization for Standardization (ISO) and Canadian Intense (CI) smoking regimens. The level of tar in the IQOS system with Heatsticks was comparable to the level found in the mainstream smoke of Kentucky reference cigarette 3R4F; however, nicotine was 29% lower. Other measures were similar to those reported by the applicant. Li et al. also compared the chemicals obtained in the IQOS system with Heatsticks, two commercial CC, and reconstituted tobacco blend during simulated pyrolysis at 350°C. When the tobacco from the four products (Heatsticks, commercial CC, and reconstituted tobacco blend) were heated to the same temperature (350°C), all emitted comparable levels of chemicals., This suggests that the temperature of the IQOS system, rather than the tobacco filler ingredients, has a major impact on the levels of harmful constituents.

In summary, the level of nicotine, tar, glycerol, HPHCs, and other components in the aerosol reported in six of the eight peer-reviewed articles is similar to data reported by the applicant. Auer et al. reported higher levels of some compounds compared to the applicant but there may be methodological issues with this study. For the reasons set forth above, the chemistry reviewers do not believe these differences raise any concerns.

e. Product Stability

To maintain tobacco blend characteristics over time, (b) (4) (b) (4) , analysis of (b) (4) . The applicant has established tolerance limits for (b) (4) (b) (4)

[34] Stephens, W. (2017). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control 2017; 0:1–8.

[35] Schaller, J.P.; Pijnenburg, J.; Ajithkumar, A.; Tricker, A. (2016). Evaluation of the tobacco heating system 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the tobacco heating system 2.2 aerosol. Regul Toxicol Pharmacol 81(Suppl 2): S48–58.

[36] Mallock, N.; Böss, L.; Burk, R.; Danziger, M. et al. (2018). Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol, in press.

[37] Counts, M.; Morton, M.; Laffoon, S.; Cox, R. et al (2005). Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacol 41(3), 185–227.

[38] Li, X.; Luo, Y.; Jiang, X.; Zhang, H. et al (2018) Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. Nicotine Tob Res., 1-8.

(b) (4) . The applicant stated that (b) (4) . The analysis comprises (b) (4) (b) (4) The limits are:
(b) (4)

The applicant listed control parameters for batch release. The control parameters for (b) (4)
(b) (4)
(b) (4) The applications do not include Certificates of Analysis (CoAs) with batch release results; however, during the inspection of the Bologna (Italy) facility, CoAs for batch release were collected for the three products. The results for the control parameters are within specifications.

During manufacturing, the applicant performs controls at critical steps (b) (4) (b) (4) . The applicant provided (b) (4) stability data for the three products in support of the proposed shelf life at (b) (4) - (b) (4) stability data at (b) (4) . (b) (4) . (b) (4) . In PM0000425, the menthol specification is (b) (4) menthol/Heatstick for batch release and (b) (4) menthol/Heatstick for stability. In PM0000426, the menthol specification is (b) (4) menthol/Heatstick for batch release and (b) (4) menthol/Heatstick for stability. The applicant stated that (b) (4) (b) (4) .

FDA needed post-manufacturing product stability information from the applicant because bacterial communities and constituents in tobacco products change as a function of storage time.[39,40] Product stability is affected by factors such as fermentation processes, the addition of chemical additives (e.g., humectants, preservatives, certain flavor compounds, metabolic inhibitors), and water activity (a_w) of the

[39] Chopyk, J., Chattopadhyay, S., Kulkarni, P., Smyth, E.M., et al., 2017b. Temporal variations in cigarette tobacco bacterial community composition and tobacco-specific nitrosamine content are influenced by brand and storage conditions. Front. Microbiol. 8:358.
[40] Djordjevic, M.V., Fan, J., Bush, L.P., Brunnemann, K.D., and Hoffmann, D. 1993. Effects of storage conditions on levels of tobacco-specific N-nitrosamines and N-nitrosamino acids in U.S. moist snuff. J. Agric. Food Chem. 41:1790-1794.

product.[41,42,43,44,45,46] Additionally, factors such as pH, moisture content, nitrate/nitrite concentrations, microbial content and product storage temperature are reported to influence microbial stability and TSNA formation during tobacco product storage.[47,48,49] The applicant states that the product specifications for shelf life are a (b) (4)

Amendments MR0000085 and MR0000096 provided complete stability testing data for all the Heatsticks measured over a period of (b) (4) of product storage. Samples were collected at (b) (4) and evaluated for (b) (4) . (b) (4) The applicant concluded that a shelf life of (b) (4) is acceptable at (b) (4) and a shelf life of (b) (4) is acceptable at (b) (4) for all Heatstick varieties. (b) (4) .

Changes in the (b) (4) may be of concern if they indicate microbial changes. A key factor in determining potential to support microbial growth is the amount of water that is available, which is described in terms of a_w. A_w limit varies with various solutes (water) and humectants. The applicant provided no explanation for why (b) (4) (b) (4) Additionally, the applicant did not provide any a_w data for the Heatsticks to show that the (b) (4) is not a microbiological concern. However, the applicant states (in Amendment MR0000085) that the tobacco portion of the finished product has an approximate moisture content of (b) (4) and the humectant concentration exceeds (b) (4), under which the a_w is not expected to exceed (b) (4). It is generally recognized that no microbial proliferation occurs with a_w <0.60.[50] Additionally, the applicant submitted a graphical representation of the moisture content data of the tobacco plug recorded as part of a 15-month product monitoring study of Heatsticks that were shipped by air from the manufacturing center in Bologna, Italy to several warehouses in Japan and stored under standard warehouse conditions. Based on this data, the tested moisture content of the Heatsticks was approximately (b) (4) - below the 20% level considered necessary for microbial growth.

During inspection of the PMP S.A. site in Switzerland, FDA obtained pictures taken as part of the visual inspection of the Heatsticks. The applicant states that (b) (4) , observations on

[41] Andersen, R.A., Fleming, P.D., Hamilton-Kemp, T.R., and Hildebrand, D.F. 1993. pH changes in smokeless tobaccos undergoing nitrosation during prolonged storage: Effects of moisture, temperature, and duration. J. Agric. Food Chem. 41:968-972.
[42] Chopyk, J., Chattopadhyay, S., Kulkarni, P., Claye, E., et al., 2017a. Mentholation affects the cigarette microbiota by selecting for bacteria resistant to harsh environmental conditions and selecting against potential bacterial pathogens. Microbiome. 5:22.
[43] Ibid, Chopyk, J., Chattopadhyay, S., Kulkarni, P., Smyth, E.M., et al., 2017b
[44] Mutasa, E.S., Seal, K.J., and Magan, N. 1990. The water content/water activity relationship of cured tobacco and water relations of associated spoilage fungi. Int Biodeterior. 26: 381-396.
[45] Smith, T.E. 1964. A literature review of aging and fermentation of tobacco. http://legacy.library.ucsf.edu/tid/ubb93f00/pdf.
[46] St. Charles, F.K. 1989. Reduction of the water activity of wet snuff/259. Brown & Williamson Tobacco Corporation Research and Development. http://legacy.library.ucsf.edu/tid/aaj41f00/pdf.
[47] Brunnemann, K.D., Prokopczyk, B., Djordjevic, M.V., and Hoffmann, D. 1996. Formation and analysis of tobacco-specific N-nitrosamines. Crit. Rev. Toxicol. 26:121-137.
[48] Fisher, M.T., Bennett, C.B., Hayes, A., Kargalioglu, Y., et al., 2012. Sources of and technical approaches for the abatement of tobacco specific nitrosamine formation in moist smokeless tobacco products. Food Chem Toxicol. 50:942–948.
[49] Rutqvist, L.E., Curvall, M., Hassler, T., Ringberger, T., and Wahlberg, I. 2011. Swedish sSnus and the GothiaTek Standard. Harm Reduct J. 8:11.
[50] Beuchat, L.R. 1983. Influence of water activity on growth, metabolic activities, and survival of yeast and molds. J. Food Protect. 46:135-141.

visual quality of the product ((b) (4)) were not related to safety or product performance. However, the applicant states that it will add a_w testing to future high humidity stability studies, and, if high a_w is detected, microbiological testing will be performed.

3. Heating System

a. Holder

The Holder heats the tobacco using a g(b) (4) ceramic blade, which is pushed into the tobacco plug by the act of inserting the HeatStick into the Holder. The Holder has a small battery, which stores enough energy for a single use (i.e. complete use of one HeatStick). (b) (4) The Holder needs to be recharged prior to each HeatStick use. The Holder is activated by a button and its status is indicated through an interface that includes a colored light-emitting diode (LED).

In Amendment MR0000085, the applicant describes changes to(b) (4) (b) (4) . These changes were made to (b) (4) .

b. Charger

The Charger is a pocket-sized recharging case for the Holder. It contains a larger battery and charging electronics, which recharges the Holder battery when the Holder is placed inside. The Charger battery holds sufficient charge to recharge the Holder 20 times. The Charger is recharged using an AC adaptor.

When the Holder is inserted in the Charger, it is possible to initiate the blade cleaning process. This procedure heats the blade to a higher temperature than during Holder use to facilitate the removal of deposits left by multiple inhalation experiences, and thus ensures consistent heating performance in normal use. The Charger status is displayed and controlled through an interface that includes colored LEDs and two buttons.

Amendment MR0000085 describes changes in (b) (4) ; this change was made to (b) (4) . The amendment also (b) (4) (b) (4) .

c. Manufacturing, Process, and Controls

The IQOS THS is designed and manufactured in accordance with published external standards when available and applicable for the product category and all systems/sub-systems. These standards have been third-party tested per the regulatory compliance standards. The engineers requested the IQOS Charger battery be tested under IEC62133:2012 and all test units passed. In addition, the IQOS THS follows applicable European Directive which is intended to improve environmental policies associated with batteries sold in the European Union.

The manufacturing and assembly processes for the product components are described in the applications and reviewed in detail in the Engineering review. The applicant submitted part-by-part and sub-assembly details for the following components:

- (b) (4)

(b) (4) [redacted]

In summary:

1. (b) (4) [redacted]
2.
3.
4.

(b) applicant provided a detailed Bill of Materials in Amendment MR0000085 with changes (b) (4) [redacted]

The filters (mouth piece filter and PLA filter) of THS 2.2 were designed to mimic the look and feel of a conventional cigarette filter. (b) (4) [redacted]

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(b) (4) [redacted]

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d. Quality Assurance/Sample Testing

The heating blade specifications are included in the submission and individual data points and acceptance criteria related to the heating system temperature profiles are in Amendment MR0000085. The applicant provides a detailed summary of the testing method for the heating blade; this is summarized in the Engineering review. (b) (4) [redacted]

(b) (4)

The Holder and Charger contain microcontrollers and firmware (b) (4)
(b) (4)
Details are in the Engineering review. The Engineering review notes that the Holder and Charger firmware architecture is based on (b) (4)

The heating blade cleaning function (b) (4)

(b) (4)

The product is designed to use interchangeable batteries. The applicant provided the supplier manufacturing specifications, which are aligned with the product battery specifications for the Holder and the Charger. To ensure a "full experience" with each use, the applicant has established minimum battery standards.

The applicant submitted product battery samples of the IQOS Holder and Charger batteries (50 samples each) to Winchester Engineering and Analytical Center (WEAC) in September 2017. Engineering requested evaluation of conformance to certain requirements of IEC62133:2012 (second edition) to be measured for the new products. Testing was performed on all the products with 5-10 replicates, depending on the parameter. No individual data points were out of specification when compared to the applicant's range limits.

4. Inspections of Manufacturing Facilities

FDA inspections were performed of the applicant's research and manufacturing sites in Lausanne, Switzerland (product testing), Neuchatel, Switzerland (product design and research), Bologna, Italy (HeatStick production), (b) (4)).

(b) (4)

(b) (4) There were no discussion items or deficiencies identified.

PMP S.A., located in Neuchatel, Switzerland, is a subsidiary of PMI[51] with headquarters in Lausanne, Switzerland. Activities conducted at this site include (b) (4) .

(b) (4)

(b) (4)

PM Manufacturing and Technology Bologna is in Bologna, Italy. (b) (4) There were no discussion items or deficiencies identified.

During the inspection of the Bologna (Italy) facility, CoAs for batch releases collected included the specifications and the results obtained for one batch of each of the three Heatsticks, PM0000424-426. All the results obtained were within specifications. The inspection report (FEI: 3011169041) for the facility in Italy notes discrepancies in weight specifications between the application and the batch records collected. The batches collected were for the Japanese market. In the batch records the specifications for weight of the crimpled PLA filter are (b) (4) for PM0000425 and (b) (4) for PM0000426. In the

[51] The cover letter of the PMTAs notes: The application refers to Philip Morris International (PMI) which includes: Philip Morris International Inc., Philip Morris Products S.A. (the PMT and MRTP applicant), Philip Morris International Management S.A., Philip Morris International Research Laboratories Pte. Ltd., and Philip Morris Manufacturing & Technology Bologna S.p.A.

applications, the weight specifications are (b) (4) for PM0000425 and (b) (4) for PM0000426. In addition, in the (b) (4) process, the specification for weight is (b) (4) for the three Heatsticks. In the batch record for Marlboro Smooth Menthol Heatsticks and Marlboro Fresh Menthol Heatsticks, the specification for weight is (b) (4) . The applicant indicated that the differences are mainly due to different cigarette paper used in the Japanese and the U.S. markets.

5. Summary of Engineering, Chemistry, Product Stability, and Manufacturing Findings

The engineering review concludes that the PMTAs contain adequate information with respect to the following:

- A complete characterization of the design parameters
- An adequate description of manufacturing steps and quality control measures
- Adequate process controls and quality assurance procedures to help ensure that the products meet manufacturing specifications for the IQOS Holder, Charger, and Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks and that the products are manufacture in a consistent manner that minimizes the variability in product quality
- Performance testing to verify the product design

The engineering review concludes that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the products meet the manufacturer's specifications.

As TPL, I agree with the engineering conclusions. In addition to the above information, the applicant has made changes to the Holder and Charger which are likely to lead to a more consistent manufacturing process and improve product reliability. The applicant has provided a description of the function and design of the Heatstick filters. The applicant has no efficiency requirements for Heatstick filters as the filters do not control nicotine delivery. The applicant has provided an adequate description of the firmware functionality for control of the heating blade temperature and cleaning function, as well as for function and battery management of the Holder and Charger. Additionally, the applicant has described battery specifications for the vendors that will help to ensure product consistency and reduce concerns of malfunction. The battery testing performed at the Winchester Engineering and Analytical Center demonstrated consistent battery performance, which reduces concerns of malfunction.

The chemistry review concludes these PMTAs contain adequate information as follows:

- A complete list of uniquely identified components, ingredients, and additives by quantity in each new tobacco product as well as the applicable specifications and a description of the intended function for each
- An adequate description of manufacturing steps and quality control measures in place
- Sufficient information to assure FDA that the products meet manufacturing specifications for (b) (4) , nicotine, (b) (4) , phenol, carbon monoxide, acrylamide, and menthol and that the products are manufactured in a consistent manner that minimizes the variability in product quality
- Data on chemical endpoints establishing the stability of the product through the stated shelf life
- Product analyses for verifying the product formulations
- Testing data to demonstrate that the new products contain significantly lower levels of certain HPHCs including formaldehyde, acrolein, carbon monoxide, NNN, NNK, compared to major types of combusted cigarettes on the U.S. market
- There were small weight differences between the application and the batch noted during the inspection of the Bologna Italy facility. The difference was due to different cigarette paper used in Japan vs. the U.S. and do not raise any concerns regarding product quality.

The chemistry review concludes that these PMTAs contain sufficient information to characterize the product composition in terms of ingredients and additives and describe the manufacturing processes and controls that can affect the product composition, chemical stability, and HPHC levels to help ensure that the products meet the manufacturer's specifications.

As TPL, I agree with the chemistry conclusions.

The microbiology review concludes the applicant provided adequate microbiology-related information to demonstrate full product characterization and stability over product shelf-life and to address factors that can potentially affect the microbial stability of the product as well as adequate quality control information. Specifically:

- The applicant has provided information to support (b) (4) shelf life for all three Heatsticks.
- Based on the information provided, adequate measures are being taken to address the quality (b) (4) and stability of the Heatsticks exposed to high heat and humidity conditions.

As TPL, I agree with the microbiology conclusions. Although there was (b) (4) (b) (4), it is unlikely this is related to product safety or performance as the moisture content of the Heatsticks is well below the level necessary for microbial growth.

The OCE manufacturing review identified no significant compliance issues during the five manufacturing inspections conducted.

C. Toxicological Risk Assessment

1. Harmful and Potentially Harmful Constituents (HPHCs)

a. General Overview

Tobacco fermentation is a microbial-mediated reduction of nitrate reacting with alkaloids present in tobacco to produce tobacco-specific nitrosamines (TSNAs).[52,53] TSNAs are primarily formed during tobacco curing and fermentation of processed tobacco, as well as during aging/storage of the processed and packaged tobacco product. Factors such as nitrate and nitrite concentrations, moisture content, microbial content, pH, and storage temperature are reported to influence microbial stability and TSNA formation during tobacco product storage. Although the tobacco component of the Heatsticks does not include any fermented tobacco, (b) (4) tobacco is included.

HPHCs are formed by the incomplete combustion and thermal degradation of the tobacco, additives, and paper as the cigarette burns. The temperature at the center of a burning cigarette is 600–800^{o} C but can reach temperatures as high as 900^{o} C.[54] The IQOS system is designed to heat tobacco to approximately 300^{o} C and employs a thermal monitoring system that prohibits temperatures from exceeding 350^{o} C. The HPHC analysis submitted by the applicant demonstrates that some thermal degradation products that are generated as tobacco burns are also found in Heatstick aerosols, albeit at lower levels. It is possible that

[52] Di Giacomo, M., Paolino, M., Silvestro, D., Vigliotta, G., et al.,2007. Microbial community structure and dynamics of dark fire-cured tobacco fermentation. Appl Environ Microbiol. 73:825–837.
[53] Ibid, Fisher, M.T., Bennett, C.B., Hayes, A., Kargalioglu, Y., et al., 2012.
[54] Baker RR. Temperature distribution inside a burning cigarette. *Nature.* 1974;247(5440):405-406.

other unmeasured constituents may be formed at temperatures below the combustion threshold for tobacco.[55] The applicant conducted a series of in vitro and in vivo nonclinical studies assessing certain toxicities of Heatstick aerosol compared to 3R4F, which should detect adverse effects caused by aerosol constituents not identified by physical characterization of the aerosol.

The applicant submitted the following testing data obtained for PM0000424 – PM0000426 manufactured under commercial manufacturing conditions:

- TNCO levels using the ISO regimen
- FDA 18+6: This study measured yields of 18 chemicals on the current FDA HPHC list in the Heatstick aerosols (measured under ISO and modified CI regimens) and six constituents found in Heatstick filler.
- PMI-58 study: This study compared yields of 55 chemicals (measured under the modified CI regimen) on the current FDA HPHC list that are found in Heatstick aerosols and 3R4F smoke. The applicant also reported yields of (b) (4), nicotine, tar, (b) (4). For 18 of the aerosol compounds, the applicant compared the levels found in Heatstick aerosols to mean levels in the smoke of 30 commercially available cigarettes. A comparison was also done for six Heatstick filler constituents.
- Amendment MR0000114 (study 93-FDA-HPHCs) included additional information on yields of all 93 chemicals on the current FDA HPHC list for both Heatstick aerosols and 3R4F smoke. In Heatstick aerosols, levels of 39-40 of the chemicals were too low too to be quantified; for the other 53-54 chemicals that could be quantified, the previously reported levels in the PMI-58 study were verified.
- Non-Targeted Differential Screening: This study, submitted in Amendment MR0000097, provides the levels of 80 individual constituents present in the aerosol of one or more of the Heatsticks at higher concentrations than in the mainstream smoke of 3R4F.
- P1 characterization: This study includes chemical constituents present at concentrations higher than 100 ng/Heatstick in the aerosol of MR0000059 under a modified CI smoking regimen.

In the FDA 18+6 study and the Non-Targeted Differential Screening, the applicant compared the quantity of each constituent to data obtained from the Kentucky reference cigarette 3R4F. The comparison was performed both per unit (quantity in Heatstick aerosol compared to quantity in cigarette smoke) and per amount of nicotine.

The FDA 18+6, PMI-58, and 93-FDA-HPHCs studies were performed by Labstat International ULC. Labstat submitted method details in TPMF (b) (4) in December 2017. TNCO and Non-Targeted Differential Screening studies were performed by PMP S.A. The analytical method used to determine water and tar content by PMP S.A. was modified to account for a larger amount of water in the aerosol (80%) of the IQOS compared to the amount of water in the mainstream smoke of CC (20%). Ghosh et al. demonstrated that the difference in tar mean values between the in-situ methodology and the standard ISO 4387 methodology was -50% for the heated tobacco product and -4% for CC by ISO smoking regimen. In the heated tobacco product, tar is 9.39 mg/Heatstick using the standard extraction and 4.71 mg/Heatstick using the in-situ extraction.[56] This approach is appropriate for analysis of this product.

[55] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-not-burn tobacco cigarettes: Smoke by any other name. JAMA Internal Medicine. 2017.

[56] Ghosh D., Jeannet C. An Improved Cambridge Filter Pad Extraction Methodology to Obtain More Accurate Water and "Tar" Values. In Situ Cambridge Filter Pad Extraction Methodology. Beiträge zur Tabakforschung International/Contributions to Tobacco Research. 2014, Volume 26 (2), 38-49.

b. Constituents Unique to IQOS

The non-targeted differential screening of Heatstick aerosols and 3R4F cigarette smoke found 80 chemicals that were either present in higher concentration in Heatstick aerosols than 3R4F smoke or not found in 3R4F smoke: 4 are possibly carcinogenic, 30 are identified by the applicant as Generally Recognized as Safe (GRAS), and 46 additional ingredients (mostly flavoring ingredients).

The applicant indicates the four possible carcinogens (glycidol, 3-chloro-1,2-propanediol [3-MCPD], 2-furanmethanol, and furfural) do not pose a toxicological concern because the levels are below recognized dietary or occupational exposure limits. The applicant provided the following toxicological assessments:

- Comparison against occupational exposure limits (OELs)
- Use of OSHA's Permissible Exposure Limit (PEL) as a standard for some exposures
- Compared the exposure from IQOS aerosol for the four chemicals to maximum dietary intake

The assessment of these carcinogens is not considered adequate. Comparison of estimated exposures from use of tobacco products to OELs is not appropriate for a risk assessment of chemicals found in tobacco product smoke and aerosols. OELs are not health values and are not intended for use to evaluate potential health hazards from inhaled tobacco products. OSHA PELs are intended for a specific scenario in the workplace including exposure during an 8-hour work shift within a 40-hour work week. PELs are also intended to be used together with proper engineering controls (e.g., monitoring the work environment, application of feasible technological controls) and good work practices (e.g., wearing respirators) to minimize hazardous substance generation and exposure. Extrapolation of risk from dietary exposure to determine risk from inhalation is inappropriate, as the most sensitive effects and target organs drastically differ depending on whether a toxicant is ingested or inhaled. Extrapolation from dietary limits for inhalation exposure ignores differences in toxicokinetics or distinct effects at the portal of entry. The explanation provided by the applicant does not support a conclusion that these pose no risk to IQOS users; however, the levels of exposure to these possible carcinogens appear low and when considered with other data does not preclude a conclusion the products are appropriate for protection of public health.

Initially the applicant did not provide any analysis of the GRAS compounds. In response to a request for additional information, the applicant provided predictive toxicology modeling and available toxicological data for 30 chemicals present in higher levels in Heatstick aerosol compared to 3R4F smoke. Four of the 30 chemicals have known respiratory effects (irritation, sensitization, respiratory depression) and one has potential to influence nicotine metabolism. For other chemicals, toxicological data via the inhalation route is not available and their individual contributions in inhalation toxicology are unknown. Genotoxicity and carcinogenicity information for many of these chemicals is not available. The applicant analyzed all 30 chemicals with the OECD quantitative structure-activity relationship (QSAR). Eleven chemicals were identified with genotoxic potential. Based on the available toxicological data and predictive toxicology modeling analysis submitted by the applicant, 20 of the 30 chemicals exhibit concerns for potential health effects. Many of the chemicals do not have sufficient inhalation toxicity or genotoxicity/carcinogenicity data to inform the toxicological evaluation of heated tobacco products. The data provided by the applicant is not sufficient to support their conclusion that these compounds pose no risk to IQOS users; however, although there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for protection of public health.

The applicant analyzed the remaining 46 chemicals (primarily flavor ingredients) with the OECD QSAR Toolbox to detect structural alerts for DNA binding or carcinogenicity. Of these 46 chemicals, 8 were identified as potentially genotoxic and/or carcinogenic. Along with the 11 noted above, the applicant

indicates that 19 of the 80 chemicals that were either unique to Heatstick aerosols or found at higher concentrations than in 3R4F produced a structural alert for genotoxicity and 20 more GRAS compounds have potential health effects.

c. Comparison to Cigarette Smoke

PMI-58 study

The PMI-58 study included measurement of 55 HPHCs in the mainstream aerosol generated from PM0000424, PM0000425, and PM0000426 and in smoke generated from the 3R4F reference cigarette using a CI smoking regimen. On a per stick basis, measured HPHC levels (except nicotine) were reduced in Heatstick aerosols by ~54-99.9% compared to 3R4F. Nicotine levels in Heatstick aerosols were reduced by ~26%-39% compared to 3R4F.

While the Heatstick aerosols generated by smoking machines contained less nicotine than smoke from 3R4F research cigarettes on a per stick basis, the clinical data indicate that humans can absorb nicotine from Heatstick aerosols at levels comparable to their current cigarette brands. Consequently, HPHC yields normalized to nicotine yield are more likely to reflect actual human exposure levels than HPHC yields expressed on a per stick basis. When normalized to nicotine yield, the yields of HPHCs that were measured were reduced by 24.8%-99.8% compared to the smoke from the CC evaluated by the applicant.

The applicant measured 18 HPHCs plus tar and water in smoke generated from 31 different Philip Morris USA brand CC marketed in the U.S. with a rotary smoking machine using the CI smoking regimen. Results are shown in Table 2 below. Except for nicotine, HPHC yields in Heatstick aerosols on a per stick basis are reduced by 40.0%-99.9% when compared to the smoke from the CC; nicotine levels are 36-42% lower. When normalized to nicotine yield, HPHC yields are reduced by 38.2%-99.8% when compared to the smoke from the CC evaluated by the applicant. The applicant quantified the levels of 6 HPHCs (nicotine, ammonia, cadmium, arsenic, NNN, and NNK) in the tobacco filler.

Data were not provided comparing these levels to 3R4F; however, the applicant indicates there is (b) (4) mg of nicotine in the tobacco filler of an unused Heatstick, but only 1.19-1.29 mg of nicotine is volatilized into the aerosol. The applicant did not provide the nicotine levels for used Heatsticks.

The applicant also included measures of tar, water and total particulate matter (TPM). Although TPM is 20-32% higher in the aerosol of the Heatsticks than in CC, the composition is different. The TPM produced by the IQOS system contains 76% (b) (4) and 10% (b) (4) while the TPM produced by the reference cigarette 3R4F contains 32% water and 5% glycerol.[57] In the three products, the level of tar is 20-36% lower in the aerosol compared to the reference cigarette 3R4F.

Formaldehyde and acrolein are produced by glycerol and propylene glycol.[58] 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 compared to cigarette smoke.

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[57] Schaller, J.P., Keller, D., Poget, L., et al. (2016). Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regulatory Toxicology and Pharmacology, 81, S27-S47.

[58] Sleiman, M., Logue, J., Montesinos, V., et al. (2016). Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. Environ. Sci. Technol., 50, 9644-9651.

NNN and NNK are formed by nitrosation of alkaloids present in the tobacco plant during tobacco processing, curing, and storage. NNN and NNK are 92-98% lower in the aerosol of the Heatsticks 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.[59] While NNN and NNK levels may be lower in the aerosol of the IQOS system due to the lower heating temperature for the tobacco, the main reduction is likely caused by selecting tobacco blends with a lower propensity for TSNA formation and by limiting the use of nitrogen fertilizer.[60]

Nitrogen oxides are 97-99% lower in the aerosol of the Heatsticks than in mainstream cigarette smoke. Reconstituted tobacco can produce high levels of CO and nitrogen oxides during combustion.[18] The lower levels are likely related to lack of combustion.

Table 2: Comparison of HPHC Yields from Heatstick Aerosols and Combusted Cigarettes

HPHC	Unit	31 US Brands	PM0000424			PM0000425			PM0000426		
		Mean ± SD‡	Mean ± SD#	Change (per stick)	Change** (per nicotine)	Mean ± SD#	Change (per stick)	Change** (per nicotine)	Mean ± SD#	Change (per stick)	Change** (per nicotine)
Nicotine	mg/cig	2.03 ± 0.45	1.29 ± 0.047	↓36.4%	N/A	1.19 ± 0.05	↓41.4%	N/A	1.17 ± 0.03	↓42.4%	N/A
Tar	mg/cig	30.61 ± 5.78	19.4 ± 1.62	↓36.1%	↓0.6%	19.5 ± 1.3	↓35.8%	↑1.1%	18.1 ± 1.1	↓40.4%	↓6.2%
Water	mg/cig	15.65 ± 2.42	30.2 ± 2.17	↑93.8%	↑204.9%	35.6 ± 0.59	↑128.4%	↑259.4%	36.0 ± 0.49	↑131.0%	↑263.5%
1,3-Butadiene	µg/cig	116.46 ± 19.14	0.207 ± 0.016	↓99.8%	↓99.7%	0.223 ± 0.030	↓99.8%	↓99.7%	0.192 ± 0.006	↓99.8%	↓99.7%
1-Aminonaphthalene	ng/cig	34.55 ± 9.39	0.0427 ± 0.00513	↓99.9%	↓99.8%	0.043 ± 0.012	↓99.9%	↓99.8%	0.060 ± 0.003	↓99.8%	↓99.7%
2-Aminonaphthalene	ng/cig	21.20 ± 5.02	0.0223 ± 0.00321	↓99.9%	↓99.8%	0.022 ± 0.007	↓99.9%	↓99.8%	0.031 ± 0.009	↓99.9%	↓99.8%
4-Aminobiphenyl	ng/cig	3.45 ± 0.76	0.0087 ± 0.0012	↓99.7%	↓99.6%	0.009 ± 0.002	↓99.7%	↓99.6%	0.010 ± 0.002	↓99.7%	↓99.5%
Acetaldehyde	µg/cig	1443.41 ± 218.35	192 ± 11.6	↓86.7%	↓79.1%	206 ± 6	↓85.7%	↓77.5%	192 ± 9	↓86.7%	↓79.1%
Acrolein	µg/cig	157.59 ± 17.91	8.32 ± 0.755	↓94.7%	↓91.7%	9.79 ± 1.66	↓93.8%	↓90.2%	9.32 ± 0.569	↓94.1%	↓90.7%
Acrylonitrile	µg/cig	24.05 ± 3.67	0.145 ± 0.0112	↓99.4%	↓99.1%	0.127 ± 0.017	↓99.5%	↓99.2%	<0.107 (LOQ)	Unknown	Unknown
Ammonia	µg/cig	32.01 ± 9.95	12.2 ± 0.973	↓40.0%	↓38.2%	11.1 ± 1.1	↓65.3%	↓45.4%	10.7 ± 0.943	↓66.6%	↓47.4%
Benzene	µg/cig	86.18 ± 11.99	0.452 ± 0.0395	↓99.5%	↓99.2%	0.453 ± 0.046	↓99.5%	↓99.2%	0.473 ± 0.036	↓99.5%	↓99.1%
Benzo[a]pyrene	ng/cig	14.95 ± 3.12	0.736 ± 0.0973	↓95.1%	↓92.3%	0.539 ± 0.081	↓96.4%	↓93.9%	0.448 ± 0.073	↓97.0%	↓95.3%
Carbon monoxide	mg/cig	28.95 ± 3.60	0.347 ± 0.0462	↓98.8%	↓98.1%	0.32 ± 0.00	↓98.9%	↓98.3%	0.48 ± 0.000	↓98.3%	↓97.4%
Crotonaldehyde	µg/cig	51.07 ± 6.25	<3.29 (LOQ)	Unknown	Unknown	<3.29 (LOQ)	Unknown	Unknown	<3.29 (LOQ)	Unknown	Unknown
Formaldehyde	µg/cig	98.23 ± 35.09	14.1 ± 0.43	↓85.6%	↓77.4%	15.2 ± 0.0	↓84.5%	↓75.7%	10.0 ± 0.773	↓89.8%	↓84.0%
Isoprene	µg/cig	1031.85 ± 155.79	1.51 ± 0.129	↓99.9%	↓99.8%	1.51 ± 0.31	↓99.9%	↓99.8%	1.27 ± 0.281	↓99.9%	↓99.8%
NNN	ng/cig	178.67 ± 57.79	10.1 ± 0.205	↓94.3%	↓91.1%	7.01 ± 0.51	↓96.1%	↓93.8%	7.75 ± 0.766	↓95.7%	↓93.2%
NNK	ng/cig	128.32 ± 34.76	7.80 ± 0.423	↓93.9%	↓90.4%	6.63 ± 0.53	↓94.8%	↓91.9%	5.52 ± 0.34	↓95.7%	↓93.2%
Toluene	µg/cig	149.18 ± 23.81	1.42 ± 0.162	↓99.0%	↓98.5%	1.28 ± 0.12	↓99.1%	↓98.6%	1.03 ± 0.272	↓99.3%	↓98.9%

‡ Source: MR0000085; # Values from Tables 2, 3, and 4; ** Normalized to nicotine yield

P1 Characterization study

In the P1 characterization study, the applicant reported 498 compounds present in the aerosol of PM0000424 at concentrations of 100 ng/Heatstick or higher. All compounds were also identified in the mainstream smoke of the Kentucky reference cigarette 3R4F. (Chemicals that are unique to Heatstick aerosols are present in concentrations < 100ng/Heatstick.) All the compounds reported in the Non-Targeted Differential Screening study with concentrations higher or equal to 100 ng/Heatsticks were reported in the P1 characterization study, except for eight compounds that did not overlap between the studies (lanost-8-en-3-ol, 24-methylene; 12,14-labdadiene-7,8-diol, (8a,12E); isolinderanolide; ethyl 2,4-dioxohexanoate;

[59] Ding, Y.S., Zhang, L., Jain, R.B., et al. (2008). Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. Cancer Epidemiology, Biomarkers & Prevention, 17 (12), 3366-3371.
[60] Centers for Disease Control and Prevention (CDC). (2010). Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm in How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: CDC.

benzoic acid, 2,5-dihydroxy-methyl; ergosterol; isoquinoline 3-methyl; and pyridoxin). For these eight compounds, there were limits of detection, changes in the evaluation of the fragmentation pattern, and some of the compounds in the Non-Targeted Differential Screening study were identified as adducts of the compounds reported in the P1 characterization study.

d. Environmental Exposure from Heatstick Aerosol

Cigarette combustion generates environmental tobacco smoke (ETS), which consists of both side-stream smoke emitted from the cigarette and smoke exhaled by a smoker. The applicant states that the Heatstick does not produce side-stream smoke and submitted three peer-reviewed manuscripts as well as slides from a meeting presentation in support of this assertion.[61,62,63,64] Overall, the studies indicate that heated tobacco products, including Heatsticks, emit detectable levels of some HPHCs, but those levels are much lower than emissions from CC.

2. In Vitro Studies

A common generation and collection method was used for the Heatstick aerosols and 3R4F smoke for the in vitro studies (Ames test, mouse lymphoma assay, neutral red uptake assay) submitted by the applicant. Some of the methodology raises questions regarding interpretation of the data; however, there are no validated regimens for generating Heatstick aerosols. The applicant does not provide any rationale or justification for the differences in TPM or gas vapor phase (GVP) collection, and it is unclear what effect the collection methods may have on results of the studies; however, similar results for nicotine and acrolein levels measured by the two different methods indicate that the applicant's methodology is acceptable.

a. Neutral Red Uptake (NRU) Assays

Neutral Red Assay (NRU) can determine cytotoxicity. Studies RLS-ZRH-2015-249 and RLS-ZRH-2015-250 measured nicotine concentrations in the TPM from Regular and Fresh Menthol Heatstick aerosols as well as 3R4F smoke. Similarly, the applicant measured acrolein concentrations in the GVP from Regular and Fresh Menthol Heatstick aerosols as well as 3R4F. Cytotoxicity in the NRU results is expressed as the reciprocal of the effective concentration that reduces the number of viable cells by 50% ($1/EC_{50}$). The $1/EC_{50}$ values were calculated for both TPM and GVP fractions and expressed on both a per item and per nicotine basis. On a per stick basis, $1/EC_{50}$ values were 94%-95% lower for Regular Heatstick aerosols compared to 3R4F. Similarly, $1/EC_{50}$ values were 95% lower for Fresh Menthol Heatstick aerosols when compared to 3R4F. When normalized to nicotine yield, the NRU $1/E_{50}$ values were 91-92% lower for TPM and GVP from Heatsticks than for 3R4F RCS, indicating a reduced cytotoxic potential.

Clinical evidence provided by the applicant indicates that Heatstick users are frequently exposed to nicotine levels that are comparable to cigarette smokers. As such, assay results that are normalized to nicotine content are most appropriate for comparing cytotoxicity of Heatstick aerosols to 3R4F smoke.

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[61] Frost-Pineda K, Zedler BK, Liang Q, Roethig HJ. Environmental tobacco smoke (ETS) evaluation of a third-generation electrically heated cigarette smoking system (EHCSS). *Regulatory Toxicology and Pharmacology.* 2008;52(2):118-121.

[62] Tricker AR, Schorp MK, Urban H-J, et al. Comparison of Environmental Tobacco Smoke (ETS) Concentrations Generated by an Electrically Heated Cigarette Smoking System and a Conventional Cigarette. *Inhalation Toxicology.* 2009;21(1):62-77.

[63] O'Connell Peter Wilkinson G, Burseg K, J Stotesbury S, D Pritchard J. Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation. *Journal of Environmental Analytical Chemistry.* 2015;02.

[64] Goujon-Ginglinger C. MS. Indoor Air Quality Assessment of the Tobacco Heating System THS 2.2, Electronic Cigarettes and Cigarettes using a Dedicated Exposure Room. Paper presented at: Atmos'Fair 2016; Lyon, France.

b. Bacterial Reverse Mutation (Ames) test

The Ames test (studies RLS-ZRH-2015-253 and RLS-ZRH-2015-254) detects chemicals that induce mutations in bacteria that restore the functional capability to synthesize an essential amino acid (e.g., histidine). Bacteria that undergo these changes are called revertants – the more revertants, the more mutagenic the substance. In these studies, the applicant exposed five Salmonella typhimurium strains to varying concentrations of TPM from Regular and Fresh Menthol Heatstick aerosols, as well as 3R4F reference smoke, for 48-72 hours. The study reports did not contain information from an Ames test with GVP from Heatstick aerosols or 3R4F. The HPHC information submitted by the applicant indicates that Heatstick aerosols contain mutagens that are typically found in GVP (e.g., formaldehyde, propylene oxide). As such, an Ames test with GVP from Heatstick aerosols and 3R4F smoke would provide additional information about the mutagenic potential of the products.

The TPM fraction from Regular and Menthol Heatsticks did not produce a positive mutagenic response at any dose used in the Ames tests submitted by the applicant. In contrast, TPM from the 3R4F dose-dependently increased revertants in three bacterial strains, but only with metabolic activation. The positive controls used by the applicant produced a several-fold increase (typically by 300%-500%) in revertants when compared to untreated or vehicle-treated cultures.

c. Mouse Lymphoma Assay (MLA)

The MLA is a qualitative test that can determine clastogenicity and mutagenicity in a mammalian cell line by measuring the resistance to a lethal pyrimidine analogue (i.e., triflurothymidine [TFT]). The frequency with which these mutations occur (i.e., mutant frequency [MF]) is commonly expressed as the number of mutants per million (10^6) viable cells. The applicant submitted study reports (studies RLS-ZRH-2015-251 and RLS-ZRH-2015-252) on MLAs conducted with aerosols from Regular and Fresh Menthol Heatsticks, as well as 3R4F. The applicant reported that relative total growth (RTG) was measured for the cytotoxicity assessments. The MFs were derived from the plating efficiencies of cells grown in TFT selective and non-selective media.

Both TPM and GVP from Regular and Fresh Menthol Heatstick aerosols produced cytotoxicity in the MLA, with the highest concentrations reducing RTG to less than 20%. The concentrations of TPM and GVP from 3R4F and Heatstick aerosols that were used in the MLA produced similar maximum levels of cytotoxicity (15-20% RTG), but TPM and GVP from 3R4F produced these effects at much lower concentrations, indicating greater cytotoxic potency. For example, the concentration of TPM from 3R4F that reduced growth by 50% was about 13 times less than the concentration of TPM from Regular Heatsticks required to produce the same effect. The difference in cytotoxicity from GVP was even more pronounced: GVP from 3R4F produced 50% RTG at concentrations 29 times lower than GVP from Regular Heatsticks.

The study reports by the applicant indicate that TPM and GVP from Regular and Fresh Menthol Heatstick aerosols, as well as 3R4F, are cytotoxic; however, 3R4F produces cytotoxicity at much lower concentrations than Heatstick aerosols. Similarly, TPM and GVP from Regular and Fresh Menthol Heatstick aerosols, as well as 3R4F, are mutagenic. The lowest observed genotoxic effect levels (LOGELs) produced by 3R4F TPM were 15-30 times lower than the IQOS TPM. The LOGELs of 3R4F GVP were 8-24 times lower than the IQOS GVP. The applicant indicates this difference in LOGEL is an index of mutagenic potency. However, guidance from major public health resources (e.g., OECD, ICH, Health Canada, EPA) does not support this method of relative comparisons of mutagenic/genotoxic potency between tobacco products (or other chemicals).

d. Summary of In Vitro Studies

Limitations of these assays affect the conclusions that can be drawn from test results. 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 of mammalian cells. The NRU test detects cytotoxicity in a mammalian cell line. When normalized to nicotine yield, TPM and GVP from Regular and Menthol Heatsticks were approximately 90% less cytotoxic than TPM and GVP from 3R4F reference cigarette smoke. The MLA detects mutagenicity in a mammalian cell line. Evidence from the MLA also indicates that GVP and TPM from 3R4F smoke produces cytotoxicity at a lower concentration than TPM and GVP from Heatstick aerosols. Since different mutagenicity assays detect different types of genetic damage; it is not expected that a chemical will generate uniformly positive or negative results in the various assays.

Overall, the evidence submitted indicates that although both Heatstick aerosols and 3R4F smoke produce cytotoxic changes in vitro, 3R4F produces cytotoxicity at much lower concentrations than Heatstick aerosols. Similarly, both Heatstick aerosols and 3R4F are mutagenic, though 3R4F appears to produce genotoxic effects at a much lower level than Heatstick aerosols. As noted above, the level of substance required to produce these effects may not be an accurate indicator of mutagenic potency. Consequently, it is difficult to determine from these in vitro evaluations whether long-term use of Heatsticks will have the same carcinogenic potential as CC smoke.

3. In Vivo Studies

a. 90-day Nose-only Inhalation Studies

The applicant submitted study reports from two separate 90-day nose-only inhalation studies with adult male and female Sprague-Dawley rats with a 42-day post-exposure recovery period. The first 90-day inhalation study (Study #15006) determined toxicity produced by repeated exposure to either aerosols from Regular Heatsticks, 3R4F smoke, or filtered air (sham control). In the second study (Study #15025), rats were exposed to aerosols from either Fresh Menthol Heatsticks, 3R4F, smoke from one of two mentholated versions of the 3R4F, or filtered air (sham control).

The applicant reported urinary levels of BOE to the harmful and potentially harmful constituents NNK (total NNAL), acrolein (HPMA, 3-hydroxypropylmercapturic acid), benzene (SPMA, S-phenylmercapturic acid), and acrylonitrile (CEMA, 2-cyanoethylmercapturic acid) for all groups. Levels of these BOE were typically lower in rats exposed to Regular and Fresh Menthol Heatstick aerosols than in rats exposed to 3R4F smoke and similar to the sham control. Other measures collected during the study included: food consumption and weight, plasma BOE, respiratory physiology, lung inflammation, hematology and clinical chemistry measures, and necropsy with gross pathology and histopathology.

Overall, the incidence of basal cell hyperplasia (nose and larynx) and squamous cell hyperplasia (nose and larynx) were similar in rats exposed to either Heatstick aerosols or 3R4F, while goblet cell hyperplasia/hypertrophy (lung) and macrophage aggregation (lung) were only observed in rats exposed to 3R4F. 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 pre-neoplastic changes while intra-alveolar macrophage aggregation can be an early indicator of fibrosis and goblet cell hyperplasia can be an early sign of chronic bronchitis. 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.

b. 18-month Carcinogenicity Study with A/J mice

The applicant conducted an 18-month carcinogenicity study where A/J mice were exposed to either Marlboro Heatstick aerosol, 3R4F smoke, or fresh air (sham control). Data supplied by the applicant suggest that male mice are more sensitive to the toxic effects of Marlboro Heatsticks than female mice; the study was halted in Month 15 for male mice. The applicant reports lung tumor incidence data during Month 5 and 10 in all groups of female mice; no lung tumor incidence data from male mice was provided.

The preliminary report, submitted after 10 months of data, showed that Female A/J mice repeatedly exposed to 3R4F exhibited significant hematological effects (i.e., increased RBCs, decreased WBCs, increased mediators of immune response), altered clinical chemistry, elevated mediators of immune response, elevated markers of inflammation in bronchial-alveolar lavage fluid (BALF), impaired lung function consistent with emphysema, histopathological changes in lungs, and elevated incidence neoplastic and pre-neoplastic lesions in the lungs when compared to sham controls. Female A/J mice repeatedly exposed to the same concentration of Regular Heatstick aerosols (i.e., 13.4 µg/L) commonly exhibited some changes to these same parameters, but the changes were typically less severe or transient.

The incidence of bronchioloalveolar adenoma during Month 10 is similar in female mice exposed to either 3R4F or Regular Heatstick aerosols (50% and 54.5%, respectively). However, the applicant reports the incidence of bronchioloalveolar adenoma during Month 10 to be numerically higher in sham controls (25%) than in female mice repeatedly exposed to the low- or high-concentration of Regular Heatstick aerosols (9.1% and 16.7%, respectively). No explanation for the lack of a dose-response relationship for Regular Heatstick aerosols and bronchioloalveolar adenoma incidence was provided.

The final report for this study was received September 4, 2018. The applicant concludes the study demonstrated no increase in lung cancer risk due to THS 2.2 aerosol exposure compared to sham group. Per the applicant, toxicity is limited to adaptive responses in the upper respiratory tract organs and stress-related responses to exposure, both of which were of lower severity compared to the mice exposed to 3R4F smoke.

c. Nicotine Pharmacokinetic (PK) Study with Rats

The objective of this study was to model the inhalation of the nicotine-containing aerosol, conversion of nicotine to cotinine in the liver, distribution of nicotine and cotinine between the blood and liver compartments, and cotinine excretion. While the applicant reported trends in estimated values for $t^{1/2}$ and C_{max}, the PK model developed was not sensitive enough to detect significant group differences between test articles. Due to this variation, the applicant noted that the study power was not sufficient to detect significant group differences. This study does not provide relevant information for determining the health effects of Heatsticks; however, human PK studies were submitted and are more informative. These are reviewed in Section II.D.1.a.

d. Summary

In vivo studies, such as the 90-day inhalation study, can provide important information about non-cancer toxicology endpoints, but are not generally sensitive enough to determine systemic toxicities from chronic tobacco product use. Despite that, the data submitted by the applicant indicate that sub-chronic exposure to Heatstick aerosols produce fewer or less severe histopathological changes than sub-chronic exposure to similar concentrations of 3R4F. Development of PK modeling of nicotine and cotinine sensitive enough to distinguish differences in nicotine and cotinine exposure will require the addition of sampling time points during inhalation exposure and model adjustments.

Similar to the in vitro studies, it is difficult to determine the carcinogenic potential of long-term exposure to Heatstick aerosols from these evaluations. The data suggest there is potential for carcinogenic effects from Heatstick aerosols, but at much higher exposure levels than required for CC smoke. The 18-month carcinogenicity study results reported by the applicant showed no increase in risk due to the Heatstick aerosol exposure compared to CC smoke and the changes noted were similar to the sham control group. How this correlates with clinical changes in humans is unknown.

4. Systems Toxicology Studies

a. Acute and Repeated Exposure Studies with Human Organotypic Tissues

The applicant submitted data from five separate in vitro organotypic studies assessing the effects of acute and repeated exposure to Regular HeatStick aerosols and 3R4F smoke on human gingival, buccal, nasal, bronchial, and coronary arterial epithelium cultures. Both 3R4F and Regular Heatstick aerosols produce toxicity (e.g., oxidative stress, DNA damage, increased proinflammatory mediators) in human gingival, bronchial, buccal, nasal, and small airway tissues, as well as epithelial tissues from human coronary arteries. The toxic effects produced by 3R4F smoke were generally more severe than those produced by Regular Heatstick aerosols or similar toxic effects were produced at much lower 3R4F smoke concentrations. However, there is variability in the 3R4F and Regular Heatstick aerosol concentrations and the post-exposure timepoints used in the applicant's statistical analysis.

The experimental approach taken in these studies included using methods that are exploratory, have not been independently validated, and have unknown utility for regulatory use. The applicant attempts to extrapolate from acute exposure studies with naïve tissues that have little or no genetic variability to predict toxicity in a diverse population with a history of cigarette smoking. This limits the use of these data. Thus, this data does not significantly contribute to the overall toxicological profiles of the products under review in these applications.

b. $ApoE^{-/-}$ Mouse Switching Study

The applicant conducted an 8-month switching and cessation study with female ApoE-/- mice; the report is in Section 7.5 of the submission. In this study, mice were exposed to 3R4F smoke, Regular Heatstick aerosols, or sham conditions 3 hours per day, 5 days per week, for 8 months. Additional groups of mice were exposed to 3R4F smoke under the same regimen but were switched to either Regular Heatstick aerosols (the "switching group") or to filtered air (the "cessation group") after 2 months. The study report includes information about biomarkers of HPHC exposure, hematologic effects, BALF, histopathology, lung function and volume, aortic arch morphometry, and tissue functional genomics evaluations (i.e., transcriptomics, lipidomics, and proteomics) performed at multiple time points.

This study was intended to model continued cigarette smoking vs. switching to Heatsticks vs. smoking cessation. There were limitations to the study design that affect interpretation of the data. Specifically, no male A/J mice were used in this study and the 3R4F exposure period for the switching group may have been too brief to allow determination of how Heatstick aerosols affect progression of the toxic effects caused by cigarette smoke. The histopathologic changes seen in the switching group were similar to cessation, but it is not clear whether a longer smoking period would lead to the same result. However, the overall pattern of changes related to switching from 3R4F to Heatstick was positive. Although the results from Heatstick exposure were not the same as sham (or smoking abstinence), some effects seen after 3R4F exposure were either less prominent or occurred less frequently in the mice that "switched" to Heatsticks, indicating that

switching to IQOS could be beneficial to smokers. Dual exposure to cigarette smoke and Heatstick aerosol was not evaluated.

5. Nonclinical Evaluation of Carbon Monoxide from Heatstick Aerosol

Reconstituted tobacco can produce high levels of CO and nitrogen oxides during combustion. However, despite containing only reconstituted tobacco, the three Heatsticks produce much lower CO compared to regular CC. The applicant considered the (b) (4) (b) (4) The product specifications for CO, as set by the applicant, are (b) (4) /stick for PM0000424 and (b) (4) /stick for PM0000425 and PM0000426 – as measured in the respective Heatstick aerosols generated by a CI smoking regimen.

The established product specifications were achieved. The measured CO produced by Heatstick aerosol was 0.2-0.3 mg CO/Heatstick (ISO regimen) and 0.3-0.5 mg CO/Heatstick (CI regimen). This is 99% lower than the CO level in combusted cigarette smoke (~28-33 mg/cig CI regimen). During the inspection of the Bologna (Italy) facility, CoAs for batch release collected included the specifications and the results obtained for one batch of each of the three products; measured CO levels were 0.41-0.43mg/Heatstick.

In the ApoE-/- Mouse Switching Study, the applicant indicated that carboxyhemoglobin (COHb) levels in the blood were measured during Months 2, 4, and 7. Mean COHb levels were consistently higher in mice from the 3R4F group than in mice from the switching, cessation, or sham control groups, though the applicant did not provide a statistical analysis of these data. The applicant also indicates that mice in the cessation and sham control groups had similar COHb levels but did not indicate whether COHb levels in mice from the switching group were significantly different from controls. See Figure 3 below.

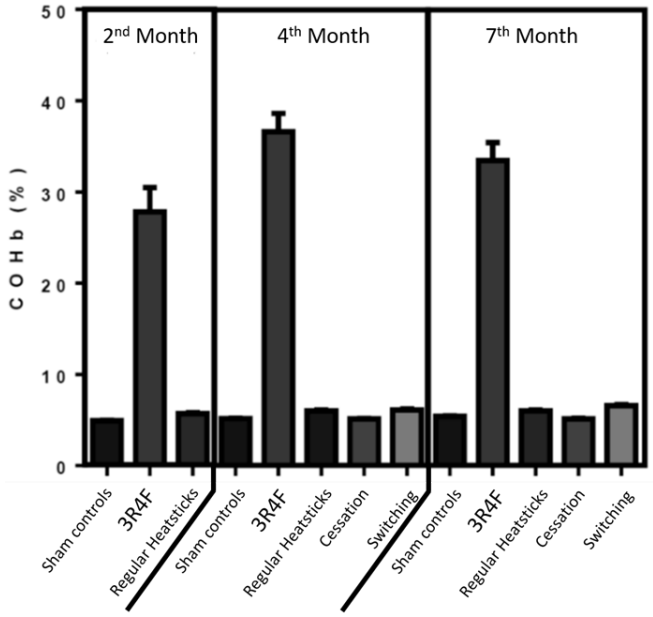
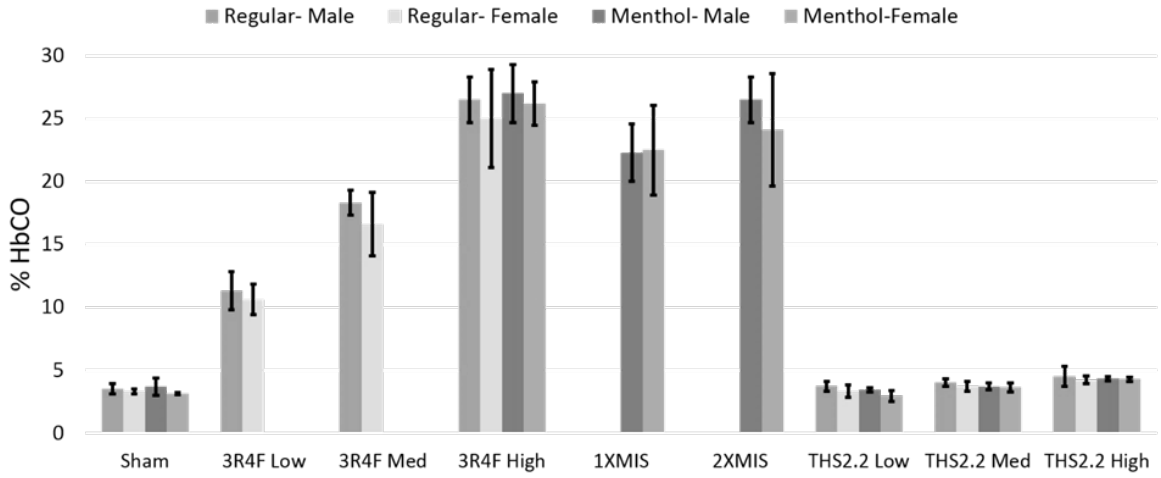


Figure 3: Carboxyhemoglobin Levels after Repeated Exposure to 3R4F, Regular Heatstick Aerosols, or Sham Conditions

Source: "15015_CVD_Resp_ApoE_SW_SR_Part 1", Figure 9, page 59

In the 90-day nose-only Inhalation studies conducted in rats, COHb levels in all Heatstick Regular and Menthol exposure groups were equivalent to sham controls while rats exposed to 3R4F smoke were

substantially elevated. During the 42-day recovery period, COHb levels in the 3R4F exposed group returned to normal levels.



Data source: "15006 THS SR Part 1", page 170 and "15025 THS SR Part 2, page 48; Measurement made at day 47 (week 6) for the Heatstick menthol study; measurement date not noted for Heatstick regular study

Figure 4: Plasma Carboxyhemoglobin Levels at Week 6 for 90-day Rat Inhalation Study

6. Summary of Toxicological Findings

The toxicology review provides this summary of key findings:

- There are HPHC reductions in Heatstick aerosols relative to smoke from 3R4F reference cigarette and 30 commercially available CCs.
  - In the PMI-58 study, the 54 measured HPHC levels were reduced by 54.4-99.9% on a per stick basis when compared to 3R4F smoke. Machine-generated nicotine yields were reduced 35.9-39.4%, but clinical data indicates human CC smokers and Heatstick users absorb similar amounts of nicotine.
  - For 18 of these compounds, the applicant determined that yields in Heatstick aerosols were reduced by 40-99.8% when compared to the mean of 31 CC commercially available in the U.S. (on a per stick basis).
  - Side-stream aerosol from Heatsticks emit detectable levels of some HPHCs, but levels are significantly lower than emissions from CC.
- The non-targeted differential screening assay indicates that Heatstick aerosols contain four probable of possible carcinogenic chemicals that are unique to IQOS or present in higher levels than 3R4F smoke. The aerosols also contain 15 other chemicals that are possibly genotoxic and 20 more GRAS compounds that have potential health effects. When balanced against the significant decreases in the number of HPHCs and HPHC yields, however, these chemicals, which are present at very low levels, do not raise significant concerns from a public health perspective.
- TPM from Heatsticks did not produce a positive response for mutagenicity in the Ames assay at any dose tested, either with or without metabolic activation.
- The NRU assay results indicate that cytotoxicity for the Heatstick TPM and GVP are reduced by ~95% (per stick) and ~90% when normalized to nicotine content and compared to 3R4F.
- The in vitro MLA shows a biologically relevant mutagenic response in mammalian cells from Heatstick aerosols and 3R4F smoke (both with and without metabolic activation) after 4 hours of exposure, but the minimum Heatstick TPM concentration required to produce this positive result was 15-30 times greater than the concentration required for the 3R4F cigarette. The applicant

indicates that this difference is an index of mutagenic potency; however, this concept is not supported by guidance documents from major public health resources (e.g., OECD, ICH, Health Canada, EPA). The applicant's conclusion that both Heatsticks and 3R4F have cytotoxic and mutagenic potential appears accurate; however, CTP agrees with the public health groups that the level of a substance required to produce a genotoxic effect may not be an accurate indicator of mutagenic potency.

- Heatstick aerosols generally produced fewer pathophysiological changes and adverse effects than 3R4F smoke in organotypic studies. However, the experimental approach taken in these studies included using methods that are exploratory, have not been independently validated, and have unknown utility for regulatory use. Thus, this data does not significantly contribute to the overall toxicological profiles of the products under review in these applications.
- The 90-day inhalation study in rats showed that changes related to Heatstick aerosol exposures were not observed or much less severe than changes noted due to 3R4F exposure.
- An 8-month mouse switching/cessation study suggested switching to Heatsticks after a short period of cigarette smoke exposure led to histopathological changes similar to smoking cessation. However, as noted in the discussion above, study design limitations preclude reliance on these data.
- The 18-month carcinogenicity study shows that the incidence of neoplastic lesions appeared to be higher in some groups exposed to either Heatstick aerosols or reference cigarette smoke compared to the sham control group. However, other evidence indicates repeated exposure to Heatstick aerosols produced fewer histopathological changes than repeated exposure to 3R4F smoke. The applicant concludes this long-term study demonstrated no increase in lung cancer risk due to THS 2.2 aerosol exposure compared to sham group. Per the applicant, toxicity is limited to adaptive responses in the upper respiratory tract organs and stress-related responses to exposure, both of which were of lower severity compared to the mice exposed to 3R4F smoke.

As TPL, I agree with the toxicology review conclusion. After consideration of all the toxicological data presented, the demonstrated reductions in measured HPHC exposures and reduced histopathological changes with reduced potential for atherosclerotic effects indicate the potential for a relative benefit compared to CC for smokers who switch completely to IQOS. The toxicological profiles of the Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks are essentially identical; the only difference in the Heatsticks is the quantity of menthol added to each product. Marlboro, Smooth Menthol, and Fresh Menthol Heatstick aerosols contain some chemicals which are different from those found in CC. Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC.

D. Behavioral and Clinical Pharmacological Assessment

1. Pharmacokinetics, Exposure/Response and Clinical Pharmacology

a. Pharmacokinetic/Pharmacodynamic (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 in participants using THS 2.2 compared to smoking own-brand CC and nicotine replacement therapy (NRT) products. The NRT product varied by the location of the study. The primary PK parameters in these studies were maximum nicotine plasma concentration (C_{max}) and area under the nicotine plasma concentration vs. time curve from time zero to the last observation ($AUC_{0\text{-}last}$). Products were administered following ≥ 24 hours nicotine abstinence; participants used their assigned product once: one Heatstick, one CC *ad libitum,* two 1 mg sprays of nicotine nasal spray (NNS) dosed at one spray per nostril or one piece of 2

mg nicotine gum used for 30 minutes. As a PD response measure, exposure to CO was assessed as exhaled CO (eCO) and as carboxyhemoglobin (COHb) blood saturation. Measures related to craving (QSU-Brief) and reinforcement (MCEQ) were part of the PD assessment.

The clinical pharmacology review analyzed the PK/PD studies using non-compartmental data analysis and population PK data analysis. In the two Japanese studies (ZRHR-PK-02-JP and ZRHM-PK-05-JP), the geometric mean (GM) values of C_{max} and $AUC_{0\text{-}last}$ calculated by noncompartmental analysis were similar between THS 2.2 and CC for both Regular and Menthol products. In the Irish and U.S. studies (ZRHR-PK-01-EU and ZRHM-PK-06-US), the GM values of nicotine exposure parameters in the THS 2.2 arm were lower than in the CC arm for both C_{max} and $AUC_{0\text{-}last}$. The Irish and U.S. studies resulted in lower nicotine exposure in the THS 2.2 arm than the Japanese studies. In all studies, the CC arms had similar GM C_{max} values while the GM $AUC_{0\text{-}last}$ values were highest in the U.S. study. This finding may be explained by the CC characteristics (no limit of 1 mg ISO nicotine level in own brand CC as used in three other studies), prolonged duration of *ad libitum* CC use (longer time to reach C_{max}, T_{max} values), genetic differences, and differences in puffing behavior between the populations.

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 BOE in smokers who switched to THS 2.2, continued to smoke CC, or abstained from smoking (SA). Nicotine plasma concentrations were measured as a secondary objective once daily and frequently on Day 5 of the confinement period and were compared across the three arms. Two REX studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US) had an 85-day ambulatory phase extension after the 5-day confinement period for total study duration of 90 days. Plasma nicotine and cotinine concentrations were measured in the mornings of Days 30, 60, and 90. In addition, urinary nicotine equivalents (NEQ) (nicotine, cotinine, 3'-Hydroxycotinine and their glucuronides) were measured in 24-hour urine daily on Days 1-5, and on Days 30, 60, and 90 in the extended studies. The GM values of nicotine and cotinine concentrations in plasma and GM values of urinary NEQ were similar between the THS 2.2 and CC arms.

The population PK modeling of nicotine (ZRH-POP-PK-01) was conducted with four goals:

- Describe the nicotine PK with physiologic parameters (clearance, volume of distribution)
- Assess sources of variability in nicotine PK parameters
- Assess the predictive performance of the model
- Distinguish between the exposure due to product use and background exposure

The plasma concentration data were combined from all studies following use of nicotine-containing products (i.e., THS 2.2 and its comparators: CC, nicotine gum, and NNS). The analysis dataset included all participants that used a product at least once and had at least one measurable nicotine plasma concentration. It included baseline demographic variables, daily cigarette consumption at baseline, and some product-related information (e.g., type of product, presence of menthol, and nicotine dose). Model evaluation and selection of the base model were adequately performed using the standard statistical criteria of goodness-of-fit.

The typical initial and terminal half-lives of nicotine were 1.35 hours and 17 hours, respectively. These values are markedly longer than previously published; however, they appear to be reasonably assessed. The previous reports of a shorter terminal half-life may have failed to capture the terminal phase of nicotine PK due to the shorter sampling period as well as lower assay sensitivity (most analytical methods report low limit of quantification [LLOQ] from 0.5 to 1 ng/mL; the applicant reported LLOQ as 0.2 ng/mL). The model adequately captured the median nicotine PK profile for every product in both periods of studies. The

observed 90th percentile was generally within the prediction interval. The lower nicotine concentration range was difficult to predict, possibly due to fewer observations in that range.

b. Intrinsic and Extrinsic Factors Affecting Nicotine Pharmacokinetics

The covariate analysis for the selected base model was conducted in accordance with the FDA Guidance on Population Pharmacokinetics. The covariate analysis of the final model explained the effects of the following intrinsic factors: baseline body weight, CYP2A6 activity, sex and race. Clearance in female participants was 26% higher than in males. In addition, clearance was positively correlated with the baseline activity of cytochrome P450 2A6 isoform (CYP2A6): a doubling in CYP2A6 activity appeared to increase nicotine clearance by 25%. In addition, the effect of African American race increased C_0 by 50%.

The covariate analysis of the final model evaluated the effects of the following extrinsic factors: the nature of product, the nicotine ISO yield, and the presence of menthol. The bioavailability of CC, NNS, and nicotine gum relative to THS 2.2 was 102%, 24%, and 61%, respectively. Bioavailability decreased with increasing nicotine ISO yield (a doubling in nicotine ISO yield would result in a 33% relative decrease) and with increasing body weight (a 10% increase in body weight would result in a 6.6% relative decrease). The apparent central volume of distribution was 9.5% larger with Menthol than with Regular products. The absorption duration (T_{dur}) from the nicotine gum lasted 45 minutes vs. 5.3 minutes for other products. Menthol products marginally, but significantly, increased T_{dur} by 5% vs. Regular products. Menthol had no effect on bioavailability relative to THS and apparent clearance, which are the determinants of plasma exposure (AUC) at a given nicotine ISO yield.

The population PK model structure allowed the separate derivation of exposure parameters based on both total and background-adjusted concentrations of nicotine from four different nicotine-containing products (CC, THS 2.2, NNS and NRT gum) with different routes of administration (inhalation, oral, and nasal) in different populations (American, European and Japanese).

c. Nicotine Equivalents (NEQ) in Urine

NEQ measured in 24-hour urine is often used to estimate nicotine exposure in clinical studies since it reflects at least 80% of the daily nicotine uptake in smokers.[65] NEQ consists of nicotine and five major metabolites: nicotine-glucuronide, cotinine and its glucuronide, trans-3'-hydroxycotinine and its glucuronide. Urinary NEQ adjusted for creatinine were measured daily in the confinement period of all REX studies and on Days 30, 60, and 90 in the ambulatory period of studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US.

The 24-hour NEQ urinary concentrations adjusted for creatinine between the THS 2.2 and CC arms were similar on each day of studies ZRHR-REXC-03-EU and ZRHR-REXC-04-JP. Nicotine exposures measured by NEQ between mTHS 2.2 and menthol CC (mCC) arms during the confinement period were also similar in study ZRHM-REXA-07-JP. In study ZRHM-REXA-08-US, NEQ was slightly lower after the use of mTHS 2.2 compared to the mCC arm. On Day 5, the differences in NEQ in each of the studies were not statistically significant. During the ambulatory period of studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US, differences in NEQ were not statistically different at any day with confidence intervals (CIs) including zero.

[65] Wang, J., Liang, Q., Mendes, P., & Sarkar, M. (2011). Is 24h nicotine equivalents a surrogate for smoke exposure based on its relationship with other biomarkers of exposure? Biomarkers, 16(2), 144-154.

d. Summary

Overall, the population PK model accounts for the variability in nicotine PK among all clinical studies with consideration of the influence of the statistically significant intrinsic (body weight, CYP2A6 activity, sex, and race) and extrinsic (nicotine ISO yield, presence of menthol) factors. Based on this model, nicotine PK in smokers who switched to THS 2.2 is similar to those who continued to smoke CC.

2. Behavioral Pharmacology

a. Use Behavior and Topography

The applicant conducted four PK/PD studies, four REX studies, and one Actual Use study. These studies collected data on product use behavior (e.g., daily consumption, topography), subjective effects of product use on nicotine dependence, product satisfaction and reinforcement, and product misuse at different durations of use (single use, 5 days, 6 weeks, and 3 months). Tobacco product use behavior plays a critical role in exposure to nicotine and other constituents and can signal compensatory behaviors. Subjective effects can indicate the likelihood of continued use of a product and abuse liability. Although these measures can be considered from a public health perspective, for both users and nonusers, the provided studies only include current daily CC smokers, who may also use other tobacco products.

THS 2.2 topography is limited by its intrinsic properties, which limit the number of puffs to 14 and smoking duration to a maximum of six minutes. (b) (4)

The applicant states tha (b) (4)

In the CC arm of the REX studies, topography measures were generally stable over time. Differences in topography over time were expected when consumers switched from CC to THS due to adaptation to the new product. Compared to the CC arm, participants in the THS 2.2 arm took more puffs (three of four studies), had a shorter smoking duration (two of four studies), had a higher puff frequency (four of four studies), and did not differ in total puff volume. The applicant attributes these differences to adaptation to the intrinsic properties of the new product as well as to differences in nicotine delivery, product satisfaction, ritual, sensory factors, and taste. Findings were similar for Menthol and Regular flavor products.

b. Product Use/Consumption

Tobacco product consumption rates play a critical role in exposure to nicotine and other constituents. Level of consumption (secondary outcome) was measured as the number of CC or Heatsticks used per day. In the conducted studies, product use was recorded by study staff, documented by product dispensation and collection, or recorded by participants in a diary. Use of other nicotine products was recorded (yes/no), but frequency was not measured. Self-report data is susceptible to inaccuracies. Compliance to the assigned study product was controlled during confinement periods. During ambulatory periods participants were instructed to use their assigned product but noncompliance did not result in study removal and accuracy of reporting is likely not optimal.

In the 5- and 90-day REX studies, both THS 2.2 and CC arms showed minimal changes in product use over time (see Figure 5 below). Inclusion of dual use data in the analyses (i.e., combined CC and Heatstick use) did not have a major effect on changes in consumption for the THS 2.2 arm during the confinement or

ambulatory periods. These results were consistent across the REX studies, despite differences in environment (confined vs. ambulatory), populations, dual/exclusive use, and flavor (Menthol vs. Regular).

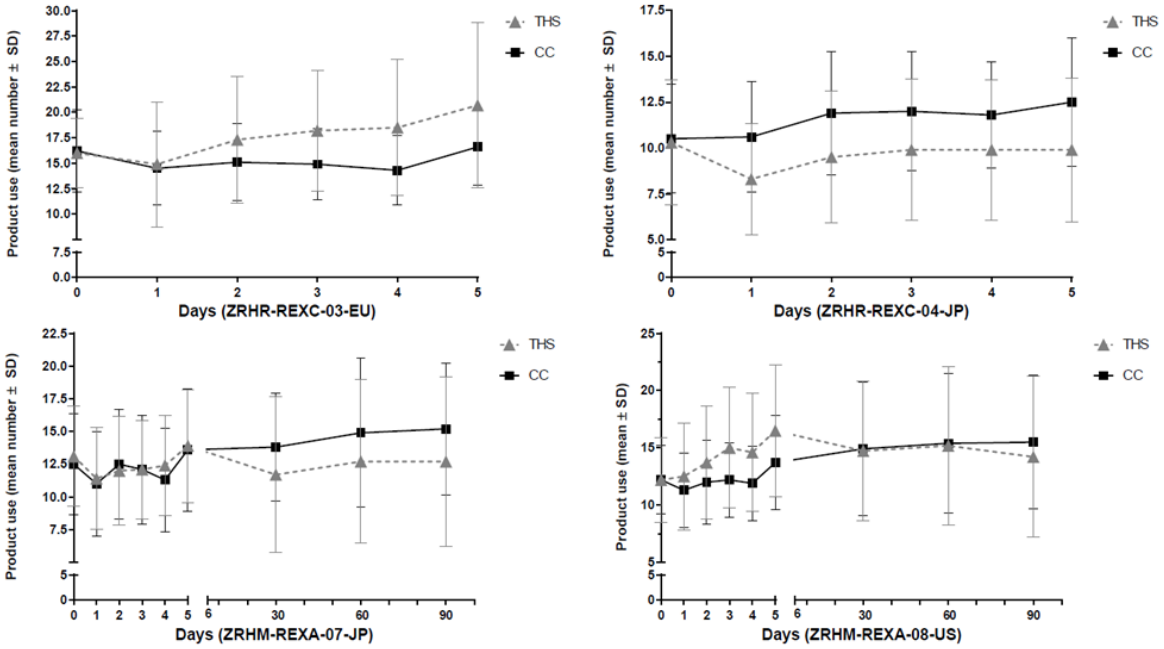


Figure 5: Product Consumption (Number of Products Used) During the REX Studies
Source: Section 6.2.2 Note: Day 0 = Baseline

One single-group, prospective observational study (THA-PBA-07-US) was conducted with a primary aim to investigate how U.S. adult daily smokers of CC used THS 2.2 in near to real-world conditions (i.e., naturalistic setting). During this Actual Use study, participants were exposed to IQOS system material and those with positive "intention to use" were invited to participate in the study. After a one-week baseline period where they smoked own brand CC and potentially used other tobacco products as well as NRTs, participants received the IQOS system kit and instructions for use. Menthol preferences were honored. Participants could consume THS 2.2, CC, and other tobacco products as well as NRTs 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. Relevant secondary endpoints included product consumption and THS 2.2 misuse; data on hypothetical purchasing of THS 2.2 were also reported, but not listed as an endpoint.

In the Actual Use study, the average number of products (CC and Heatsticks combined) used per day was slightly lower during the observational period compared to baseline (9.3 products per day vs. 10.2 CPD) for the overall sample (N=987). This decrease was similar for participants who used THS 2.2 > 70% of the time (N=141): participants used 8.1 products per day during the observational period compared to 9.0 CPD at baseline. Findings were similar for users of Menthol and Regular products. Data were descriptive, and no statistical analysis was provided.

Several aspects of study design may have contributed to differences in product consumption across study arms of the REX studies, as well as overall use and use patterns in the Actual Use study. Participants received the THS 2.2 for free while those in the CC arm of the REX studies continued to pay for their cigarettes. Information provided to the participants about THS 2.2 might have influenced perceptions of product safety profiles, thereby contributing to differences in use behavior and exposure. In addition to differences in

labeling on CC compared to THS 2.2 Heatstick packages, participants in different REX studies were exposed to different product information in the informed consent documents. For example, the informed consent for the ZRHR-REXC-04-JP study suggests the investigational product is less harmful than CC, 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 this language was not included in the informed consent for study ZRHM-REXA-08-US.

c. Product Acceptability

Dual use of THS 2.2 and CC was evident in the REX studies and the Actual Use study. During the last 30 days of the ambulatory period in the REX studies, dual use was low in the Japanese study; at least 84.6% reported using THS 2.2 exclusively (100%) and at least 85.9% reported using THS 2.2 > 95% of the time. In contrast, dual use was higher in the U.S. REX study; at least 55.0% reported using THS 2.2 exclusively, and at least 63.8% reported using THS 2.2 > 95% of the time. Notably, only 7.5% of cigarette smokers reported using THS 2.2 > 95% of the time at the end of the Actual Use study. The higher rates of complete switching in the REX studies may have occurred because participants were instructed to use the THS 2.2 exclusively and were confined and monitored to ensure compliance during the first five days of the study. Concurrent use of other tobacco products or NRTs was not considered in this analysis.

A further analysis considered use of tobacco products other than mCC in the mTHS 2.2 arm of the REX studies. To meet criteria for "compliant" exclusive use, participants were not allowed to use "any nicotine or tobacco-containing product other than the assigned product." In the extended REX study conducted in Japan, 65 of 78 participants (83.3%) met this stricter exclusive use criteria during the last 30 days of the ambulatory period; however, in the U.S. extended REX study only 41 of 80 participants (51.3%) met this stricter exclusive use criteria during the last 30 days of the ambulatory period.

d. Abuse Liability

The degree to which current smokers and nonsmokers are likely to use the product and become addicted or dependent was evaluated by self-report questionnaires. Participants reported perceived effects of THS 2.2 on nicotine dependence and dependence symptoms (e.g., craving, withdrawal), reward/reinforcement following use, product valuation (i.e., hypothetical purchasing) compared to own-brand CC, and product misuse.

The Questionnaire of Smoking Urges – Brief (QSU-Brief) measures craving from two perspectives: (1) the intention and desire to smoke and anticipation of positive effects from smoking (positive reinforcement) and (2) the anticipation of relief from negative affect and nicotine withdrawal, and urgent and overwhelming desire to smoke (negative reinforcement). In the four PK/PD studies, relief from craving (QSU-Brief) showed a similar time curve following both THS 2.2 and CC arms: highest smoking urge prior to use, sharp decline following use, and continued decline to approach baseline over 12 hours. In the four REX studies, relief from craving (QSU-Brief) did not differ significantly between the THS 2.2 and CC arms and remained stable throughout the study. Findings were similar for Menthol and Regular products.

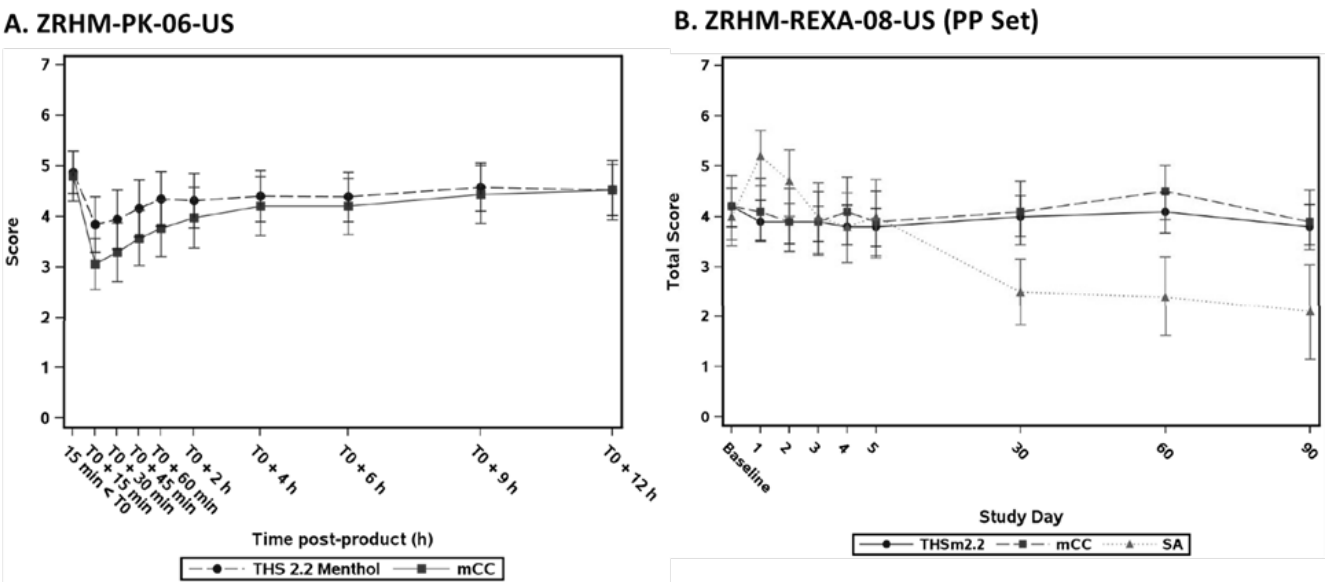


Figure 6: Arithmetic Mean and 95% CI Total Scores for QSU-Brief Total

Source: Section 7.3.1 ZRHM-PK-06-US Final Study Report, Section 7.3.1 ZRHM-REXA-08-US Final Study Report

Note. QSU-Brief scores reported on a 7-point scale. Higher values indicate greater intensity of urge.

The Minnesota Nicotine Withdrawal Scale – Revised (MNWS) measures relief from withdrawal based, in part, on withdrawal symptoms identified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases – 10th Edition (ICD-10) and a question on craving. In the REX studies, MNWS was administered prior to product use and reflected the previous day's experience; these data were exploratory. No differences were found between study arms, at Days 5 or 90, on the MNWS questionnaire.

The Fagerström Test for Nicotine Dependence (FTND) is a test of physical dependence. In the two 90-day REX studies, FTND was administered at baseline and at the end of the ambulatory period (Day 90). No statistical analyses were conducted. No differences in dependence severity were found between THS 2.2 and CC arms at Day 90; both arms showed no change in the Japanese study or equally reduced symptom severity in the U.S. study.

The Prochaska "Stage of Change" Questionnaire assessed participants' past-year quit attempts and quit intent in the next 30 days or six months. This questionnaire was administered in the U.S. REX study at screening, baseline (Day -2), Day 30, Day 60, and Day 90. No statistical analysis was conducted. At Day 90, some participants in both study arms reported "seriously thinking of quitting smoking" within the next 30 days (10.4% THS 2.2 arm, 13.8% CC arm).

Reinforcing and aversive effects were measured using a self-report questionnaire (Modified Cigarette Evaluation Questionnaire [MCEQ]) whose subscales include: smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations, and craving reduction. In the PK/PD studies, MCEQ was administered after product use and was a secondary outcome measure. In the REX studies, MCEQ was administered at the end of the day (8-11 pm). Data were exploratory and descriptive.

In the PK/PD studies, when compared to CC, THS 2.2 had significantly lower MCEQ ratings on four of five MCEQ subscales: craving reduction (two studies), enjoyment of respiratory tract sensations (four studies), psychological reward (one study), and smoking satisfaction (four studies). Scores on the aversion subscale

showed no difference between THS 2.2 and CC. Findings were similar for Menthol and Regular products. In the REX studies, THS 2.2 had significantly lower ratings than CC on Day 5 (end of confinement) but no differences were found on Day 90 for the two extended REX studies. This may reflect a learning or adaptation period to the new product.

In the Actual Use study, participants were asked at the end of the observational period (Week 6) about their likelihood to purchase the IQOS system "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." 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 THS 2.2 > 70% of the time (Week 6, N=138), nearly 50% reported they "probably or definitely" would buy IQOS. Although descriptive data were provided, this was not listed as an outcome measure. It is unclear if participants assumed that they had already owned the IQOS system and were being asked about buying Heatsticks only, or if they assumed the question was referring to purchasing both the IQOS system and Heatsticks.

There are limitations to interpretation of questionnaire data, including:

- Recall bias and other inaccuracies associated with self-report
- No assessment of the relationship between subjective measures and behavior
- No data was provided on the validation of translated versions of the questionnaires used in studies not conducted in the U.S.
- The QSU-Brief was not modified to replace references to cigarettes with Heatsticks/IQOS/THS 2.2, so it is unclear if participants were aware of which product was being asked about
- Scoring of the MNWS differed between studies
- Intent to quit results have limited generalizability to participants who have quit intent of greater than six months (inclusion criteria) and are difficult to interpret because it was not clear whether the intent to quit refers to quitting all tobacco vs. switching completely from smoking CC to THS 2.2

e. Summary

As noted above, there are limitations for self-reported data; however, this is an informative method for obtaining information of this type. These are validated questionnaires for outpatient tobacco research and are commonly used in studies of tobacco use behaviors. Systemic nicotine exposure was similar after single and multiple uses of THS 2.2 and CC (both Regular and Menthol). Nicotine exposures appear sufficient to provide user satisfaction, which can facilitate partial or complete switching to THS 2.2. THS 2.2 use rates were similar to CC use rates. Self-report questionnaires found that THS 2.2 produces reinforcing effects reaching or close to levels of CC reinforcement. Likeability scores for THS 2.2 increased over the 90-day period for those who used it more consistently which may indicate the need for an "adjustment" or transition phase from CC, (i.e., dual use).

The data indicate that THS 2.2 has addictive potential and abuse liability similar to CC. This is important as it signifies THS 2.2 can provide an adequate nicotine source for dependent populations, including current CC users; however, there is also a risk tobacco-naïve new THS users will develop nicotine addiction.

3. Summary of Behavioral and Clinical Pharmacology Findings

The behavioral and clinical pharmacology (BCP) review concludes that the similar systemic exposure to nicotine as well as similar use rates, reinforcement, and withdrawal/craving reduction profiles between THS 2.2 and CC suggest a similar abuse liability of these tobacco products. Thus THS 2.2 use may sustain

addiction to a similar level as CC in current smokers and have a similar risk of nicotine addiction as CC in nonsmokers.

As TPL, I agree with the BCP review conclusions. IQOS provides nicotine at a high enough level to satisfy the withdrawal and craving symptoms of current smokers. The nicotine levels do pose an addiction risk for non-tobacco users who initiate use of these products; however, the risk is no higher than for other, currently available, tobacco products.

E. Individual Health Impact

1. Biomarkers of Exposure (BOE)

The BOE selected correspond with 14 HPHCs identified by FDA as being found in cigarette smoke or filler. 1-hydroxypyrene is considered a general proxy for PAHs. HEMA, and the aromatic amine o-Toluidine were also measured. Exposures to acetaldehyde, formaldehyde, isoprene and ammonia were not assessed as biomarkers as there are not suitable biomarkers for these exposures.

The four clinical REX studies assessed changes in systemic exposure of HPHCs and their metabolites in smokers who switched to THS 2.2 or abstained from smoking CC during the 5-day confinement period. Two of these studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US) had an ambulatory period extension of 85 days. All REX investigations were randomized, controlled, open-label, 3-arm parallel group studies. Studies ZRHR-REXC-03-EU and ZRHR-REXC-04-JP investigated Marlboro (non-mentholated) Heatsticks, whereas studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US investigated Menthol Heatsticks. Participants who were "willing and able" to use IQOS after a demonstration were randomized to one of three study arms in a 2:1:1 ratio by sex and past month mean smoking rate (10-19 CPD vs >19 CPD at screening).

During the five-day confinement period, assigned products were used *ad libitum* from 6:30 am to 11:00 pm. Dual use of THS 2.2, CC, and other tobacco products as well as NRTs was not permitted during the confinement period. Participants in the SA arm were not provided with "medication supportive for smoking abstinence" during confinement. 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 5-day confinement period to evaluate if the results achieved under controlled conditions were maintained. Participants in the SA arm were instructed to remain abstinent with or without NRT, for which they were reimbursed, during the ambulatory period. Data were collected daily during confinement and on days 30, 60, and 90 during the ambulatory period. Nicotine abstinence was not required prior to the assessments during Day 30, 60, or 90 visits.

Exposure to 16 HPHCs (including nicotine for a total of 17) were evaluated in the clinical studies, by either measuring the parent compound (e.g., 4-aminobiphenyl), by measuring one or several of their metabolites, or by using a surrogate BOE as representative of a chemical class of compounds. The list of all selected biomarkers, their classes, and related major toxicities is presented in Table 3. An assessment of markers reflecting an overall exposure to HPHCs, was also performed, including:

- Activity of CYP1A2, an enzyme which can be induced by polycyclic aromatic amines
- Urine mutagenicity potential, a measure to assess exposure to various carcinogenic/mutagenic substances

These markers are not associated with a specific HPHC.

Table 3: Selected HPHCs, Chemical Class, Measured BOE, and Toxicity Class

HPHC	Chemical Class	Selected BOE	Toxicity Class			
			Carcinogenic	Cardiovascular	Respiratory	Reproductive
Acrolein	Carbonyl	3-hydroxypropylmercapturic acid (3-HPMA) [1]		X	X	
Acrylonitrile	Acid derivatives	2-cyanoethylmercapturic acid (CEMA) [3]	X		X	
4-Aminobiphenyl	Aromatic amines	4-aminobiphenyl (4-ABP) [3]	X			
Benzene	Aromatic hydrocarbon	S-phenylmercapturic acid (S-PMA) [1]	X	X		X
Benzo[a]pyrene	PAH	3-hydroxybenzo[a]pyrene (3-OH-B[a]P) [3]	X			
1,3-Butadiene	Aliphatic dienes	Monohydroxybutenyl-mercapturic acid (MHBMA) [1]	X	X		X
Carbon monoxide (CO)	Gas	blood carboxyhemoglobin (COHb)[1,2] and exhaled CO[2] (eCO)				X
Crotonaldehyde	Carbonyl	3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	X			
Ethylene oxide	Epoxide	2-hydroxyethylmercapturic acid (HEMA) [3]	X		X	X
1-Aminonaphthalene	Aromatic amines	1-aminonaphthalene (1-NA) [3]	X			
2-Aminonaphthalene	Aromatic amines	2-aminonaphthalene (2-NA) [3]	X			
Nicotine	Alkaloids	Nicotine equivalents (NEQ) Plasma nicotine[2,3], cotinine[2,3]				X
NNK	Nitrosamines	total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) [1]	X			
NNN	Nitrosamines	total N-nitrosonornicotine (total NNN) [3]	X			
o-Toluidine	Aromatic amines	o-toluidine [3]	X			
Pyrene[4]	PAH	total 1-hydroxypyrene (1-HOP) [3]	X			
Toluene	Aromatic hydrocarbon	S-benzylmercapturic acid (S-BMA) [3]			X	X

Note. [1]Primary endpoints; [2]BOE not measured in urine; [3]Secondary endpoints; [4]Pyrene is not on HPHC list but its metabolite 1-HOP serves as a surrogate for PAH in general. Source: FDA Generated

The four REX studies found that systemically measured BOE to HPHCs were significantly reduced (p values < 0.05) among smokers completely switching to THS 2.2, with their BOE levels similar to the participants in the SA arm. At the end of the 5-day confinement period, systemic exposure to 15 of 17 selected BOE decreased by 47-96%. Nicotine levels were not decreased and results for urinary S-BMA levels were mixed; they were elevated in study ZRHR-REXC-03-EU and reduced in study ZRHR-REXC-04-JP. For Menthol Heatsticks, decreases in systemic levels of 15 BOE were less pronounced by the end of the 90-day ambulatory period. This may be due to decreased compliance or other reasons associated with the differences in the populations. The changes from the GM baseline values were in the range of 34-92% (ZRHM-REXA-07-JP) and 15-82% (ZRHM-REXA-08-US); all changes remained statistically significant. The urinary S-BMA levels were significantly higher in both studies on Day 90. The U.S. study results are shown in Figure 7.

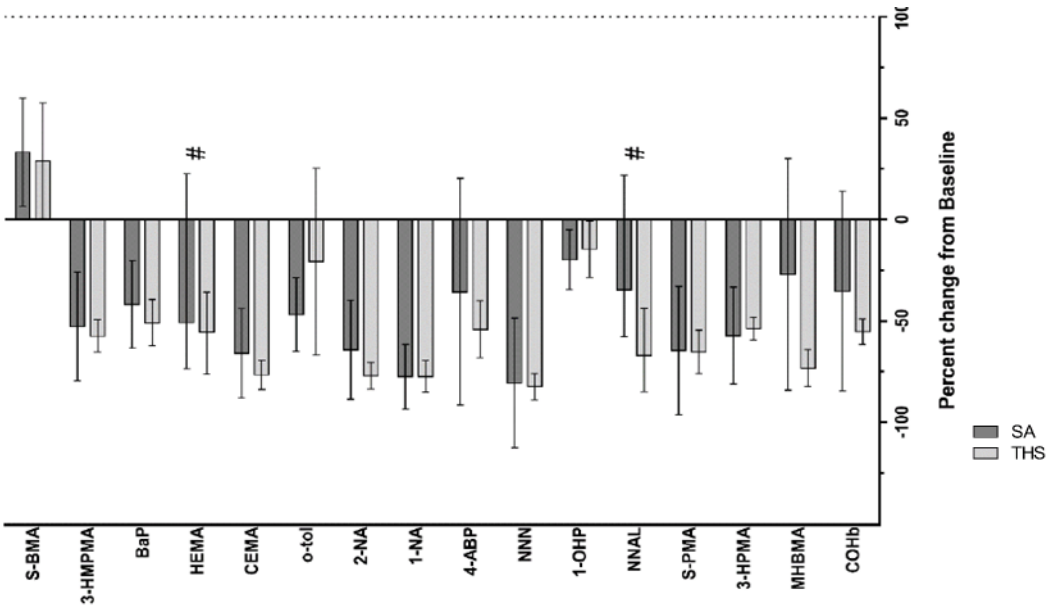


Figure 7: Percent Change from Baseline of Geometric Mean Levels and 95% CIs at Day 90 in ZRHM-REXA-08-US

Source: Application Section 6.1.3.2

Note. Because of the limited number of participants 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 2.2 and SA arms.

The reductions of systemic exposure to 15 HPHCs or their biomarkers seen after switching from CC to THS 2.2 in all REX studies were statistically significant. The exposures to S-BMA, a biomarker of o-toluene, were not different among the THS 2.2, CC, and SA arms. This is most likely due to environmental sources of exposure to this biomarker. The profiles of decline of the other BOE observed in the THS 2.2 arm were to similar levels observed in the SA arm.

The only BOE with urinary levels that were slightly higher in the THS 2.2 than the SA arms, throughout the whole exposure period, were 3-HPMA and total NNN; however, the urine levels for these BOE in THS 2.2 were lower than in the CC arms. A smaller reduction in urinary 3-HPMA was reported in the Japanese studies (ZRHR-REXC-04-JP by 47%; ZRHM-REXA-07-JP by 49%), probably due to the presence of acrolein in non-combusted tobacco and its possible formation from glycerin at temperatures below 400C^{o}. From the studies with ambulatory periods, the Japanese study (ZRHM-REXA-07-JP) had high compliance and thus provided convincing evidence of BOE reduction. Compliance in the SA arm of the U.S. study (ZRHM-REXA-08-US) was poor and the variability was high; results from the SA arm of this study may be less reliable. Details for primary endpoint BOE measures are discussed below.

FDA statistical reviewers analyzed the results of the four PK/PD studies and the BOE measures. Their statistical analyses demonstrated a statistically significant 50% or more reduction in levels on Day 5 of the studies for the primary BOE: MHBMA, 3-HPMA, S-PMA, COHb; and for total NNAL (urine) on Day 90 when comparing THS to CC. Reductions associated with the secondary BOE on Day 90 of the studies ranged from 25% to 90%.

a. COHb – BOE for Carbon Monoxide

At baseline, COHb levels ranged from 4.65% to 6.66% across the REX studies. A normal COHb level for non-smokers is < 2% and for smokers is 5-13%.[66] By Day 5 across all four studies, COHb decreased in study participants randomized to switch to THS 2.2 (1.06-2.48%) and SA study arms (0.99-2.5%). In contrast, COHb at Day 5 stayed similar to baseline levels in smokers who continued to smoke cigarettes (CC study arms) (4.5-6.07%). On Day 90 of the extended REX studies, COHb levels ranged from 2.66% to 2.97% and from 2.84% to 3.04% in the THS 2.2 and SA arms, respectively.[67] The COHb levels in the CC arms remained generally unchanged, ranging from 5.62% to 5.73% at Day 90.

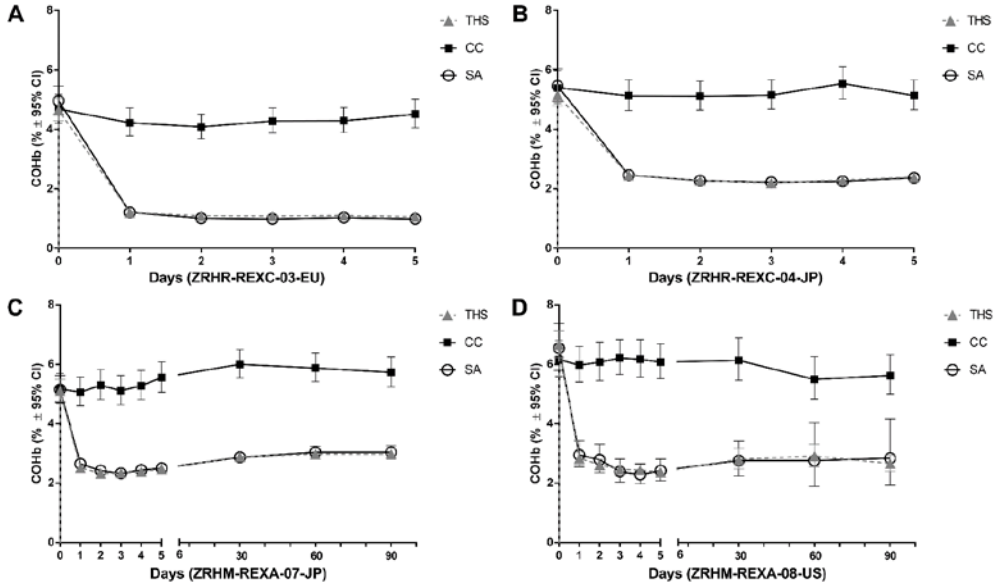


Figure 8*:* Geometric Mean and 95% CIs of COHb Concentrations (%)
Source: Section 7.3.1

b. Monohydroxybutenyl-mercapturic acid (MHBMA) – BOE for 1,3-Butadiene

1,3-butadiene is a carcinogen as well as a respiratory and reproductive or developmental toxicant. Baseline values of MHBMA, the BOE for 1,3-butadiene, varied between studies from 490 pg/mg creatinine in study ZRHR-REXC-04-JP to a mean level of 2317 pg/mg creatinine in study ZRHR-REXC-03-EU. This high variability may be explained by differences in CC between geographical locations, as well as differences in daily CC consumption, which tends to be substantially higher in Poland.

In the THS 2.2 arm, urinary MHBMA concentrations decreased to minimal values over a two-day period in all studies and were similar to values measured in the SA arm. In the two ambulatory studies, this decrease was maintained with percentage decreases from baseline to Day 90 ranging from 64% to 73% in the THS 2.2 arms and 27% to 66% in the SA arms. Participants who continued with their own CC brand showed variable levels across studies, from a relative decrease compared to baseline of 12% in the Japanese study to an increase of 36% in the U.S. study.

[66] Prockop, Leon D; Chichkova, Rossitza I; Carbon monoxide intoxication: an updated review**,** Journal of the neurological sciences. 2007, Vol.262(1-2), p.122-130.

[67] CO levels would be expected to be higher in a community environment than in a confined laboratory setting. The levels of CO were not statistically different between THS and SA arms and were well within the range for normal environmental CO.

c. 3-Hydroxypropylmercapturic acid (3-HPMA) – BOE for Acrolein

Acrolein is a respiratory and cardiovascular toxicant. At baseline, urinary levels of 3-HPMA, adjusted for creatinine, were similar overall among studies and across arms. In participants who switched to THS 2.2 as well as those in the SA arm, a rapid reduction of 24-hour urinary 3-HPMA compared to CC use at baseline was found in all four REX studies. Urinary 3-HPMA levels during the confinement periods in all four studies decreased by 47% to 59% from baseline at Day 5 for the THS 2.2 arms and 65% to 76% for the SA arms. In ambulatory studies these reductions were maintained, to a lesser magnitude, with Day 90 ranging between 37% and 54% in the THS 2.2 arms and 48% to 57% in the SA arms. A significant reduction in acrolein exposure was achieved for Menthol and Regular THS 2.2 as well as for both Caucasian and Asian ethnicities ($p's < 0.001$).

The applicant explains that the higher levels of 3-HPMA in the THS 2.2 arm compared to the SA arm may be due to residual acrolein in THS 2.2 that can be produced within a relatively low temperature range. Acrolein is naturally present in tobacco and is further produced by combustion. In non-combusted tobacco, it may also be formed through heating of glycerin, a constituent that is present in THS 2.2. The reduction of 3-HPMA urinary concentrations in smokers who switched to THS 2.2 was statistically significant at Day 5, with a sustained reduction on Day 90.

d. S-phenylmercapturic acid (S-PMA) – BOE for Benzene

Benzene is a carcinogen as well as a cardiovascular and reproductive or developmental toxicant. At baseline, urinary S-PMA concentrations adjusted to creatinine ranged from 784 to 2765 pg/mg creatinine, with the highest levels observed in the Polish population and the lowest levels in the Japanese populations. (The 2.6-fold differences in S-PMA urinary concentrations were explained by the lower emission profiles in Japanese CC and the prevalence of heavy smokers in the Polish study; this rationale appears acceptable.)

S-PMA decreased during the confinement period between 77% and 92% for THS 2.2 and between 84% and 92% for the SA arms. In the ambulatory periods, urinary S-PMA concentrations in the THS 2.2 arm were reduced from baseline by 81% and 65% in ZRHM-REXA-07-JP and ZRHM-REXA-08-US studies, respectively. After Day 30, the urinary S-PMA concentrations in the U.S. study's THS 2.2 arm slightly increased compared to the SA arm; however, the reduction of S-PMA systemic exposures in the THS 2.2 arms compared to CC arms were statistically significant in each study.

e. Total NNAL - BOE for NNK

Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) is a major metabolite of nitrosamine ketone (NNK); both are classified as carcinogens. At baseline, urinary levels of total NNAL concentrations adjusted to creatinine were highly variable among studies and across arms, with values ranging from 77.0 to 150.01 pg /mg creatinine. The highest levels were observed in the U.S. population and lowest levels in the Japanese populations. The differences are likely related to differences in CC in Japan.

Percent decreases of urinary total NNAL levels from baseline to Day 5 in all four studies ranged from 48% to 61% for the THS 2.2 arms and 59% to 64% for the SA arms. On Day 5, total urinary NNAL concentrations were similar among all REX studies, with levels ranging from 33 to 57 pg/mg creatinine in the THS 2.2 arms and from 28 to 54 pg/mg creatinine in the SA arms. During the ambulatory periods, the decreases in total urinary NNAL concentrations continued: in ZRHM-REXA-07-JP, the maximum reduction was reached on Day 90; in ZRHM-REXA-08-US, the urinary NNAL concentrations were lowest on Day 60. On Day 90, percentage decreases from baseline were 69% to 67% (median value) in the THS 2.2 arms. On Day 90, the total urinary NNAL concentrations were higher for the U.S. population, with 23 and 47 pg/mg creatinine in the THS 2.2

arms and 13 and 48 pg/mg creatinine in the SA arms for ZRHM-REXA-07-JP and ZRHM-REXA-08-US, respectively.

While baseline levels of total urinary NNAL varied among studies, a steady decline in total urinary NNAL concentrations was observed in all studies. In smokers who switched to THS 2.2, systemic exposure to total NNAL was statistically significantly lower than those who continued CC smoking.

f. CYP1A2 Activity

At baseline, mean CYP1A2 activity ranged from 70% to 121% across all four studies. By Day 5 across all four studies, CYP1A2 activity decreased in study participants randomized to switch to THS 2.2 (55% to 91%) and SA arms (52% to 94%). In contrast, CYP1A2 activity at Day 5 stayed similar to baseline levels in the CC arms (76% to 123%). In the two ambulatory studies, the changes from baseline ranged at Day 90 from decreases of 20.2% to 32% in THS 2.2 users and from 15.8% to 35.4% in the SA arms, respectively.

g. Urine Mutagenicity

At baseline, median urinary levels of mutagenicity ranged from 12574 to 25823 rev/24h across all four studies. Overall, the relative change in urine mutagenicity levels from baseline during the 5-day confinement periods ranged from decreases of 42.8% to 72% for the THS 2.2 arms, decreases of 37% to 74% for the SA arms, and from a decrease or 24.4% to an increase of 40% for the CC arms. In the two ambulatory studies, the decrease from baseline ranged at Day 90 from 61.4% to 61.6% in THS 2.2 users and from 45.2% to 67.9% in the SA arms, respectively. In contrast, at Day 90, the relative change from baseline in the CC arms was an increase of 10.9% to 16.2%.

h. Summary

The BCP review concludes that the reductions in systemic exposures to 15 BOE seen after switching to from CC smoking to THS 2.2 may lead to reduced likelihood of smoking-related diseases.

As TPL, I agree with the BCP conclusion that reduced BOE may lead to reduced risk of tobacco-related disease. The BOE chosen by the applicant are well established in peer-reviewed literature as measures of exposure to HPHCs. Biomarkers of some other particularly concerning chemicals found in CC smoke were not assessed in the clinical studies; e.g., acetaldehyde, formaldehyde, isoprene, ammonia, arsenic, cadmium, and lead. (There are not suitable biomarkers for acetaldehyde, formaldehyde, isoprene and ammonia; the applicant demonstrated low levels of arsenic, cadmium and lead in nonclinical studies.).

Although the applicant's data show reductions in BOE during short-term exposures, these measures were not intended to evaluate long-term disease risk. In the reduced exposure studies, all but one of the measured BOE were consistently and substantially lower in the groups who switched completely from CC to THS 2.2. In the case of 3-HPMA, the applicant's explanation for slightly higher levels in the THS users compared to those in the SA arm is reasonable and the level of 3-HPMA is decreased in the THS users compared to continued CC use.

There are some limitations to these trials:

- The small sample sizes limit extrapolation of results to the entire U.S. population. Study ZRHM-REXA-08-US, the only REX study conducted in the U.S., enrolled 164 subjects. The size of the PK/PD studies limits analysis of sub-groups (e.g., youth, low socio-economic status, minorities).

- The studies were not designed as nationally representative of the U.S. smoking population. Participants were moderate smokers; therefore, data may not generalize to light or non-daily smokers. IQOS products, but not own-brand cigarettes, were provided free of charge for participants in the REX studies, which may affect product use rates.
- The applicant did not estimate the percent change in BOE in the subset of participants who did not completely switch to IQOS and continued to use IQOS and CC (dual use). Dual use was particularly common in the Actual Use study and may account for a substantial proportion of IQOS users in a real-world setting. Whether this user population will achieve an exposure reduction when compared to exclusive CC use, and to what magnitude, is unclear.
- The applicant compared CC to THS use to SA. Participants in the SA arms differ from never-users; they may have residual or continued exposure to HPHCs or other chemicals with longer half-lives. A comparison to never-users would have been helpful to determine to what extent THS users (i.e., switchers) are still exposed to HPHCs compared with never users.
- No biomarker studies of secondhand exposure to these products were conducted by the applicant. This type of study could have helped to better understand potential risks to non-users. There were also no comparisons between IQOS and other tobacco products (e.g., e-cigarettes). Given that IQOS and e-cigarettes may both be considered by consumers to be a substitute for cigarettes, a comparison of the differences in exposure would be useful. However, the popularity of e-cigarettes in the U.S. has increased significantly in recent years; this change largely occurred during or after the time during which the applicant conducted the clinical trials submitted in these PMTAs.

Overall, the BOE reductions were statistically significant over five days and the decreases persisted up to three months. For those that switch completely from CC to THS 2.2, these reduced BOE exposures, which indicate reduced HPHC exposures, are likely to result in reduced risk of tobacco-related disease although that reduced risk has not been demonstrated in the studies submitted by the applicant.

2. Biomarkers of Potential Harm (BOPH)

All REX studies included measurements of several BOPH as secondary or exploratory study endpoints to determine if THS 2.2 use resulted in biological changes that may indicate a change in long-term disease risk. Selection of BOPH was based on key mechanisms of three major smoking-associated diseases: cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and lung cancer. Markers of oxidative stress (8-iso-F2-isoprostane-alpha [8-epi-PGF2α] and thromboxane metabolites) and inflammation (WBC, c-reactive protein [CRP], soluble intercellular adhesion molecular 1 [sICAM-1], fibrinogen) were selected due to their role in the development and progression of three major smoking-related diseases. Additionally, some disease-specific endpoints were selected for CVD (carboxyhemoglobin, lipid profile and oxysterols, HbA1c, and blood pressure), lung function (FEV1), and cancer (selected BOE). The applicant selected these biomarkers based on changes shown in previous smoking cessation studies and the general acceptance in peer-review literature of association with health risks. The applicant specified six BOPH as representative of mechanisms underlying diseases of interest. Two markers were measured in all four REX studies: 8 epi-PGF2α and 11-dehydrothromboxane B2 (11-DTX-B2). Four additional markers were measured in the ambulatory studies: high-density lipoprotein (HDL) cholesterol; WBC; soluble intercellular adhesion molecule-1 (sICAM-1); and forced expiratory volume in the first second (FEV1).

The applicant provided literature review monographs for most of the clinical measures undertaken in the REX studies. FDA conducted an independent review of the relationship of these BOPH to diseases of interest; details are provided in the medical review. The applicant monographs concluded that only WBC count and HDL were useful clinical risk markers for the evaluation of health risks of THS 2.2. Neither of these

measures changed significantly in the U.S. study. Evidence regarding the remaining markers is insufficient to allow reliance upon them as surrogate predictors of either short- or long-term health effects from switching to THS 2.2.

a. Assessment of Inflammation

Only WBC count and sICAM-1 demonstrated some differences in the two 90-day studies for the THS 2.2, CC, and SA arms. There was a reduction in WBC counts over the course of the studies. Reductions were generally largest in the SA arm, but there were consistent reductions approaching similar levels in THS 2.2 arms. The U.S. study results are difficult to interpret because of the small sample size. The study length is a limiting factor for interpretations because WBC reductions are optimally detected between six and ten months after smoking cessation.

In the two ambulatory REX studies, smokers in the THS 2.2 arm had lower sICAM-1 levels than participants in the CC arm after adjusting for baseline sICAM-1 levels, sex, and baseline CC consumption. The sICAM-1 levels in the THS 2.2 arm (approximately 8.5% to 10.5% reduced from baseline values) were similar to the SA arm.

b. Assessment of Oxidative Stress

The markers for oxidative stress included 8-epi-PGF2α and 11-DTX-B2. Smokers who switched to THS 2.2 showed more than a 12% reduction in 8-epi-PGF2α levels compared with smokers who continued to smoke CC; however, these reductions were not conclusive due to high variability in the data. Although 11-DTX-B2 levels were reduced for smokers who switched to THS 2.2, as in the SA arm, the magnitude of the change was smaller than expected, especially in the U.S. study (ZRHM-REXA-08-US) – possibly due to poor compliance. The U.S. study findings were confounded by non-compliance with product use (in both THS 2.2 and SA arms), resulting in a reduced sample size and a greater-than-expected variability in 11-DTX-B2 results.

c. Assessment of Cardiovascular (CV) Risks

CV risks were assessed by measurements of blood lipids, triglycerides, apolipoprotein B, and blood pressure in the REX studies with the ambulatory period. Except for HDL, CV risk biomarkers did not change significantly over the course of the ambulatory periods. Smokers who switched to THS 2.2 had higher HDL levels compared to smokers who continued to smoke CC. In the U.S. study (ZRHM-REXA-08-US), HDL levels in the CC arm were similar to those in the SA arm; however, only nine of the 40 participants randomized to the SA arm reported adherence to SA, making results of the U.S. study difficult to interpret. The BOPH related to CV risk did not significantly change, suggesting no improvement in CV risk during the relatively short study period.

d. Assessment of Lung Function

Spirometry measurements were included primarily as a safety measure. In the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS 2.2 had an increase of 1.91% of predicted value in FEV1 compared to smokers who continued to smoke CC, with no notable differences between THS 2.2 and SA arms. However, studies of a longer duration (at least 6-12 months) would be necessary to fully assess the impact of THS 2.2 use on FEV1. Additionally, deterioration in lung function associated with CC may not be reversible.

e. Assessment of Genotoxicity and Mutagenicity

Several indirect measures evaluated cancer-specific endpoints. There may be reduction in cancer development risk related to reduced exposure to carcinogens; for example, HPHCs, reduction in CYP450 1A2 activity, and urine mutagenicity are additional indirect measures.

CYP450 1A2 activity at baseline was markedly different among the REX studies, ranging from 70% to 122%, with the lowest values in the Japanese populations and highest in the U.S. population (due to differences in genetic factors and smoking behavior). In participants who switched to THS 2.2, CYP450 1A2 activity was significantly lower (decreased by 30% to 36%) compared to participants who continued to smoke CC on Day 5; these reductions were similar or lower than levels during the ambulatory period on Day 90 (range of 21% to 32%), and the changes in the SA arms were of similar magnitude.

In the REX studies, the baseline urine mutagenicity levels were highly variable; however, there was a clear trend toward decreased urine mutagenicity values in the THS 2.2 arm on Day 5 (by 47% to 72%); these differences were sustained in the ambulatory period and were similar to changes in the SA arm. Data in the CC arms did not follow a consistent profile through exposure periods across studies. There was an unexpected decrease in mutagenic activity in the ZRHR-REXC-04-JP, similar to what was observed in the THS 2.2 and SA arms. The high variability of results may be due to test sensitivity of dietary mutagens and the complexity of this cellular test; data should be interpreted with caution. However, the results observed indicate a lower level overall of mutagenic compounds in the urine of THS 2.2 users compared to the CC arm.

f. Summary

The applicant notes that many of these endpoints are more appropriate for longer-term studies as changes in these measures are expected to take months to years. Some BOPH had a desirable trend in improvements for THS 2.2 users compared to the CC arm during the 90-day exposure, specifically: HDL: lipid pathway; 8-epi-PGF2α: oxidative stress; 11-DTX-B2: platelet activation; sICAM-1: endothelial dysfunction; WBC (leukocytes) count: inflammation; FEV1: lung function parameter.

The medical, epidemiology, and BCP reviews concluded that:

- The minor improvements in some BOPHs in the THS 2.2 arm relative to the CC arm may not be of clinical significance and it is unclear how predictive the chosen BOPH are for long-term tobacco-related disease risk.
- While no deaths, CV disease, COPD, or lung cancer were reported during the clinical studies, these diseases have a long latency and are unlikely to be observed during studies of this type.

FDA medical reviewers conducted an independent review of the literature and concluded that while each of the six markers has data suggesting a relationship with one or more of the three identified diseases of interest, none were strong predictors of future health risks and many will take months to years before change can be measured. WBC had the most data to suggest utility; however, it is a non-specific marker that can change for numerous reasons independent of tobacco product use.

The epidemiology review notes that while the BOPH can be informative with respect to key mechanisms of smoking-related diseases, they are not necessarily replacements of clinical endpoints. In general, there are continued questions about the credibility of BOPH as surrogate endpoints.

The statistical reviewers evaluated the two 90-day studies and concluded that they were not designed to ascertain any effect associated with the "risk endpoints." The BOPH were secondary endpoints and were not the basis for sample size/power calculations; it is not clear from a statistical perspective whether the data generated from the studies are clinically meaningful.

As TPL, I agree with the BCP, medical, epidemiology, and statistical reviews. Compared with the significant reductions in BOE, the changes in BOPH were less pronounced. One explanation is that none of the BOPH are specific to tobacco use. Changes in BOPH may be attributed to other factors (e.g., weight, diet, exercise). Also, biologic responses related to exposure to tobacco smoke and reversal of these harmful effects may take more time to manifest than the duration of the ambulatory periods of the current studies; many of the effects, e.g., effects of CC, may not be reversible. These factors limit the interpretation of results related to the effects of long-term exposures.

Overall, the studies conducted by the applicant have not demonstrated evidence of reduction in long-term disease risks. BOPH may be informative, however, for understanding potential effects on biological processes such as inflammation and oxidative stress. Long-term tobacco related diseases, e.g., cardiovascular disease, cancer, chronic lung disease, begin as inflammatory processes. Reduction of inflammation and oxidative stress may eventually lead to reduced disease risks. Use of THS appeared to reduce these processes to some degree during the studies, but, as noted, the data are not sufficient to show that these small changes are associated with long-term results.

3. Clinical Effects of IQOS

The application included several types of health-related data and supporting information that aid in the evaluation of short-term health risks of IQOS. Safety data reports for THS 2.2, including cumulative safety summary information from the eight completed clinical studies, two ongoing clinical studies, premarket safety surveillance covering six market research studies and one perception and behavior study, as well as post-market surveillance studies outside the US, were submitted.

a. Analysis of Adverse Events in Clinical Studies

In the eight clinical trials (four PK/PD and four REX studies), adverse events (AEs) associated with acute exposures to THS 2.2 were like those ordinarily encountered with CC use. A total of 717 AEs was reported. Most (>95%) were non-serious,[68] mild to moderate in severity, expected,[69] and temporary. They encompassed acute, short-term health effects including cardio-pulmonary, nasopharyngeal, neurologic, and laboratory abnormalities. The number of reported severe[70] AEs was relatively low across the eight clinical studies (N=19). Of these 19 severe AEs, 16 occurred in the 90-day U.S.-based clinical trial. No deaths were reported for any subjects participating in the clinical trials. Although the applicant determined that most of the reported AEs were unrelated to product use, THS 2.2 exposure cannot be ruled out as contributing to or exacerbating those AEs typically associated with tobacco exposure (e.g., cough, headache, syncope).

Two serious AEs were reported in ZRHM-REXA-08-US; both occurred in Subject 1119, who was enrolled and exposed but not randomized. Both AEs were not related to IQOS or to the investigation and resolved with

[68] Serious adverse event (SAE) = Event that results in death, life-threatening condition or event, persistent or substantial disability or incapacitation, hospitalization or prolonging of current hospitalization, or congenital anomaly or birth defect.
[69] Unexpected adverse event = The nature or severity of the event is not consistent with information currently known about the product and/or has not been previously observed or described in the investigator's brochure.
[70] SAE = Event that interferes with most daily activities.
NOTE: these definitions were used by the applicant.

treatment. Twelve severe AEs were reported during the ambulatory period; all were due to abnormal clinical laboratory results and were unrelated to product use.

Notably, 56 subjects in study ZRHM-REXA-07-JP were discontinued by the applicant due to non-compliance with International Conference on Harmonization Good Clinical Practices (ICH GCP) at the Seishukai Tokyo Clinic. The 56 subjects were exposed to IQOS. Their subject-level data were excluded in the data analysis in the full analysis set/per protocol and the safety population, so no further safety analysis was possible; however, identification and removal of 56 subjects' data prevented a potential compromise of data validity and integrity.

In the Actual Use study (THS-PBA-07-US), a single prospective multi-center study that exposed 1,158 daily smokers of CC to THS 2.2 in a naturalistic, close to real-world setting, 121 AEs were reported by 48 participants. Most were expected; 102 AEs were non-serious and 19 were serious. Headache was the most frequently reported non-serious AE. Severity was not reported in 50% of the cases.

b. Review of Published Clinical Literature

Post-marketing AE reports about IQOS have been sparse, despite increasingly widespread international marketing since its commercial introduction in Japan and Italy in 2014. A Safety Update Report (PMI-SURV-2016_SUR01), published in April 2016, reported two serious AEs (nervous system disorders/syncope). The serious AEs involved "THS 2.2 and 2.4/All variants" and were reported from an unspecified "spontaneous source." A review of published clinical literature provided by PMI at the time of the application found one case report of a serious AE from THS 2.2. A young adult Japanese male developed acute eosinophilic pneumonia after increasing his consumption of Heatsticks. This disease has a known association with tobacco products and is not unique to THS 2.2.[71]

FDA conducted an independent clinical literature review to ascertain whether any serious adverse experience had been reported from products referred to in the literature as tobacco heating systems. A search was completed on 1/31/17 and repeated on 12/5/17; details are in the medical review. Only the case described above pertained to a new generation tobacco heating system. Although the device in this case report was not explicitly named, the description was consistent with IQOS. The remaining articles described small studies of earlier generations of heated tobacco products and showed "minor but favorable" changes in some cardiopulmonary and inflammatory parameters for those using the "heat-not-burn" product compared to a conventional cigarette. Two studies of the Eclipse product, which uses a carbon-burning heat source, showed increases in CO measurements.

c. Summary

The medical review noted additional limitations related to information about health effects of IQOS:

- The eight clinical studies did not specifically evaluate the possible risks or benefits of dual/poly tobacco product use.
- The reported AEs and compliance rates in a controlled clinical setting and small sample population may not be reflective of general use. Detection of other more clinically significant, serious, or severe AEs may occur with use of the product by a diverse population, especially for chronic and exclusive users.

[71] Kamada, T., Yamashita, Y., & Tomioka, H. (2016). Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. Respirology Case Reports, 4(6).

As TPL, I agree with the medical review. There are limited data related to short-term health effects of IQOS and even less data for longer-term effects. IQOS has been available in other countries for several years; no health-related short-term issues uniquely related to IQOS were identified in three searches of published clinical literature. There are limitations to the clinical studies conducted by the applicant; however, there are practical limitations to the number, size, and nature/design of clinical studies that can realistically be completed during new product development. Although limited, the data available in the clinical studies completed by the applicant do not raise concerns or identify specific health-related issues uniquely related to IQOS.

4. Likelihood of Product Misuse or Malfunction

The Actual Use study assessed self-reported misuse of the THS 2.2. Of 985 participants, 47 (4.8%) reported using the Heatstick without the IQOS device; the majority (97.9%) lit the Heatstick like a CC, and one participant chewed the Heatstick on one occasion. Only two participants (0.2%) reported using the IQOS device without Heatsticks; one participant used the IQOS device with marijuana on one occasion and one participant used it with CC on more than ten occasions.

The applicant reports device events or malfunctions in several of the PK/PD and REX studies. Device events, malfunctions, and misuse events were relatively minor or easily correctable (e.g. device inoperable/does not charge, battery malfunction, heater broken) and did not impact subject safety. There were no battery explosions or subject burns resulting from device malfunctions. One major device event (device inoperability) was reported in the pre-randomization period and did not impact subject safety. There were no subject discontinuations resulting from a device event.

Table 4: Summary of Device Issues in IQOS Clinical Trials

Trial Number	Device Event/Malfunction/Misuse	Consequence
ZRHR-PK-01-EU	None	None
ZRHR-PK-02-JP	1 broken heater, 1 charging issue	None
ZRHR-REXC-03-EU	12 subjects reported 19 device problems; Charging issues, inoperable, stops intermittently	No AEs
ZRHR-REXC-04-JP	4 subjects reported 5 events	No AEs
ZRHM-PK-05-JP	None	None
ZRHM-PK-06-US	3 subjects reported 6 minor events	No AEs
ZRHM-REXA-07-JP	189 device events; inoperable, won't charge, battery malfunction, heater broken	No AEs
ZRHM-REXA-08-US	149 events reported by 55 subjects; most minor (inoperable, won't charge, battery malfunction, heater broken)	No AEs

The applicant evaluated the potential for consumers to attempt to re-use Heatsticks. (b) (4)

The applicant also evaluated (b) (4)

The applicant did not provide data on consumer misuse of the Holder by attempting to use a conventional combusted tobacco product (e.g., cigar, cigarette). However, heating tobacco will only generate an aerosol if

there is enough of an "aerosol forming agent," such as glycerin.[72] Although glycerin is used in conventional tobacco filler as a humectant, the level is below that required to generate a nicotine-containing aerosol. In addition, the tobacco of any conventional product inserted into the IQOS Holder would be heated only to a maximum of 350 °C - the maximum temperature of the heating blade. This temperature is much lower than the combustion threshold of tobacco (>400 °C).[73, 74] Therefore, the levels of any HPHCs generated by using a conventional combusted tobacco product with the IQOS Holder would be lower than the HPHCs generated with usual use of the conventional combusted tobacco product. Furthermore, only products with a circumference of 22.9 mm or less would fit inside an IQOS Holder, which excludes most conventional U.S. cigarettes.[75]

Overall, although self-report data has limitations, the Actual Use study suggests that consumer misuse of the IQOS device and Heatsticks is uncommon. Studies of this type are generally accepted by FDA for evaluating how consumers will actually use a product. The applicant has considered how consumers could re-use a Heatstick or inappropriately use other conventional tobacco products with the IQOS Holder. (b) (4)

[redacted]

5. Bioresearch Monitoring (BIMO) Inspection

Bioresearch monitoring (BIMO) inspections of two clinical investigators were conducted in support of the applications. Protocol ZRHM-REXA-08-US had the largest number of reported AEs (N=301). In addition, overall in the safety population at post-randomization, eight AEs were classified as related to THS 2.2 exposure and 12 severe AEs occurred. Protocol ZRHM-REXA-08-US was conducted at two clinical sites in the U.S. – Daytona Beach, FL and Dallas, TX. No significant issues were identified during inspection of the Daytona Beach site; final classification was No Action Indicated (NAI). There were issues related to documentation of study records identified at the Dallas site. These were discussed with the study sponsor, monitor, and IRB. The appropriate samples were removed from final sample data analysis. Final classification was Voluntary Action Indicated (VAI).

Overall, BIMO inspection findings indicate the conduct of the U.S.-based study at the two clinical sites generally complied with study-related procedures, documented and monitored AEs, and followed procedures to ensure informed consent and human subject protection. The inspection revealed no major BIMO issues or clinically-significant protocol deviations that would compromise data validity and integrity.

6. 2017 Safety Update Report

In a letter dated 5/16/2018, FDA received a PMI Safety Update Report (SUR). This report summarized safety information on THS for the period covering 1/1/2017 thru 12/31/2017. The SUR identified previously unrecognized short-term health risks associated with THS including hypersensitivity reactions, an accidental

[72] Nordlund, Markus; Belka, Miloslav; Kuczaj, Arkadiusz K; et al., Multicomponent aerosol particle deposition in a realistic cast of the human upper respiratory tract. Inhalation toxicology. 2017, Vol.29(3), p.113-125.
[73] Barontini, Tugnoli, Tetteh, et al., Volatile products formed in the thermal decomposition of a tobacco substrate. Industrial and Research Chemistry. 2013, Vol 52, p 14984-14997.
[74] Senneca, Chirone, Salatino, and Nappi. Patterns and kinetics of pyrolysis of tobacco under inert and oxidative conditions. Journal of Anal. Appl. Pyrolysis. 2007, Vol 79, p. 227-233.
[75] Agnew-Heard KA, Lancaster VA, Bravo R, Watson C, Walters MJ, Holman MR., Multivariate Statistical Analysis of Cigarette Design Feature Influence on ISO TNCO Yields. Chem Res Toxicol. 2016 Jun 20;29(6):1051-63.

child exposure, and a reported weather-related (heat and humidity) “burning sensation.” No AEs were reported as actual consumer burns necessitating clinical treatment; however, consumers did report Heatstick discomfort with the “perception of hot aerosol causing burning sensation and thermal burns.”

The data showed that hot aerosol AEs were reported more frequently during the summer months. The results of the initial assessment indicate that (b) (4) [redacted]. The minimum time to sense pain and react to it at any temperature is 0.3 seconds in average adults. The thermal threshold for pain in the oral cavity varies between individuals but is normally around 46 - 47°C.[76, 77] To sustain a burn in humans, the skin needs to reach and remain at a temperature of 50°C for over 100 seconds – an unlikely occurrence. The applicant has made no product changes but has provided Customer Care agents with a consumer communication script, reminding product users not to expose HeatSticks to high temperature and humidity but to keep them in a dry environment, especially during summer months. This consumer communication was initiated in November 2017 and the applicant plans to use it in the U.S. following IQOS commercialization. Further information and instructions on how to handle the product, aiming at minimizing and preventing the risk of hot aerosol sensation, are provided in the IQOS User Guide supplied with each THS pack. Users are advised not to use the product if “it has been exposed to excessive heat or moisture” or if “it becomes wet or is immersed in any liquid” and to “store the product in a clean, dry, cool place.”

The safety update also reported battery leakage due to short circuiting and THS-potentiated risks of thermal burns. In response to FDA’s request for additional information, the applicant clarified that the device malfunction was the result of a short circuit (b) (4) [redacted].

Based on the root cause analysis performed, PMI concluded that the battery electrolyte leakage was a result (b) (4) [redacted]

The applicant reports that (b) (4) [redacted] (b) (4) [redacted]. These improvements/modifications are expected to decrease the occurrence rate of AEs.

The applicant states that this “improved” THD 2.4 is the product that is the subject of these applications and intended for U.S. marketing (if authorized). This product reflects modifications have been made as part of continuous product improvement processes. These modifications include:

(b) (4) [redacted]

[76] Green B.G. Heat pain thresholds in the oral-facial region. Perception and Psychophysics. 1985, Vol 38(2), p. 110-114.
[77] Dirler, Winkler, Lachenmeier. What temperature of coffee exceeds the pain threshold? Foods. 2018, 7, 83.

The applicant confirmed that all device modifications were implemented prior to the September 8, 2017 amendment submitted to FDA. A CB Test Certificate was provided, dated 12/28/2017, for THD 2.4, stating that it is compliant with IEC 60335-1:2010 (safety of electrical appliances for household and similar purposes) and Test Report IEC 60335, dated December 1, 2017 for THD 2.4. The applicant reports no changes have been made to the design of HeatSticks since submission of the PMTAs. The engineering review provides details of the risk analysis and the subsequent modifications.

The applicant reports that new post-market safety surveillance data and published literature reports of acne, chest discomfort and rash resulted in heightened awareness and monitoring for these potential safety signals. Serious adverse events (SAEs) were reported in the SUR Supplement 1. Definitive conclusions could not be determined on the 14 SAEs reported as cardiac disorders (e.g. angina pectoris, arrhythmia, myocardial infarction); the summaries provided were incomplete and anecdotal and many cases lacked a verifiable consumer medical history. THS use habits were inconsistent, not reported or unknown; SAE seriousness, severity, and outcomes were inconsistently reported.

The SUR included report of one death in an 88-year-old Caucasian male with a medical history of hypertension, gastroesophageal reflux disease, and cigarette smoking (1 pack/day) since age 13. On 12/28/2015, the subject was enrolled in the ZRHR-ERS-09-EXT-US clinical study and on 1/4/2016 he received THS 2.2 for one week prior to randomization to the CC arm. After randomization, the subject continued smoking 1 pack/day. The subject was lost to follow-up for a month before the investigator learned of his death from an obituary. The MedWatch Report stated the subject died of unknown causes on 8/14/2016; no autopsy was performed. The investigator reported that the SAE was unrelated to THS, conventional cigarette use, or any study procedures.

The new AE safety information, including the unexpected death of the study participant, does not change the conclusion that short-term risk of THS use is no greater than the risk of CC smoking**.**

7. Summary of Individual Health Findings from Clinical Studies, Literature, Adverse Experience Reports, and Safety Updates

The medical review concludes that THS 2.2 has the potential to benefit certain individuals seeking to reduce their HPHC exposure by completely switching from CC. The review concludes that short-term health effects data from the clinical studies and additional longer-term information from published literature provided in the applications do not raise unique or additional health concerns or identify unique, specific health-related risks for the IQOS system. The following rationale for this conclusion is provided:

- Reducing exposures to HPHCs in THS 2.2 through complete switching can potentially reduce the risk of adverse health effects compared to CC
- Data about BOPH are insufficient to draw meaningful conclusions about the ability of THS 2.2 to impact disease risk
- Clinical trial data about AEs related to THS 2.2 are limited but suggest that the short-term risk is no greater than risk from CC
- The relatively low incidence of serious and severe AEs in the international post-marketing surveillance SUR and the published literature suggest that switching to THS 2.2 may not increase the incidence of short-term adverse health effects for U.S. users relative to CC. However, the short-term AE data do not demonstrate a reduction in long-term health risk relative to CC.

As TPL, I agree with the medical review overall conclusions. The 5-day studies demonstrate improved BOE in those that completely switched to THS 2.2, which indicates reduced HPHC exposures. These improvement

trends persisted in the 90-day studies despite reduced compliance and use of other tobacco products. The currently available evidence indicates CC smokers who switch completely to IQOS will have reduced toxic exposures and, consequently, although not demonstrated in the studies in the application, are less likely to be at risk of tobacco-related diseases.

Additional health effects information was included in a late amendment to the submissions (see section II.F.6 below). MR0000117 included results of a randomized, controlled, open-label, 2-arm, parallel group, multi-center clinical study of six months of *ad libitum* use of the non-menthol THS 2.2 compared to continued CC users in an ambulatory setting. In this study, CC smokers who use IQOS while continuing to smoke (dual use) do not appear to have increased HPHC exposures; the limited available information shows trends, although not statistically significant, toward reduced HPHC exposures in this population.

Experience with IQOS is limited, even when considering data from other countries. There have been no specific, health-related or product quality issues unique to IQOS products found in the clinical studies, the current world-wide markets, or the published literature. Misuse of IQOS appears to be uncommon and the product design makes it unlikely users will have a satisfactory experience (e.g., no significant nicotine is delivered with reusing a Heatstick and use of CC in the Holder is not effective).

F. Population Health

The applicant includes the following studies for evaluation of IQOS and population health effects:

- PBA-05-NOC: a U.S. study assessing perceptions and intentions regarding IQOS use in current smokers with and without intent to quit, former smokers, never smokers, and young adult never smokers
- Four observational studies (Table 5 summarizes design features)
  - PBA-07: Actual Use pre-market study conducted in the U.S.
  - Whole Offer Test (WOT): Post-market study conducted in five countries in Asia and Europe
  - Two post-marketing surveys conducted in Japan
- Population Health Impact Model (PHIM)

Table 5: Summary of Pre- and Post-Market Studies of IQOS Use Patterns Among Current Tobacco Users

	PBA-07	Whole Offer Test (WOT)	Post-Market Online Cross-Sectional Study	Post-Market *IQOS* Purchaser Study
Study Design	Longitudinal	Longitudinal	Cross-sectional	Longitudinal (did not assess changes in individuals)
Location, Duration	United States, September 2015 - January 2016, 6-week observational period.	Japan, 2013 Italy, 2013 Germany, 2014 Switzerland, 2014 South Korea, 2015 4-week observational period.	Japan, September 2016	Japan, January-July 2016
Sample size	1,106	Japan - 638 Italy - 535 Germany - 377 Switzerland – 416 South Korea - 843	2,000 (5.2% response rate*)	~11,000
Attrition rate	12.4% (N=137) of participants included in the analyses did not have week 6 data.	All participants had data for all 4 weeks. The following proportions did not complete the follow-up period: Japan: 11.1%, Italy: 6.3% Germany: 14.9% Switzerland: 19.4% South Korea: 9.9%	N/A	Not Reported
Population source	Market research consumer-based databases from across the US.	Market research consumer-based databases from each country.	Online panels that recruited from across Japan.	Japanese adults who purchased *IQOS* and registered product in online database.

	PBA-07	Whole Offer Test (WOT)	Post-Market Online Cross-Sectional Study	Post-Market *IQOS* Purchaser Study
Eligibility criteria	Aged ≥18 years; current daily smoker of regular and/or menthol cigarettes with no intent to quit in the next 30 days (mean CPD = 10.2); expressed positive intent 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 intent to use IQOS after trying one Heatstick; 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 in the past 3 weeks and reported using ≥10 *HeatSticks* and/or cigarettes per week. Proportion of cigarette smokers unknown.
How IQOS was obtained	IQOS system and Heatsticks provided free (regular and/or menthol).	IQOS system and Heatsticks provided free (regular and/or menthol; only regular was available in Italy and Germany).	IQOS not provided. The device was purchased by the respondent or someone else.	Respondents were required to have purchased an IQOS device.
Assessment of IQOS and cigarette use	1-week baseline period 6-week observational period; daily record in e-diary or cigarette smoking and IQOS	Self-report average number of cigarettes per day in enrollment interview. 4-week observational period; daily paper/pencil record of cigarette smoking and IQOS	One-time online survey asking if respondents were current daily or some days users of cigarettes, "heat not burn" products, and other tobacco products.	Self-reported use of IQOS and CC in an online survey.

CPD = cigarettes per day.
*The study report states "38,235 contacts were made to reach the sample size." It is not clear whether this large number of people was contacted to fill age, gender, and geographic location quotas that they were trying to meet during recruitment or because there was a high refusal rate among eligible individuals.
Source: Sections 7.3.2, 7.3.3 of the PMTAs, March 16, 2017 amendment, and September 13, 2017 amendment

There were design features of the PBA-07 and WOT studies that may have influenced the findings with relation to frequency of IQOS use:

- The observation periods were 4-6 weeks. Additional follow-up time would have been informative to understand whether IQOS use patterns were sustainable over time.
- Both studies provided the IQOS device and Heatsticks to participants at no charge. This may affect use patterns.
- Participants in the PBA-07 study were shown labeling and marketing material with modified risk information prior to making their decision about "interest" in IQOS. It is unclear what effect this may have had on study participation or results.

Although the PBA-07 and WOT studies are not generalizable to U.S. cigarette smokers, the information gained from these studies provides useful trends for consideration in review of these applications for marketing in the U.S. The sample for PBA-07 was a non-probability sample recruited from marketing research databases. Furthermore, the dataset used in the analyses only included participants who used at least one cigarette during the baseline period and at least one Heatstick during the observational period, thereby potentially overestimating the prevalence of IQOS use after excluding 230 participants who did not meet these criteria. Similarly, the WOT analysis only included participants who completed at least 26 of the 28 days during the observational period. If participants who did not complete the observational period were less likely to use Heatsticks, the estimates for initiation of IQOS and switching to IQOS would be overestimated, while the estimates for switching from IQOS back to CC (e.g., 0% in Japan) would be underestimated. The results from the international actual use studies pose additional challenges with respect to generalizability to cigarette smokers in the U.S. population due to different cultural contexts and differences in the availability of e-cigarettes or other heated tobacco products.

The FDA statistical reviewers evaluated four studies submitted by the applicant in support of the PMTAs and their benefit to the health of the population as a whole: THS-PBA-05-NOC-US, THS-PBA-06-US, THS-PBA-07-US, and WOT. In general, the statistical reviewers found the information for these studies to be descriptive in nature: computation of summary statistic (proportions and means) and standard deviation. Statistical inference was not part of the conclusion-making process in relation to these studies.

1. Likelihood of IQOS Use by Current Cigarette Smokers

PBA-05-NOC

This study was designed to assess the likelihood of use, comprehension, and risk perception among current smokers with and without intent to quit, former smokers, never smokers, and young adult never smokers. The objective of this study was to assess perception associated with exposure to THS 2.2 label, labelling, and marketing materials. A total of 1,817 participants were recruited from multiple consumer databases across the U.S. Enrolled participants were randomized into one of four arms - 384 individuals per arm (96 smokers intending to quit, 96 smokers not intending to quit, 96 former smokers, 96 never smokers). Each arm was presented with a separate label, labeling or advertising material:

- Arm 1: THS 2.2 brochure with product information and a Surgeon General's Warning
- Arm 2: THS 2.2 HeatSticks pack with a Surgeon General's Warning and a statement that THS 2.2 heats but does not burn tobacco
- Arm 3: THS 2.2 HeatSticks pack with a Surgeon General's Warning but without the statement that THS 2.2 heats but does not burn tobacco
- Arm 4: THS 2.2 direct mail with product information and a Surgeon General's Warning

All four Surgeon General's warnings were used but each participant saw only one of the statements on the information received.

The applicant developed two items assessing intentions to try IQOS and one item assessing intentions to use IQOS regularly, if one tries it and likes it. Table 6 shows results from PBA-05-NOC across the study arms; in addition to the top two categories (*Definitely* or *Very likely*), FDA reviewers included those who responded *Somewhat likely*. 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. As the applicant acknowledges, self-reported intentions to use products are limited in terms of predicting behavior and can overestimate the likelihood of purchase, particularly when participants' responses have no consequences. For example, although participants viewed price information about IQOS and Heatsticks, they were not asked to make a choice between the product and money.

Table 6: Intention to Try and Use IQOS among Current Smokers (PBA-05-NOC)

	"Very likely" or "Definitely"	"Somewhat likely"	"Very likely," "Definitely" or "Somewhat likely"*
Intentions to try IQOS			
Smokers not intending to quit	27-44%	31-43%	69-82%
Smokers intending to quit	34-43%	36-43%	71-85%
Intentions to try IQOS if offered by a friend			
Smokers not intending to quit	22-68%	21-68%	83-93%
Smokers intending to quit	16-58%	23-70%	81-95%
Intentions to use IQOS regularly, if one tries it and likes it			
Smokers not intending to quit	16-32%	26-44%	53-72%
Smokers intending to quit	28-33%	29-41%	57-71%

Notes. *The proportion of respondents that reported "Somewhat likely," "Definitely," or "Very likely" to try or use IQOS across the four PBA-05-NOC study arms. FDA Reviewer drafted this table using data from the application.
Source: csr-app-15_2-tables.pdf, pg. 32-47.

Although participants in this study do not constitute a representative sample of the U.S. population, FDA statistical reviewers were able to replicate the statistical analysis provided by the applicant for PBA-NOC-05-US.

Actual Use (PBA-07) and WOT

Both studies used self-reported data on the use of IQOS in a "real-world" situation – PBA-07 was conducted in the U.S. and WOT in five other countries where IQOS is currently marketed. Primary outcomes in the pre-market studies included the prevalence of initiating IQOS use, switching from CC to IQOS, and switching from IQOS back to CC. All participants in these studies were current CC smokers.

At the end of the observational period, the prevalence of initiating IQOS use (i.e., consuming ≥100 Heatsticks) was lowest in the U.S. at 33.8% of participants. In the WOT, the proportion of participants who initiated IQOS use was highest in South Korea (76%) and Japan (61%). For the European countries, initiating IQOS use occurred in 50% of participants in Germany, 49% in Switzerland and 36% in Italy. (See Table 7 for details.)

A participant was considered to have switched back to CC if Heatsticks accounted for less than 30% of their total CC plus Heatstick consumption, after having switched to IQOS in an earlier week. The prevalence of switching back to CC was highest in the U.S., where in the last week of the study about 15% of those who switched to IQOS had switched back to predominantly using CC. Switching back to CC was lowest in Asia; Japan (none) and South Korea (6%).

In the U.S. Actual Use study, 62.7% of participants were classified as predominantly CC users in the last week of the observational study period; however, among those who initiated IQOS use, 16.3% were "exclusive" IQOS users at study end. Other countries' "exclusive IQOS use rate" at study end varied from a low of 7.8% in Switzerland to a high of 21.5% in Japan.

Table 7: Prevalence of Heatstick Trial and Switching at Study End, by Country

Country N=Enrolled population at end of study	Initiated IQOS use[a] among all smokers	"Switched" to IQOS[b] among those who "initiated" IQOS use	"Exclusive" IQOS use[c] among those who "initiated" IQOS use	"Switched" back to CC[d] among those who previously "switched" to IQOS
PBA-07				
United States (N=1,106)	33.8%	32.7% (N=116 of 374)	16.3% (N=58 of 355)	15.5% (N=30 of 194)
Whole Offer Test				
Japan (N=638)	61.3%	46.3% (N=181 of 391)	21.5% (N=84 of 391)	0.0% (N=180)
South Korea (N=843)	76.3%	47.4% (N=305 of 643)	20.1% (N=129 of 643)	6.4% (21 of 328)
Italy (N=535)	36.1%	29.0% (N=56 of 193)	12.9% (N=25 of 193)	10.3% (N=6 of 58)
Germany (N=377)	50.1%	37.0% (N=70 of189)	15.3% (N=29 of 189)	7.5% (N=5 of 67)
Switzerland (N=416)	49.5%	18.0% (N=37 of 206)	7.8% (N=16 of 206)	8.5% (N=4 of 47)

Note: 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] Initiated IQOS = consuming ≥100 Heatsticks during the observational period.

[b] Switched to IQOS = Heatsticks comprising ≥70% of total product use during the last week of the observational period.

[c] Exclusive IQOS use = Heatsticks comprising ≥95% of total product use during the last week of the observational period.

[d] Switched back to CC = Heatsticks comprising ≤30% of total consumed in a week after having switched to Heatsticks in an earlier week.

The statistical reviewers agree with the applicant's statistical analysis of the WOT results. Generalizability of the results to the populations of the respective countries may be limited by the non-probability nature of sampling as participants in the samples may not be representative of the respective country's smoker population with respect to smoking behavior and other factors related to tobacco use.

The PBA-07 study also assessed the mean number of cigarettes smoked per day at baseline to: (1) the mean total number of Heatsticks plus cigarettes per day (CPD) during the observational period; and (2) the mean number of CPD during the observational period. Daily cigarette consumption decreased between baseline and the observational period for all IQOS use groups, with the largest decrease occurring in participants who were predominant Heatstick users at Week 6 (average decrease of 7.6 CPD). It is unknown whether the changes were statistically significant. Across all groups, the applicant notes there was minimal change in average daily total use of tobacco products (i.e., Heatsticks plus cigarettes) between baseline and the observational period, suggesting that most participants who used IQOS were replacing a proportion of their CC use for Heatsticks rather than increasing their total tobacco product consumption. Less than 20% of smokers who switched to IQOS (≥70% Heatstick use) switched back to predominantly using CC (≤30% Heatstick use). Among smokers who switched to IQOS in the U.S, 16% were considered to have switched back to CC during the last week of the PBA-07 study.

Among current smokers who used 100 or more Heatsticks within the Actual Use study, 47% to 69% expressed interest in purchasing the product; likelihood of purchase among did not appear to differ by type of Heatstick (Menthol vs. Regular) requested by the participants.

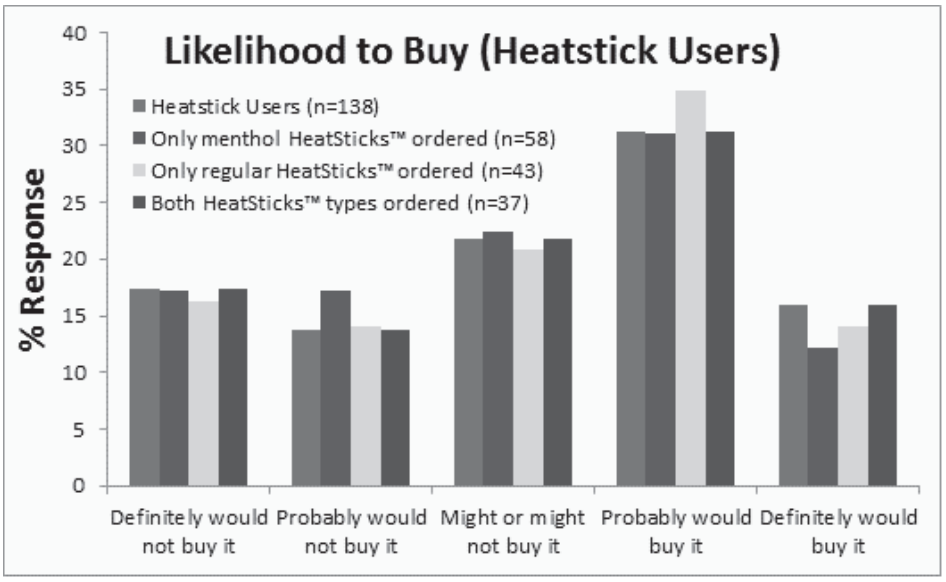


Figure 9: Likelihood of Heatstick Purchase among Current Smokers who used at least 100 Heatsticks in PBA-07 Actual Use Study

Note. FDA Reviewer drafted this figure using data from the application. Data Source: ths-pba-07-us-study-report-add-HSType_fdafixed.pdf.

The PBA-05-NOC study distinguished between smokers with and without an intention to quit smoking to evaluate whether marketing IQOS would have negative effects on smokers who intend to quit, such as causing them to delay their quit attempts. The applicant considered a change in quit intention from any intention to quit smoking in the next 30 days or 6 months pre-exposure to no longer intending to quit after exposure to the LLA materials; the FDA social science reviewer also included those changing from intending to quit in the next 30 days to an intention to quit in the next 6 months, as well as a change from any quit intention to no intention to quit. When considering the social science reviewer's broader definition of change in quit intentions, 4-19% of current smokers delayed a quit intention or no longer held an intention to quit cigarettes and 4-10% of current smokers with an intention to quit all tobacco had a lower or no intention to quit all tobacco after exposure to LLA materials.

The applicant explained in the September 2017 amendment that the decision was made to prioritize specificity over sensitivity in order to minimize false positive predictions of actual (post-market) trial/use. As there is no consensus in the literature on how intention should be measured, it is difficult to know what kind of assessment most accurately predicts actions that will be taken by the respondents in the future. Additionally, most cigarette smokers express intention to quit at some point; however, the success rate for any given quit attempt is low. The uncertainty of smokers' intentions in this study is consistent with our current knowledge. Thus, the broader approach used by the social science reviewer may not predict actual behaviors.

Overall, pre- and post-market observational studies found that IQOS use patterns varied across the U.S., Asia, and Europe. In the U.S., 34% of cigarette smokers in the Actual Use study initiated IQOS use, defined as using at least 100 Heatsticks. In the WOT, conducted in multiple countries where IQOS is currently marketed, the prevalence of initiating IQOS use ranged from 36% in Italy to 76% in South Korea. The findings suggest that some smokers will find IQOS appealing and acceptable enough to initiate use of the product. In the U.S. Actual Use study, daily cigarette consumption decreased between baseline and the observational period for all IQOS use groups, with the largest decrease occurring in participants who were predominant

Heatstick users at Week 6 (average decrease of 7.6 CPD). Participants in both the PBA-07 and WOT had to express interest in using IQOS prior to study enrollment. Study participants may be more likely to find the product appealing than smokers in the general population, leading to overestimation of the prevalence of IQOS initiation among smokers.

2. Poly-use of IQOS and cigarettes or other tobacco products

Dual use of IQOS and CC was common in all countries in the pre- and post-market studies. In PBA-07, the applicant used 100 or more Heatsticks as a threshold for initiation and defined dual use as using 30 to 70% of Heatsticks out of the total number of cigarettes + Heatsticks consumed per week. FDA notes the definition of dual use could include the "predominant" categories given that participants are using cigarettes and Heatsticks concurrently in those use categories. As illustrated in Table 8, among current smokers in the Actual Use study (PBA-07), the potential for dual use of CC and IQOS appears to be high. A majority (57.6%) used the IQOS in addition to CC when dual use is defined as between 5% to 95% Heatsticks. The patterns of use overall are similar when considering the type of Heatstick ordered by the participant (Menthol, Regular, Both); switching, dual use, and exclusive cigarette use did not differ by the type of Heatstick respondents requested at baseline.

Table 8: IQOS and CC Use Over 6-Week Observational Actual Use Study (PBA-07)

Behavior at Week 6	Denominator	N	%	Range During 6-Week Observational Period
Exclusive *Heatsticks* use (95-100% *Heatsticks*/CC and *Heatsticks*) during the study	1,106	73	7.5%	7.1% to 8.5%
Predominant *Heatsticks* Use (70-95% *Heatsticks*/CC and *Heatsticks*) during the study	1,106	68	7.0%	7.0% to 12.1%
Combined mostly *Heatsticks* Use (60-70% *Heatsticks*/CC and *Heatsticks*) during the study	1,106	36	3.7%	3.7% to 5.5%
Combined balanced use (40-60% *Heatsticks*/CC and *Heatsticks*)	1,106	119	12.3%	12.3% to 22.5%
Combined mostly CC use (30-40% *Heatsticks*/CC and *Heatsticks*)	1,106	62	6.4%	6.4% to 13.6%
Predominant CC use (5-30% *Heatsticks*/CC and *Heatsticks*)	1,106	273	28.2%	28.2% to 32.5%
Exclusive CC use (0-5% *Heatsticks*/CC and *Heatsticks*)	1,106	334	34.5%	6.4% to 34.5%

Alternate definition of dual use

Applicant's definition of dual use, "combined use"

Note. FDA Reviewer drafted this figure using data from the application.
Data Source: Table 15.2.6.1.2, Table 15.2.6.2.2, ths-pba-07-us-tables.pdf, pg. 9263.

When using the applicant's definition for switching (i.e., ≥95% Heatstick use), less than 8% of participants in the PBA-07 study met the criteria for switching from CC to IQOS. Participants who became exclusive IQOS users, however, seemed less likely to return to using mostly CC, indicated by the steady prevalence of exclusive IQOS use throughout the 6-week observational period. Although it is possible that with additional follow-up time more participants would have become exclusive IQOS users, data from the PBA-07 study and the WOT study show that most smokers were dual users during their initial period of IQOS use.

Despite the high proportion of incomplete switching or dual use in the study, the applicant notes that there was a reduction in average daily cigarette consumption across all IQOS use groups in the PBA-07 study, even among the group of participants who were predominantly using cigarettes at Week 6. However, when FDA considered baseline cigarette use compared to each of three follow-up visits (as opposed to compared to the 6-week average daily use highlighted by the applicant), participants appear to reduce by about 1 CPD over the entire study period and add about 2-4 Heatsticks per day. Accordingly, even though the average daily total appears relatively stable, participants may be using more total units of tobacco products when both cigarettes and Heatsticks are considered. Heatsticks were provided free of charge; the pattern of use during this study may not accurately reflect the use pattern of marketed product.

In PBA-07, the use of NRT products remained stable from baseline to Week 6 (2.4%), while the use of e-cigarettes increased from baseline (14.2%) to Week 6 (20.6%) and the use of other tobacco products such as cigars, cigarillos and smokeless tobacco products decreased from baseline (38.7%) to week 6 (26.9%). Those reporting no other tobacco use was 54.5% at baseline and 60.7% at week 6.

The applicant provided data from two Japanese on-line post-marketing surveys. In a 2016 Japanese online cross-sectional survey of 2000 adult smokers and nonsmokers, 3.7% of respondents reported using "heat-not-burn" (heated) tobacco products. The prevalence of heated tobacco product use was higher among those aged 20-39 (~4 %) than those aged $\geq$ 40 (~1 - 1.5%) and most (96.3%) were using "Marlboro Heatsticks with IQOS device." Among respondents currently using heated tobacco products, 84.9% also smoked cigarettes, most of them daily. In total, 91.8% of heated tobacco product users reported dual use with at least one other tobacco product. For most respondents, heated tobacco products comprised less than 30% of their average total daily tobacco consumption. A total of 15.5% of heated tobacco product users were considered exclusive users (≥95% use). All respondents in the exclusive use group were not current cigarette smokers. Although the applicant describes data from Japan, use of nicotine-containing e-cigarettes requires a prescription in Japan, which may limit generalizability of the data to the U.S. population.

In the second Japanese marketing survey, data on self-reported use of IQOS and cigarettes were also collected from 14,999 adult IQOS purchasers 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. The applicant suggests that the difference between these survey results and those of other studies reflects increasing popularity and awareness of IQOS. Of note, purchasing IQOS and registering the device was a requirement for inclusion in the larger and more recent survey; this may not be a representative sample of all users.

Dual use of CC and IQOS appears likely. There is concern about the effects that dual use of IQOS and CC (compared to complete switching) will have on long-term reduction of HPHC exposures and the health risks for tobacco-related diseases. While results from the PBA-07 study showed that IQOS use was associated with reduction in cigarette consumption, the health benefits of reducing cigarette consumption instead of quitting completely are unclear.

3. Use of IQOS by Former or Never Smokers and Youth

In PBA-05-NOC, the applicant assessed perceptions and intention to use IQOS among former smokers, young adult never smokers (aged 18-25 years), and other never smokers. The applicant also conducted research on non-smokers' use of heated tobacco products in Japan, where IQOS is on the market. The epidemiology review describes results from two published studies from Japan and Italy that reported the prevalence of IQOS use in never and former smokers after IQOS was marketed in these countries.

For PBA-05-NOC the applicant developed LLA materials, including an IQOS brochure, Heatsticks pack, and direct mail communication. Measures were developed for assessing intentions to try and use IQOS. 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*. The LLA materials provided information to distinguish IQOS from e-cigarettes including statements about "real tobacco" and an appearance similar to CC; they contain a tobacco plug wrapped in paper. In Arm 3, which presented a photo of the IQOS device with a Surgeon General's warning but no additional information about IQOS, the applicant notes, "It is likely that Risk Perceptions are primarily based on factors such as the appearance of the THS device (which is similar to some e-cigarettes) and the impression that the product is innovative and new." These perceptions related to similarities between IQOS and e-cigarettes may be important when considering potential appeal among people who do not currently smoke. The brochure included a statement that the product is intended for smokers who want to continue using tobacco and is not intended for use by non-smokers. Heatsticks would be marketed under the Marlboro brand name, which consumers may associate with CC. As a cigarette product, Heatsticks cannot be marketed with characterizing flavors aside from tobacco or menthol; the availability of different flavors is a commonly-cited reason for never smokers' use of e-cigarettes.[78] [79] These characteristics may reduce the appeal to nonsmokers.

FDA questioned the applicant's decision to define 'positive intent' as those responding *Definitely* or *Very likely* but excluding *Somewhat likely.* The applicant explained in the September 2017 amendment that the decision was made to prioritize specificity over sensitivity, i.e., to minimize false positive predictions of actual (post-market) trial/use. The applicant accurately notes there is no consensus in the literature on how intention should be measured or what kind of assessment most accurately predicts uptake.

In response to an inquiry from FDA, the applicant submitted information on intention to try and use IQOS among current and former smokers in Arm 2 and Arm 3 of PBA-05-NOC based on whether the participant viewed the Regular, Smooth Menthol, or Fresh Menthol Heatsticks pack. Former menthol cigarette smokers were assigned to view a menthol variant. Although the analyses were descriptive and sample sizes were small, a slightly greater proportion of former smokers randomized to view Smooth or Fresh Menthol variants intended to try or use IQOS compared to those that saw the Regular Heatsticks pack (7-8.1% vs. 4.8% to try IQOS; 5.4% vs. 2.9% to use IQOS). This could indicate that former smokers who used menthol cigarettes may be more likely to try and use IQOS than former regular cigarette smokers.

Never smokers in PBA-05-NOC, including young adults (legal age to 25 years), were only exposed to the Regular Heatsticks pack in Arm 2 and Arm 3. This is a study limitation since menthol cigarette smokers comprise one-third of the U.S. market. The 2011 NSDUH Report noted that while rates of menthol cigarette use among 12-17-year-olds were stable between 2004 and 2010, more than half (51.7%) of those who had smoked a cigarette for the first time in the prior 12 months smoked menthol cigarettes.[80]

Among never smokers and young adult never smokers, only 0-1% who viewed the LLA materials indicated they would *Definitely* or *Very Likely* try IQOS. The results for former smokers were slightly higher; of those

[78] Berg, C.J. (2016). Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers. International Journal of Public Health, 61(2), 225-236.
[79] Kong, G., Morean, M.E., Cavallo, D.A., et al. (2015). Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. Nicotine & Tobacco Research, 17(1), 847-854.
[80] Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (November 18, 2011). The NSDUH Report: Recent Trends in Menthol Cigarette Use. Rockville, MD (Amendment December 17, pg. 42).

who viewed LLA materials, 5-6% indicated they would *Definitely* or *Very Likely* use IQOS. When never smokers and young adult never smokers were asked about intent to use if offered by a friend, the positive responses were minimally higher; 2-7% indicated they would *Definitely* or *Very Likely* try IQOS. Former smokers indicated positive intent to try IQOS at 15-24% if offered by a friend.

When responses of *Somewhat likely* are included in estimates of positive intention to use IQOS, 4-7% of never smokers and 7-11% of young adult never smokers reported an intention to try IQOS. Among former smokers, 17-25% reported an intention to try IQOS, with 7-14% reporting an intention to use regularly if they tried IQOS and liked it. If offered by a friend, 33-42% of former smokers responded they would *Definitely, Very Likely* or be *Somewhat likely* to try IQOS.

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

In the U.S., most cigarette smokers begin trial and progression to regular use before age 18 (USDHHS 2012; USDHHS 2014). While oversampling of young adult never smokers in PBA-05-NOC is a strength of the study, the applicant did not submit any information or bridging study data to youth under age 18 and did not stratify information submitted in the PBA-05-NOC and PBA-07 studies by age beyond the 18-25-year-old age group. Excluding current smokers who started smoking cigarettes in the prior 30 days is also a limitation; this may have limited the inclusion of young adult cigarette smokers in the adult smoker groups since young adult cigarette smokers are often lighter smokers or in a recent state of transition.[81] [82] As the applicant notes, FDA clarified during a September 5, 2013 meeting (TC0000737) that studies in youth were not expected; however, the applicant did not include bridging information on youth use of other products (e.g., cigarettes, e-cigarettes). This might have helped FDA better understand youth intentions and perceptions with respect to IQOS.

The applicant conducted cross-sectional studies to monitor the prevalence of heated tobacco product use by adult non-smokers (age 20 or older) in Japan. During the first one to two years after IQOS went on the Japanese market in 2014, use by adult former and never smokers was low (1.5% among former smokers and 1.2% among never smokers). Additional internet surveys were conducted in 2015, 2016, and 2017. Panelists aged 15-69 years from a major Japanese internet research agency provided information on current use (i.e., any use in the previous 30 days) of IQOS, other heated tobacco products, e-cigarettes, and combustible cigarettes.[83] Among survey responders in 2017, there were 3.6% current IQOS users and 2.0% of those aged 15-19 years reported current use of IQOS in 2017. Of the 2017 survey responders 1.3% were never smokers, 2.1% were former smokers, 18.8% were current smokers with intention to quit, and 10.3% were current smokers with no intention to quit.

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[81] Lenk, K.M., Chen, V., Bernat D.H., Forster J.L., Rode, P.A. (2009). Characterizing and comparing young adult intermittent and daily smokers *Subst. Use Misuse*, 44, 2128-2140.

[82] U.S. Department of Health and Human Services (USDHHS). (2014). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

[83] Tabuchi, T., Gallus, S., Shinozaki, T., Nakaya, T., Kunugita, N., & Colwell, B. (2017). Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control, [Epub ahead of print].

In 2017, a face-to-face survey was conducted in Italy among 3000+ participants aged ≥15 years selected from the general Italian population.[84] Based on cigarette smoking status, 1.0% of never smokers, 0.8% of former smokers, and 3.1% of current smokers reported having ever tried IQOS. Among participants who reported that they had never tried IQOS but were intending to try it, 1.7% were never smokers, 0.5% were former smokers, and 5.0% were current smokers.

The post-market surveys conducted in Japan and Italy also measured IQOS use among youth. In Japan, 2.0% of those aged 15-19 years reported current use of IQOS in 2017. The prevalence of current use was lower in youth than in those aged 20-29 years (5.8%), 30-39 years (5.4%), 40-49 years (3.9%), and 50-59 years (3.7%). In the Italian study, 0.9% of those aged 15-24 years reported having ever tried IQOS, compared to 1.0% of those aged 25-44 years, 2.4% of those aged 45-64 years, and 1.0% of those aged ≥65 years. Youth and young adults aged 15-24 years also had a slightly lower prevalence of participants reporting that they had never tried IQOS but were intending to try it (1.9%), compared to those aged 25-44 years (2.9%) and 45-64 years (2.5%) who said they were intending to try IQOS.

Overall, the available information suggests the prevalence of IQOS use is lower in never smokers compared to current smokers and that fewer youth than adults currently use IQOS in Japan or Italy. The data from countries where IQOS is marketed, Italy and Japan, show low uptake by youth and current nonsmokers. These two published survey studies are the only data currently available on the prevalence of IQOS use in youth.

The PBA-05 study also suggests a low prevalence of intention to use IQOS among never smokers. The likelihood is slightly higher in former smokers, but still low. As noted by the applicant, these data may not be as sensitive for less decisive responses, e.g., *Somewhat likely*. There is no agreed-upon method for conducting these types of studies where theoretical choices are being made that have no true consequence. Introducing additional conditions to the study scenario, e.g., intent to try or use IQOS if offered by a friend, makes interpretation of the data even more uncertain. These studies, while providing an indication of intent among smokers, nonsmokers, and former smokers, cannot be considered as absolute indicators of behaviors when/if IQOS is a marketed product.

Certainly, the potential for rapid uptake of a novel tobacco product among youth exists. In the decade since e-cigarettes were introduced to the U.S. market, youth use rose rapidly but the limited flavor choices may reduce IQOS' appeal to youth. The limited options in terms of flavor choice and the price of the IQOS device may reduce the appeal to youth. Given that IQOS is still a relatively new product to Italy and Japan, the extent to which youth will initiate and use IQOS in these markets, or any other market that may start selling IQOS, is unknown though the trend from other countries indicates that this is uncommon. Overall, the current evidence indicates IQOS uptake by youth and nonsmokers will be low.

4. Likelihood of IQOS leading to Conventional Cigarette Smoking Cessation

Both the PBA-07 and WOT studies evaluated the likelihood of smokers switching to IQOS. During the six-week observational period of the PBA-07 study, 33.8% of current smokers initiated use of Heatsticks (defined as consuming ≥100 Heatsticks). Among those who started using Heatsticks, 16.3% were exclusively using Heatsticks (≥95% Heatstick use) during Week 6. Of those who switched to Heatsticks in an earlier

[84] Liu, X., Lugo, A., Spizzichino, L., Tabuchi, T., Pacifici, R., Gallus, S. (2018). Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control, [Epub ahead of print].

week, 15.5% had reverted to predominantly using cigarettes (i.e., Heatsticks were ≤30% of total cigarettes + Heatsticks consumed in a week) by the last week.

In the WOT, the prevalence of using Heatsticks varied by country. 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. Exclusive and predominant IQOS use was most common in Asia where these outcomes were observed in 14% and 16%, respectively, of Japanese smokers and 16% and 22%, respectively, of South Korean smokers. Although more IQOS users may quit smoking over time, data from the PBA-07 study and the WOT study show that most smokers become dual users or at least go through a dual use phase before quitting.

In the Japanese post-market study of IQOS purchasers who registered their device in an online database, 52%-65% of IQOS purchasers were considered exclusive IQOS users. However, those who take the initiative to register their device are likely to be a non-representative sample of all Japanese IQOS users and may be more motivated to become exclusive IQOS users. Also, nicotine containing e-liquid is categorized as a pharmaceutical ingredient in Japan and nicotine-containing e-cigarettes are not as readily available in Japan as they are in the U.S.

Although less than 10% of cigarette smokers in the U.S. PBA-07 study switched to exclusive IQOS use, the proportion of exclusive IQOS users remained steady during the 6-week observational period. This suggests that individuals who initiate IQOS and use Heatsticks for at least 95% of their tobacco intake are able to maintain exclusive IQOS use over time and potentially replace their use of CC with Heatsticks long-term.

5. Population Modeling

The applicant presented results from a Population Health Impact Model (PHIM) to assess the possible effects of the proposed new products on population health in the U.S. This is a computational and simulation model that tracks tobacco prevalence and deaths from four specific smoking-related diseases: lung cancer, ischemic heart disease, stroke, and COPD on a hypothetical population exposed to two tobacco products - CC and THS 2.2. The model consists of two quantitative components: The "Prevalence Component" (P-Component) in which individual smoking histories are simulated over a follow-up period from 1990 to 2009, and the "Epidemiological Risk Component" (E-Component) in which the smoking histories produced by the P-component are used to estimate smoking-related deaths for each morbidity.

The initial population in the scenarios is representative of the U.S. in 1990, and the scenarios are modeled for a twenty-year period.

- **Null Scenario**: THS 2.2 is not introduced into the market. This scenario considers three possible tobacco use statuses: never smoker (N), current smoker (C), former smoker (F).
- **THS Scenario**: THS 2.2 is introduced into the U.S. market. This scenario considers five possible use statuses: N, F, current cigarette smoker (C_C), current THS user (C_T) and current dual user (C_D).

The applicant presents results from a THS scenario called the "business case" that uses a specified set of input values and assumptions. The applicant's findings are dependent on the following basic assumptions; additional details are in the epidemiology review:

- Within 10 years of being on the U.S. market the new tobacco products will be used by 17% of U.S. smokers. Approximately 15% of users will be exclusive users and 2% will be dual users with cigarettes.
- Over a twenty-year period approximately 30% of smokers will be users of the new products.

- Most current cigarette smokers transitioning to the new products will be middle aged; younger people are less likely due to cost and older people are generally less likely to switch.
- The new products would not change the combined initiation, re-initiation, or cessation rates for cigarette smoking but would change the distribution of use of these products in the THS scenario with the introduction of new product and dual use.

The applicant concludes, "Overall, based on the modeling results and scenario specifications, introducing THS into the US population appears to lead to a sizeable public health benefit in terms of reduced cigarette smoking and tobacco-related mortality. Variation in the model parameter estimates within reasonable ranges would not materially change these conclusions."

FDA evaluated the applicant's approach. The model considers deaths from four conditions (lung cancer, COPD, ischemic heart disease, and stroke). According to the 2014 U.S. Surgeon General's Report,[85] these causes account for approximately 336,000 of 437,000 deaths directly attributable to cigarette smoking among U.S. adults. The model does not account for changes in the number of deaths from environmental tobacco smoke exposure due to use of the proposed new tobacco products. The prevalence estimates used by the applicant are higher than those observed in more recent years, with U.S. adult smoking prevalence having been 20.6% in 2009[86] and having since declined to levels around 15%.[87] As such, model estimates may tend to overestimate the number of current smokers in the baseline case compared with the present population and could overestimate any population health impact of smokers switching to another tobacco product.

The business case projects that the proposed new tobacco products will come to represent a substantial proportion of the smoking market in the U.S., accounting for ~17% of users in 10 and 30% of users in 20 years, with most being exclusive users. The modeling section does not present empirical evidence to support this forecast. If uptake of the products by consumers is lower, takes more time, or is more likely to occur as part of dual use, then the magnitude of any population health effects would be expected to be reduced. The assumption that relative exposure for dual users is the mean of relative exposure for smokers and proposed new product users may underestimate risk; exposure among dual users may not be the average of exposure of exclusive cigarette and THS users. In addition, individual harm from exposure to exclusive or dual use with the proposed products may not follow a linear dose-response relationship.

The applicant included a series of simulation results to describe the potential impact of IQOS marketing of the health of the population:

- **20 years of cessation** - This simulation assumes all current smokers would stop smoking immediately. Under this scenario, the smoking prevalence will be zero during the 20-year follow-up period and the risks associated with smoking-related diseases diminish over time. As a result, over the 20-year simulation period (1990-2009), the 100% cessation assumption would result in 934,947 fewer smoking-attributable deaths.
- **20 years of THS with no cigarettes** - This simulation assumes that all current smokers in 1990 transitioned immediately to THS rather than quit smoking. Also, it is assumed that initiation and relapse rates changed, and future smokers will use THS only. Under this scenario, two relative exposure (f-values) were considered: f-value=0.1 (THS preserved the effects of cessation by 90%)

[85] US Department of Health and Human Services. The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General, 2014. Atlanta, GA 2014.
[86] Centers for Disease Control and Prevention. Cigarette smoking among adults aged >= 18 years – United States, 2009. Morbidity and Mortality Weekly Report. 2010;59(35)1135-1140.
[87] Phillips E, Wang TW, Husten CG, et al. Tobacco Product Use Among Adults – United States, 2015. Morbidity and Mortality Weekly Report. 2017;66(44):1209-1215.

and f-value=0.3 (THS preserved the effects of cessation by 70%). Based on these assumptions, over the 20-year simulation period, the introduction of THS would result in 780,433 (if f-value=0.1) or 516,944 (if f-value=0.3) fewer smoking-attributable deaths.

- **World Health Organization 2025 target and projection**: The 2015 WHO Report targets a 30% reduction in smoking prevalence from 22.1% in 2010 to 15.4% in 2025, with a revised projection of 18.9% in 2025 representing only a 14% reduction. In this simulation, the PHIM was used to estimate the impact of reducing smoking prevalence by 30% (WHO 2025) and 14% (WHO revised) over a 15-year period (1990-2005). A null scenario (no THS into the market) was also used to compare the projected smoking prevalence assuming 30% and 14% reduction in prevalence. The results indicate that, under the null scenario, smoking prevalence remained somewhat constant over the 15-year simulation, with 27% and 24% smoking prevalence for males and females, respectively. Under the WHO 2025 scenario, in 2005 the smoking prevalence was 19% for males (29.6% prevalence reduction) and 16% for females (27.3% prevalence reduction), resulting in 172,458 fewer smoking-attributable deaths cumulatively over 1990-2009. Under the WHO revised scenario, in 2005 the smoking prevalence was 22% for males (18.5% prevalence reduction) and 18% for females (18.2% prevalence reduction), resulting in 111,102 fewer smoking-attributable deaths cumulatively over 1990-2009.

There are no major concerns with the statistical and computational aspects of the PHIM. Overall, the simulation results suggest that the introduction of THS 2.2 into the commercial market will reduce the overall morbidity and mortality from tobacco products. However, there are limitations to the PHIM modeling assumptions, input data construction, and inference procedures. The model only considers two products – cigarettes and IQOS; other tobacco products were not considered in the simulations. Furthermore, the population size does not change over time. There is also a question as to whether the general approach for modeling risk reduction with the proposed products, which is based on reduction in risk based on the time since complete smoking cessation, is appropriate when used to represent risk caused by continuing use of a tobacco product. The applicant provides very little justification and no specific empirical evidence to support the assumptions that individuals who do not currently smoke cigarettes would not be interested in using the proposed products or that young people would not find them appealing. Finally, the relatively short projection period of 20 years and use of mortality as a health outcome does not allow for adequate consideration of the long-term health effects of tobacco use initiation among youth and youth adults. The projected population health effects of the proposed new tobacco products may be overstated if specific assumptions about tobacco use behavior and risks are not realized in the actual population. Although the model is statistically valid, the overall analysis of the population model does not provide evidence to support the application.

6. Amendment MR0000117; Study ZRHR-ERS-09-US

On June 11, 2018, FDA received amendment MR0000117 to MR0000059-61, which includes the final study report for ZRHR-ERS-09-US. Although this amendment was directed to the MRTPAs, since the amendment included information with respect to the products that are the subject of the PMTAs, the amendment is considered here.

Study Title: Evaluation of Biological and Functional Changes in Healthy Smokers After Switching to THS 2.2 for 26 weeks

Study Design: This was a randomized, controlled, open-label, 2-arm, parallel group, multi-center clinical study of six months of *ad libitum* use of the non-menthol THS 2.2 compared to continued CC users in an

ambulatory setting. Participants were healthy adult (age > 29 years) non-menthol CC smokers not interested in quitting within the next six months. This study was conducted in 20 clinical sites across the continental U.S. All participants used THS 2.2 for a one-week run-in period and those who were willing were considered for randomization after this period.

Study Population: Of 984 subjects, 488 were randomized to THS 2.2 and 496 to CC. Study participants had a mean age of 44.6 years, 58.8% male, 79.2% white and 17.6% African American. Most (62%) had high school education and 31.9% had a college education or higher. Smoking duration average was 26.2 years. Mean CPD for the past year was 19.3 and most were moderately (45%) or severely (39.3%) dependent. There were insufficient data for analysis of 127 subjects, leaving 857 in the analysis population. The group descriptions and numbers are shown in Table 9.

Table 9: Study Population ZRHR-ERS-09-US

Category	**Description**	**Number (Percent) Analyzed**	
		THS Group	CC Group
THS use	≥70% THS use over entire analysis period **and** ≥70% THS use on ≥50% of the days in the analysis period	245 (51.4%)	
Dual use	1% ≤ THS ≤ 70% over the entire analysis period **or** THS-use and CC-use on <50% of the days	142 (29.8%)	
CC use	<1% < THS over the entire analysis period **and** <1% THS on >50% of the days in the analysis period	3 (0.6%)	425 (86%)
Other use	General category encompassing subjects with missing product use, those using e-cigarettes or other tobacco products, those who quit, or subjects who switched across different use patterns between consecutive analysis periods	24 (4.9%)	18 (4.2%)

Table created based on information in amendment MR0000117 Overview

Primary Study Objective: To demonstrate favorable changes after six months across eight co-primary clinical risk endpoints (referred to by FDA as BOPH) for those switching from CC to THS as compared to continued CC use.
The co-primary endpoints are: HDL-C, sICAM-1, total WBC, COHb, 11-DTX-B2, 8-epi-PGFS2α, FEV1, and total NNAL. The applicant defined success as:

1. Statistically significant improvements in at least five of the eight endpoints
2. All endpoints changing in the direction observed with smoking cessation

Primary Study Results:
Five of the eight endpoints showed a statistically significant change in smokers who switched from cigarette smoking to THS use. All BOPH shifted in the direction seen when smokers quit, as described in literature. Results are summarized in Table 10.

Table 10: Primary Analysis of CREs between THS Use and CC Use at Six Months for ZRHR-ERS-09-US

Endpoint	Change from CC-use	LS Mean Difference or Relative Reduction	1-sided p-value *=statistically significant
HDL	Difference	3.09 mg/dL	<0.001*
WBC count	Difference	-0.420 GI/L	0.001*
sICAM-1	% Reduction	2.86%	0.030
11-DTX-B2	% Reduction	4.74%	0.193
8-epi-PGF2α	% Reduction	6.80%	0.18
COHb	% Reduction	32.3%	<0.001*
FEV1 %predicted	Difference	1.28% predicted	0.008*
Total NNAL	% Reduction	43.5%	<0.001*

Table created based on Table 4 in MR0000117 Overview

Secondary Study Objectives:

- Evaluate self-reported product use (THS and/or CC) and nicotine exposure levels
- Evaluate exposure reduction to selected HPHCs (BOE) in dual use and THS use groups

Significant reductions in exposure levels in the THS group and the dual use group are noted in Figure 10.

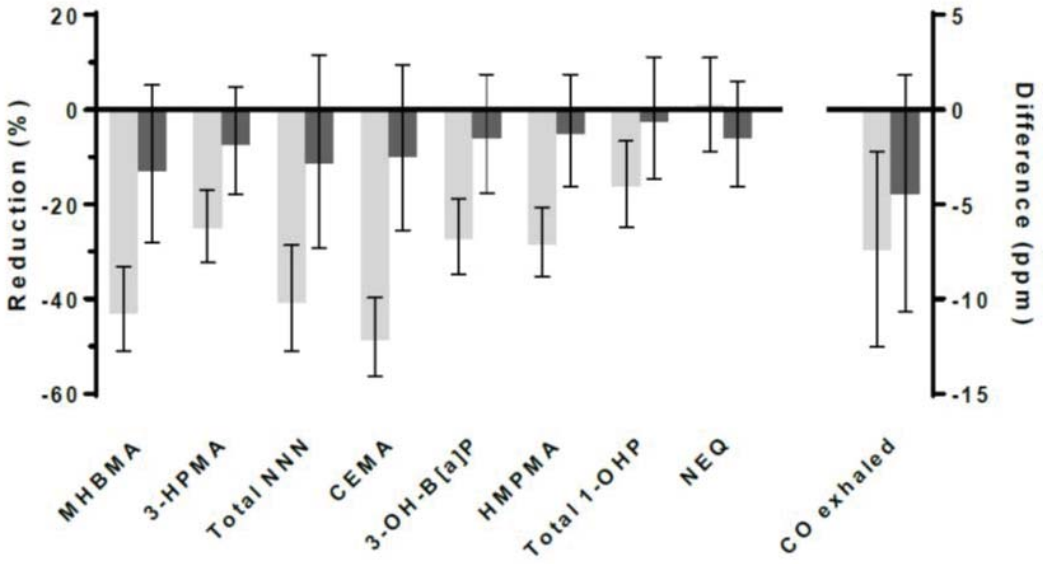


Figure 10: THS:CC (light grey) and Dual Use:CC (dark grey) Ratios (%) and Difference (ppm) and 95% CI at Month 6

Abbr.: MHBMA = monohydroxybutenylmercapturic acid, 3-HPMA = 3-hydroxypropylmercapturic acid, CEMA = 2-cyanoethylmercapturic acid, 3-OH-B[a]P = 3-hydroxybenzo(a)pyrene, HMPMA = 3-hydroxy-1-methylpropylmercapturic acid, Total 1-OHP = total 1-hydroxypyrene, NEQ = Nicotine Equivalents, CO Exhaled = Carbonmonoxide exhaled

Source: Figure 2, MR0000117 Overview

Baseline nicotine equivalents (NEQ) levels ranged from 9.2-10.3 mg nicotine/g creatinine across the category groups. At Month 6, the geometric least square mean values were almost identical in the THS and CC groups at 8.92 and 8.86 mg nicotine/g creatinine, respectively. In the dual use group, the LS NEQ values were slightly lower at 8.34 mg/g creatinine. The applicant believes these results confirm that THS 2.2 can deliver nicotine at levels comparable to CC and that adult smokers can accept THS as an alternative to CC.

Additional Analysis: Concomitant CC Use

The applicant notes this study assessed the effect of THS as "actually used" considering that a significant amount of concomitant use (up to 30%) may occur and this could reduce the risk reduction potential of THS. The applicant believes the level of concomitant use seen in this study is consistent with the experience in markets where THS is commercialized. In these markets, the applicant has observed that 70-90% of THS users use THS in >70% of all tobacco use experiences. The applicant also notes that the primary study objective was met and HPHC exposures (BOE were secondary endpoint) were reduced, even with the concomitant use pattern.

Adverse Events (AEs) Associated with the Study

There were 19 serious AEs reported by 13 subjects: 8 events in 6 subjects in the THS arm, and 11 events in 7 subjects in the CC arm. None of the serious AEs was believed related to THS or CC by the applicant. There were two deaths:

Subject 04-384 was randomized to the THS 2.2 arm on Oct 7, 2015. On Dec 16, 2015 the subject was found deceased in the bathtub at his residence; cause of death was acute and chronic alcohol abuse.

Subject 14-101 was randomized to the THS 2.2 arm on Jan 11, 2016. He died of a self-inflicted gunshot wound on Jan 25, 2016.

During the exposure period, 415 subjects reported 758 AEs: 358 events in the THS arm and 400 in the CC arm. Most AEs were mild or moderate in severity. Three subjects discontinued the study from the THS arm and two from the CC arm. The most common AEs were upper respiratory tract infections (4.3% in THS, 4% in dual use, and 6.2% in CC).

Applicant's Conclusions

- Among subjects randomized to use THS, 34% used THS exclusively (defined as ≥95% use). Another 34% dual-used THS and CC. The applicant believes these results show the product was well accepted considering that before switching, subjects were naïve to the product.
- Overall, all the clinical risk endpoints (BOPH) evaluated in those switching from CC to THS followed the same direction as seen following smoking cessation. The changes were statistically significant in five of the eight BOPH measured.
- In addition to NNAL and COHb measured as BOPH, eight BOE were assessed. In all cases, there was significant reduction in THS users compared to CC users.
- Exposure to nicotine was comparable between THS and CC users.
- With respect to dual use (defined as subjects whose THS use was 1-70%):
    - BOPH showed a shift (although minor and not generally significant) in the favorable direction at six months compared to CC use.
    - BOE showed slight reductions compared to CC at six months (2.6-13%)

FDA Statistical Analysis

There are limitations to the applicant's statistical approach:

- Although the report describes this as a controlled clinical trial, the study design is ambulatory. The study staff did not control participants' exposure to the products. This is part of the study design and does not affect data validity.
- While the initial randomization scheme is acceptable, the applicant used modified groups for the primary analysis. In the newly-defined post-randomization "Actual Product Use Categories," only 245 of the randomized 488 participants in the THS 2.2 group were included in the primary analysis.

Eliminating about 50% of participants breaks the initial balance between the THS 2.2 and CC study arms obtained via randomization. Therefore, significant differences between the THS 2.2 and CC study arms may be due to factors unrelated the exposure.

- The data analyses assumed that the individual outcomes (changes in BOPH) are independent for each of the eight primary biomarkers. This is unlikely. The BOPH selected are affected by multiple factors, including general health, other medical conditions, infections or other inflammatory processes, genetics, age, diet, exercise, and medications. It is difficult to consider these biomarkers as individual measures of tobacco-related disease and the levels are unlikely to change independently. Nonetheless, the measured changes in BOPH are valid, even if not independent.
- The applicant provided no scientific justification suggesting that BOE and BOPH related to CVD, cancer, and lung function are appropriate to combine as an overall metric of clinical significance.
- Because the study arms became imbalanced at the six-month time point, the use of multiple comparisons performed with the Halperin-Ruger statistical method is not justified.

Due to limitations in design and statistical analysis, no definite conclusions can be made based on this study. However, despite these limitations, the study provides evidence of reduced exposures associated with switching completely from CC to THS. Additionally, those with self-reported dual use had no evidence for increased toxin exposures. The rate of self-reported dual use during this longer study was lower (~34%) than the considerably higher dual use rates in previous studies (~58% in the Actual Use study). There were no unexpected safety signals identified during the study and the rate of adverse events was similar for those exposed to THS and CC. Nicotine exposure levels were also comparable between THS and CC.

7. Summary of Population Health Findings

The social science review concludes that based on the information submitted by the applicant, we have concerns with respect to: the lack of information about youth under age 18, as well as the lack of a discussion of submitted data's applicability to youth and the lack of presentation of the data in stratified categories that would allow us to make inferences about youth, the potential for initiation among young adult never smokers, and the potential for dual use among current smokers with only a one cigarette per day decrease in use frequency. Philip Morris Products S.A.'s premarket tobacco product applications do not contain sufficient information to address these concerns from a Social Science perspective.

As TPL, I do not agree with these social science conclusions.
I agree there are limited data regarding use and possible uptake of IQOS in youth. However, I disagree that there is no data. The applicant provided data a Japanese internet research agency which included panelists ages 15-69 years; they found 2.0% of those aged 15-19 years reported current IQOS use in 2017. Additionally, the Epidemiology review team reports a face-to-face survey conducted in Italy with >3000 participants, age ≥15 years found 0.9% of those aged 15-24 reported ever trying IQOS. The data from countries where IQOS is marketed, specifically Italy and Japan, show low uptake by youth and current nonsmokers. Overall, the current evidence indicates low IQOS uptake by youth.

I agree there are concerns about dual-use. There is evidence that U.S. cigarette smokers are interested in IQOS, but limited data for use of IQOS to achieve CC smoking cessation. The company states they intend to market IQOS 'for adult smokers who wish to completely switch.' The limited data available indicates that a dual-use period is common during the switching period, but those who switch 'quickly and completely' were more likely to successfully remain off conventional cigarettes. There are data that HPHC exposures are not increased in those who dual-use IQOS and cigarettes. In fact, HPHC reductions continue through the 90 extended exposure studies even though during the last 85 days of these studies participants were not in

controlled environments and dual-use was likely. Additionally, although the changes were not statistically significant, the six-month study showed decreases in BOE for dual users as compared to exclusive CC users. The studies conducted by the applicant have not demonstrated reduction in long-term disease risk; however, the reduced exposures combined with the other available information, lead me to conclude IQOS is appropriate for protection of public health, even if there is some dual-use among smokers as they potentially transition to the product.

The epidemiology review concludes the applicant has demonstrated that the exclusive use of the products that are the subject of these applications exposes users to substantially lower exposure to many HPHCs compared to conventional cigarette smoking. The review also recommends any marketing authorization granted in response to these PMTAs be accompanied by requests for information, collected under a real-world context, on the differences in BOE in CC smokers that completely switch to the products that are the subject of these applications compared to those who dual use the products with CC. Additional clinical evaluation of the 53-62 compounds found at higher levels in the aerosol of the products that are the subject of these applications compared with cigarette smoke would also be helpful for supporting continued marketing of the products as appropriate for the protection of public health. Finally, long-term evaluation that assess changes in BOPH as well as clinical endpoints associated with complete and incomplete switching to the products that are the subject of these applications would also provide support for the continued marketing of the products as appropriate for protection of public health.

As TPL, I agree with the epidemiology review conclusions. I also agree that continued information regarding toxic exposures as the products are actually used, including both CC who switch completely and those who use multiple tobacco products, will be helpful information for supporting the continued marketing of these products as appropriate for the protection of public health. Additionally, continued information regarding long-term health effects, such as may be obtained with additional BOPH studies of longer duration, may also provide support for the continued marketing of the products as appropriate for protection of public health.

III. Product Labeling, Consumer Comprehension, and Marketing Plan

A. Proposed PMTA Labeling

The following sample labeling materials were provided:

- Heatstick pack labeling for Regular, Smooth Menthol, and Fresh Menthol
- Heatstick carton labeling Regular, Smooth Menthol, and Fresh Menthol
- IQOS device package (black kit and white kit)
- IQOS printed film for Regular, Smooth Menthol, and Fresh Menthol

The proposed labeling has been evaluated by CTP Office of Compliance and Enforcement, Division of Promotion, Advertising, and Labeling (OCE DPAL) and they conclude there is no evidence to suggest the planned labeling (other than discussed below) is false or misleading.

B. Consumer Comprehension

The submission included a copy of the IQOS Tobacco Heating System User Guide and the IQOS Quick Start Guide. The User Guide provides comprehensive instructions for use including information for device storage, cleaning, charging, and disposal. The Quick Start Guide provides the basic information needed to use the IQOS system and a high-level explanation of the device indicator lights, buttons, and accessories.

Study PBA-06-US was designed to describe the ability of prospective consumers to correctly understand and comply with THS Instructions for Use. Adult smokers (N=258) reviewed the provided instructions and were asked to perform nine tasks and answer three comprehension questions related to the materials. No product was administered during this study.

Based on the range of the proportions of subjects who correctly demonstrated or comprehended the tasks and instructions, the applicant concluded that "a relatively large majority of subjects" were able to correctly demonstrate the following tasks:

- Task 1 (How to charge the THS 2.2 Holder and Pocket Charger Simultaneously)
- Task 2 (How to Insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder)
- Task 3 (How to Heat and Consume a THS 2.2 Tobacco Stick)
- Task 4 (How to Know When a THS 2.2 Tobacco Stick Has Been Consumed)

The applicant concludes that subjects "found the following tasks more complicated:"

- Task 5 (How to Remove a THS 2.2 Tobacco Stick from the THS 2.2 Holder)
- Task 6 (How to "Heat Clean" the THS 2.2 Holder)
- Task 7 (How to Clean the THS 2.2 Holder with the THS 2.2 Cleaning Tool)
- Task 8 (How to Remove a THS 2.2 Tobacco Stick Stuck from the THS 2.2 Holder Cap)
- Task 9 (How to Re-attach the THS 2.2 Holder Cap to the THS 2.2 Holder Body)

In addition, the applicant concluded that a majority of the subjects understood that the THS 2.2 Holder is to be used only with the Tobacco Sticks (85.3% "correct" or "acceptable") and that the Tobacco Sticks should not be lit with a lighter (94.6% "correct" or "acceptable"). However, more subjects had difficulty understanding that the THS 2.2 Holder needed to be fully charged before it could be heat cleaned (66.7% "correct" or "acceptable").

FDA statistical reviewers conducted an analysis based on the percentages of participants providing a "correct" or "acceptable" response to all steps for each task. The reviewers reported the following results:

- Task 1 (How to Charge the THS 2.2 Holder and Pocket Charger Simultaneously): 63%
- Task 2 (How to Insert a THS 2.2 Tobacco Stick into the THS 2.2 Holder): 52%
- Task 3 (How to Heat and Consume a THS 2.2 Tobacco Stick): 68%
- Task 4 (How to Know When a THS 2.2 Tobacco Stick Has Been Consumed): 81%
- Task 5 (How to Remove a THS 2.2 Tobacco Stick from the THS 2.2 Holder): 34%
- Task 6 (How to "Heat Clean" the THS 2.2 Holder): 29%
- Task 7 (How to Clean the THS 2.2 Holder with the THS 2.2 Cleaning Tool): 41%
- Task 8 (How to Remove a THS 2.2 Tobacco Stick Stuck from the THS 2.2 Holder Cap): 68%
- Task 9 (How to Re-attach the THS 2.2 Holder Cap to the THS 2.2 Holder Body): 73%

Statistical inference was not the basis for informing the conclusion-making process in this study, therefore the results are not generalizable to the U.S. population. Tasks were demonstrated in a structured, monitored setting, and may not be representative of performance in a real-life setting. Also, performances were scored based on a participant's first attempt at the use tasks. Consequently, results may not be indicative of performance after users become familiarized with the product through repeated attempts. Overall, the results demonstrate sufficient consumer understanding of the products and their use. Additionally, the applicant has stated their intent to (b) (4) (b) (4) . The additional support along with the instructions that are included with the IQOS device should resolve most consumer issues related to product use.

C. Marketing Plan

At the request of FDA, the applicant provided a summary of their plans for marketing of IQOS in the U.S., assuming marketing authorization is granted. The marketing plan encompassed the following main concepts:

(b) (4)

(b) (4)

C. Nicotine is Addictive Labeling

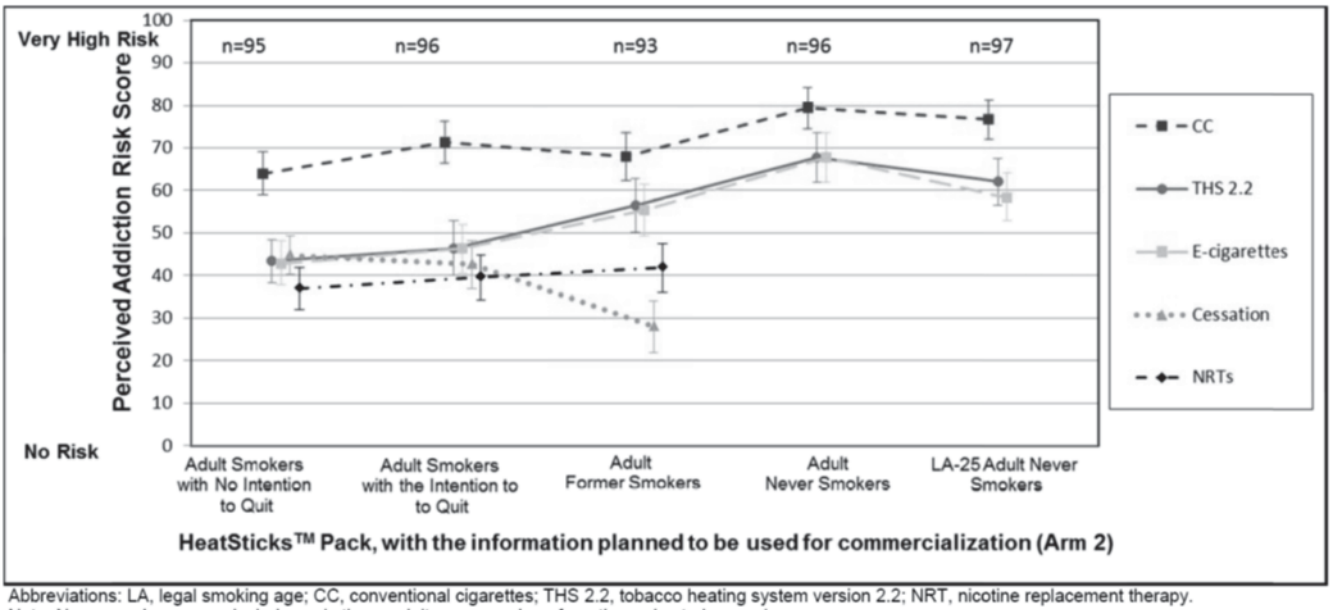
As cigarettes, if authorized without changes, IQOS Heatsticks would bear the rotating Surgeon General's warnings required under the Federal Cigarette Labeling and Advertising Act (FCLAA). These warnings do not currently include a warning related to nicotine and addiction. This raises concerns because studies suggest that people do not accurately perceive the risk of addiction associated with IQOS use. This, in turn, could have negative consequences to public health in terms of increased initiation among nonusers and decreased cessation among tobacco users.

As discussed in more detail in section II.D, II.E, and II.F above, the applicant conducted multiple studies to evaluate the nicotine delivery, addiction potential, and abuse liability of IQOS. These included four single use PK/PD studies, four reduced exposure 5-day and 90-day studies, and the U.S. actual use study, evaluating the use of IQOS in an "almost real world" environment. Systemic nicotine exposure was similar after single and multiple uses of IQOS (both regular and menthol Heatsticks) and CC. In addition, self-report questionnaires found that IQOS produced reinforcing effects close to those of CC. Overall, the data from these studies show that IQOS is addictive and has nicotine delivery, addiction potential, and abuse liability similar to combusted cigarettes.

However, study data show that consumers do not accurately perceive and tend to underestimate the addiction risk of IQOS. In the U.S. consumer perception study PBA-05-NOC, the applicant assessed the perceived addiction risk of using IQOS, combusted cigarettes, e-cigarettes, NRTs, and cessation among 1,829 current smokers, former smokers, and never smokers (including, importantly, 18-25 year old never smokers) after exposure to various IQOS label, labeling, and advertising materials containing the Surgeon General's warnings, including what the applicant described as the Heatstick pack intended for commercialization.[88] Perceived addiction risk scores for each product type were transformed and reported on a 100 point scale, with 0 = No Risk, and 100 = Very High Risk. After viewing the IQOS LLA materials with the Surgeon General's warnings, study participants rated IQOS as 10-20 points *less addictive* than combusted cigarettes. This was true across all study arms for adult current smokers, former smokers, and never smokers, including young adult never smokers. See Figure 11, showing the results for study arm 2, the Heatstick pack intended for commercialization. As shown in the figure, there was only a small overlap in the 95% confidence intervals in the adult former smoker group and no overlap in the confidence intervals in any other group, indicating a statistically significant difference in the perception of addiction risk between IQOS and combusted

[88] For more details on the study design, see section II.F.1 above and the discussion in the Social Science review.

cigarettes. This difference persisted when the applicant, prompted by FDA, conducted analyses adjusting estimates of perceived risk for age, sex, race, education, and employment status (September 2017 amendment MR0000096). The lack of understanding of the addiction risks across different population groups is further evidence of the likelihood of consumer misperception if appropriate warning language is not included on the products.



Abbreviations: LA, legal smoking age; CC, conventional cigarettes; THS 2.2, tobacco heating system version 2.2; NRT, nicotine replacement therapy.
Note: Never smokers group includes only those adult never smokers from the main study sample.
Note: Error bars presented are 95% confidence intervals
Note: Lines connecting subject groups are done to illustrate the objects belonging together
Study ID: THS-PMTA-05-NOC-US; Status: Final; Program: t15.2.2.3.2_risk.sas; Produced: 25OCT16; Source: Table 15.2.2.3.2

Figure 11: Perceived Addiction Risk for Heatsticks Pack Arm 2
Source: Figure 11-8: THS PMTA-05-NOC Report v.1.0

These findings raise concerns because they indicate that consumers, including young adult never smokers, do not fully comprehend the addiction risk of IQOS based on the currently proposed labeling, which does not include any information about nicotine or addiction. Of further concern is that consumers, including young adult never smokers, who mistakenly believe IQOS to be less addictive, may start using it when they would not have otherwise initiated tobacco use.

To mitigate the potential for consumer misperception of the addiction risk of IQOS, I recommend the inclusion of the following warning on all IQOS Heatsticks labels and in all IQOS advertising: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." Smokers exposed to tobacco product warnings generally report greater knowledge of the risks associated with use of the products. Evidence indicates warnings that are larger and more comprehensive are more effective in communicating the health risks of smoking.[89]

I further note that pursuant to deeming rule, all ENDS that are made or derived from tobacco are generally required to bear the warning statement: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." As FDA previously explained, this warning is necessary given consumers' erroneous and

[89] Hammond D, Fong, G, McNeill A, Borland R, Cummings K; Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control Four Country Survey. Tobacco Control. 2006; 15(Suppl III): iii19-iii25.

unsubstantiated beliefs that tobacco products other than conventional cigarettes are either less addictive than cigarettes or not addictive at all. *See* 79 FR 23141 at 23166. Numerous studies demonstrate that consumers tend to perceive IQOS as similar to e-cigarettes in terms of risk, including addiction risk in particular (this trend was demonstrated in PBA-05-NOC, PBA-05-RRC, PBA-05-RRC2, and PBA-05-REC). The absence of the addiction risk warning on IQOS, when e-cigarettes generally must bear such a warning, could reinforce existing false beliefs about the addiction risk of IQOS as compared to conventional cigarettes.

In conclusion, the lack of a nicotine addiction warning on IQOS labels and advertising raises significant concerns because study data show that in the absence of such a warning, consumers, including young adult never smokers, hold erroneous beliefs about the addiction risk of IQOS, particularly the relative addiction risk of IQOS compared to combusted cigarettes. This, in turn, could have negative consequences for public health in terms of increased tobacco use initiation among nonusers and decreased cessation among users. Accordingly, in order to find the marketing of the products appropriate for the protection of the public health, I recommend the following changes to the product labels and advertising for IQOS:

> Inclusion of the warning: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on all IQOS Heatstick (and Heatstick-containing kit) package labels and in all advertisements.

I recommend that the warning be subject to the same format requirements as those currently required for the nicotine warning on covered ENDS products under the deeming rule. See 21 CFR 1143.3. This includes, among other requirements: (1) occupying at least 30% of each of the two principal display panels of every Heatstick (or Heatstick-containing kit) package, and (2) occupying at least 20% of the area of every print or other advertisement with a visual component (e.g., Internet web pages). I recommend these size requirements because, as explained in more details in the preamble to the deeming rule, users are more likely to notice, pay attention to, and recall warnings that are in a larger size and that appear on the front/major surfaces of packages. This in turn directly affects the likelihood that a consumer will understand and appreciate the risks being warned against. See 81 FR 28973, 28988-89. See also 79 FR 23141 at 23164-65.

D. Carbon Monoxide (CO) Warning

CO is a highly toxic gas produced by incomplete combustion of hydrocarbons. Common sources include motor vehicle exhaust gases and combustion appliances (e.g., heating units) in which partial combustion of oils, coal, wood, kerosene and other fuels generate CO. Patients with underlying cardiac conditions are at risk for death from arrhythmias and fatal heart attacks can occur; however, CO exposure can cause chest pain and increase the risk of cardiovascular injury independent of previous cardiac disease. Carboxyhemoglobin (COHb) is the most accurate method of assessing CO exposure in humans. Normal level for non-smokers is < 2% and for smokers is 5-13%.[90] COHb levels will vary depending on duration and extent of CO exposure, ventilation, and underlying medical conditions.

As cigarettes, IQOS Heatsticks product packages and advertisements would be required to bear the rotating SG Warnings, one of which states, "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide."

[90] Prockop, Leon D, Chichkova, Rossitza I; Carbon monoxide intoxication: an updated review**,** Journal of the neurological sciences. 2007, Vol.262(1-2), p.122-130.

The applicant has provided multiple lines of evidence that although the use of Heatsticks in the IQOS device does produce CO, the exposure to CO from IQOS use is comparable to environmental exposure to CO. The applicant uses CO as one of their product specifications as shown in the table below.

Table 11: CO Acceptance Criteria for Heatsticks

Heatstick	Acceptance Criteria	Batch Analysis Results
Marlboro Heatstick	(b) (4)	
Smooth Menthol Heatstick		
Fresh Menthol Heatstick		

Source: FDA created table based o

During inspection of the manufacturing facilities in Bologna, Italy, the results were found to meet specifications. In the mouse switching study, COHb levels for mice "switched" to IQOS, those that "quit," and sham controls were ~5%. (Statistical analysis was not provided.) In the 90-day inhalation study conducted in rats, those inhaling IQOS had COHb levels in the same range as sham control.

In the clinical studies assessing exposure, baseline COHb levels ranged from 4.65-6.66%. By Day 5 across all four studies, COHb in participants who switched to IQOS fell to 1.06-2.48%. For the smoking abstinence group, COHb was 0.99-2.5%. By Day 90 of the extended REX studies, COHb levels in the IQOS arm were 2.66-2.97% and in the abstinence arm levels were 2.84-3.04%.[91] After accounting for standard deviations, the abstinence arm groups and the IQOS groups were identical.

In the 6-month ad libitum use study, baseline exhaled CO in parts per million (ppm) for the CC group was 23.6 and the THS group was 21.9. After 6 months, the CC group CO was 25.3 ppm compared to 17.2 ppm for the THS group. (Note: Exhaled CO in nonsmokers is generally <6ppm.[92] The results of this study are consistent with a significant dual-use population (including in the THS arm) as described by the applicant. Despite the high number of dual-users and the highly variable use patterns, the exhaled CO level is decreased in the THS group.)

Based on the above evidence, although IQOS Heatsticks produce CO, the CO exposure is comparable to environmental CO exposure. Use of Marlboro, Smooth Menthol Heatsticks, and Fresh Menthol Heatsticks in the IQOS device does not pose any CO-related risks. Accordingly, the required CO warning is misleading with respect to IQOS products. This warning should not be required on IQOS packaging or advertising.

IV. Conclusions and Recommendations

In its applications for the IQOS THS with Marlboro Heatsticks, Smooth Menthol Heatsticks, and Fresh Menthol Heatsticks, the applicant provided detailed information for the manufacturing process for the Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks, the Holder and the Charger. The provided information includes adequate process controls and quality assurance procedures to help ensure the three Heatstick products are manufactured consistently to meet the applicant's specifications. To verify chemical and physical data, confirmatory testing was conducted at FDA's Southeast Tobacco Laboratory in October

[91] CO levels would be expected to be higher in a community environment than in a confined laboratory setting. The levels of CO were not statistically different between THS and SA arms and were well within the range for normal environmental CO.

[92] Sandberg, AnnSofi; Skold, CM, Grunewalk, J, Eklund, A, Wheelock, AM; Assessing recent smoking status by measuring exhaled carbon monoxide levels, PLoS One. 2011:6(12):e28864.

2017. Although there were some methodological differences between the applicant's testing and the FDA testing, the results were similar. FDA also conducted a review of peer-reviewed literature describing chemical analysis of heated tobacco products. The information in published literature generally supported the data in the applications.

Product stability can be a concern for tobacco products as bacterial communities and constituents in tobacco products change as a function of storage time. The applicant provided complete stability testing data for all three Heatsticks over a period of (b) (4) of product storage and concluded a shelf life of (b) (4) (b) (4) is acceptable at (b) (4)) and (b) (4) and a shelf life of (b) (4) is acceptable at (b) (4) for Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks. The applicant has observed (b) (4) , but the changes are not related to product safety, performance, or type of Heatstick. The applicant has described additional testing for high humidity stability studies with plans for further microbiological testing if needed. However, even without that additional testing, the applicant has addressed factors that could affect microbial stability and provided adequate quality control information.

The applicant submitted part-by-part and sub-assembly details for the assembly and manufacturing processes for the Holder and Charger. A detailed summary of the testing method for the heating blade was provided; (b) (4) . (b) (4) The Holder and Charger contain microcontrollers and firmware (b) (4) . (b) (4) .

The product is designed to use interchangeable batteries. The applicant provided the supplier manufacturing specifications, which are aligned with the product battery specifications for the Holder and the Charger. The applicant submitted battery samples for testing to Winchester Engineering and Analytical Center in September 2017. No individual data points were out of specification. FDA inspections of the applicant's research and manufacturing sites were performed. Minor deviations were found during inspection of (b) (4) located in (b) (4) . During the inspection, the CTP OS subject matter expert observed that (b) (4) .

The toxicological assessment included measurement of HPHCs in the Marlboro, Smooth Menthol, and Fresh Menthol Heatstick aerosols and comparison to 3R4F reference cigarettes as well as comparison to the mean in the smoke of 31 CC. In the PMI-58 study, the 54 HPHCs measured in all three Heatstick aerosols were reduced were reduced by 54.4-99.9% on a per stick basis when compared to 3R4F smoke. Machine-generated nicotine yields were reduced 35.9-39.4%, but clinical data indicates human CC smokers and Heatstick users absorb similar amounts of nicotine. For 18 of these compounds, the applicant determined that yields in Heatstick aerosols were reduced by 40-99.8% when compared to the mean of 31 CC commercially available in the U.S. Side stream aerosol from all three Heatsticks does emit detectable levels of some HPHCs, but levels are significantly lower than emissions from CC. There are potentially concerning chemicals in the Heatstick aerosols. The applicant conducted a non-targeted differential screening assay, which found the three Heatstick aerosols contain higher levels of some chemicals than 3R4F smoke – four of these are possible or probable carcinogens and 15 others are possibly genotoxic. However, based on current

knowledge, the toxic exposures from all three Heatstick aerosols are reduced compared to CC, and many of the known HPHCs found in CC smoke are very low or undetectable in Heatstick aerosols.

The applicant conducted in vitro testing, including Ames assay, mouse lymphoma assay (MLA), and nuclear red uptake assay (NRU). Limitations of these assays, caused in part by methodological issues as noted by the reviewer, affect the conclusions that can be drawn from these in vitro tests. Notwithstanding such limitations, overall the in vitro studies show decreased cytotoxicity and mutagenicity from exposure to TPM and GVP of Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks as compared to TPM and GVP of 3R4F cigarettes, which are consistent with expected results from aerosol containing the amount of HPHCs identified in the studies discussed above.

In vivo studies included two 90-day nose-only inhalation studies in rats, an 18-month carcinogenicity study in mice, a nicotine pharmacokinetic study in rats, systems toxicology studies with acute and repeated exposures to human organotypic tissues, and a mouse "switching" study. The 90-day inhalation studies showed changes from Heatstick aerosol exposures were not observed or much less severe than changes due to 3R4F. The interim report of an 18-month carcinogenicity study shows the incidence of neoplastic lesions to be higher in groups exposed to either Heatstick aerosol or CC when compared to sham control; however, in the final study report the applicant concludes this long-term study demonstrated no increase in lung cancer risk due to THS 2.2 aerosol exposure compared to sham group. Per the applicant, toxicity is limited to adaptive responses in the upper respiratory tract. As an inhaled tobacco product, IQOS may elicit an inflammatory response in the respiratory tract but this study provides no definitive information about carcinogenicity risk for humans.

The experimental approach taken in the organotypic studies included methods that are considered exploratory and have not been independently validated; hence, the usefulness of the data is limited. The 8-month switching/cessation study suggested that switching to Heatsticks after a short period of cigarette smoke exposure led to histopathological changes similar to smoking cessation; however, there were some design limitations that reduce reliability of these data.

After consideration of all the toxicological data presented, the demonstrated reductions in measured HPHC exposures and reduced histopathological changes indicate a possible relative benefit compared to CC for smokers who switch completely to IQOS. The toxicological profiles of the Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks are identical except for the difference in the quantity of menthol added to the mentholated products. Although Marlboro, Smooth Menthol, and Fresh Menthol Heatstick aerosols contain chemicals which are different from those found in CC, and some of which may be toxic, the currently available information (discussed below) indicates the reduced exposures to the large number of HPHCs found in CC will likely result in reduced health risks for CC smokers who switch completely to IQOS. Reduced HPHC exposure also is beneficial for those who would be secondarily exposed to the aerosol as compared to environmental tobacco smoke.

To support the clinical evaluation of IQOS, the applicant provided four PK/PD studies, four reduced exposure studies, a summary of adverse events with an updated summary report submitted May 2018, review of published literature and post-marketing reports, and an actual use study which evaluated misuse of the products as well as overall use patterns in a "real world" environment.

The four single-use, randomized, 2-period, 4-sequence cross-over PK/PD studies assessed and compared the rate and extent of nicotine uptake in participants using THS 2.2 compared to smoking own-brand CC and nicotine replacement therapy products. Systemic nicotine exposure was similar after single and multiple

uses of IQOS and CC (both Marlboro and mentholated Heatsticks). THS 2.2 provides sufficient nicotine to produce user satisfaction. Self-report questionnaires found that THS 2.2 produced reinforcing effects close to those of CC. Results from the PK studies and the population model submitted account for the variability in nicotine PK across multiple factors including weight, CYP2A6 activity, sex, and race. Based on the study results, nicotine PK in smokers who switch to IQOS is similar to those who continued to smoke CC. The data indicate THS 2.2 has addictive potential and abuse liability similar to CC which means that while IQOS can provide an adequate nicotine source for dependent populations, there is a risk of developing addiction for non-tobacco users who begin using IQOS.

Four randomized, controlled, open-label, 3-arm parallel group studies (reduced exposure or REX studies) were conducted with the primary aim to investigate systemic exposure to BOE in smokers who switched to THS 2.2, continued to smoke CC, or abstained from smoking (SA) over a 5-day confinement period. Two of these studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US) had an 85-day ambulatory phase extension after the 5-day confinement period for a total study duration of 90 days. The BOE selected correspond with 14 HPHCs and two additional moieties found in cigarette smoke or filler. At the end of the 5-day confinement period, systemic exposure to 15 of the 16 selected chemicals described above decreased by 47-96%. (Nicotine - also an HPHC - was also measured and levels were not decreased.) The reductions of systemic exposure to 15 measured chemicals seen after switching from CC to THS 2.2 in all REX studies were statistically significant. The reductions were statistically significant over 5 days and the decreases persisted through the 90-day period. These BOE reductions in those that completely switched to IQOS, indicate reduced HPHC exposures, and, although not demonstrated by the studies in the application, these reductions in exposure are likely to result in reduced risk of tobacco-related disease.

All REX studies included measurements of several BOPH (referred to by the applicant as clinical risk endpoints or CREs) as secondary or exploratory study endpoints to determine if THS 2.2 use resulted in biological changes that may indicate a change in long-term disease risk. The applicant selected these biomarkers based on changes shown in previous smoking cessation studies, as well as peer-reviewed literature on the association with health risks. After independent review of the literature, FDA concludes that while each of the six markers have data suggesting a relationship with one or more tobacco-related diseases, none were strong predictors of future health risks. Many of these endpoints are more appropriate for longer-term studies, as changes in these measures are expected to take months to years. Some BOPH had desirable change trends in THS 2.2 users compared to the CC arm, but only white blood cell (WBC) count and sICAM-1 demonstrated differences in the two 90-day studies for THS 2.2, CC, and SA arms. The BOPH measures were not significantly improved over the relatively short duration of these studies; however, the trends may be informative for understanding potential effects on biological processes such as inflammation and oxidative stress.

The applicant provided a cumulative safety summary with information from the eight completed clinical studies, two on-going clinical studies, premarket safety surveillance covering six market research studies, and one perception/behavior study, as well as post-market surveillance studies outside the U.S. Although the applicant determined that most of the reported AEs were unrelated to product use, THS 2.2 exposure cannot be ruled out as contributing to or exacerbating those AEs typically associated with tobacco exposure (e.g., cough, headache, syncope). Bioresearch Monitoring inspections of two clinical investigators were conducted and no major issues or clinically significant deviations were found that would compromise data validity and integrity.

Post-marketing AE reports about IQOS have been sparse, despite increasingly widespread international marketing since its commercial introduction in Japan and Italy in 2014. A Safety Update Report published in

April 2016 reported two serious AEs (nervous system disorders/syncope). An updated Safety Report was submitted in May 2018 for the period covering 1/1/2017 thru 12/31/2017. The report identified previously unrecognized short-term health risks associated with THS including hypersensitivity reactions, an accidental child exposure, and a reported weather-related (heat and humidity) "burning sensation." The applicant reports that (b) (4)
(b) (4) These improvements/modifications are expected to decrease the occurrence rate of AEs and are therefore consistent with the conclusion that short-term risks of IQOS use are no greater than those associated with CC.

A review of published clinical literature provided by the applicant found one case report of acute eosinophilic pneumonia in a young adult Japanese male after increasing his consumption of Heatsticks. This disease has a known association with tobacco products and is not unique to THS 2.2. FDA conducted an independent clinical literature review and found no additional clinical reports. No apparent signals of adverse experience or other concerns related to product design have been identified related to IQOS in the countries where it is currently marketed. The data available in the clinical studies and other submitted information do not identify specific health-related issues for IQOS use beyond the concerns of CC use.

The Actual Use study assessed self-reported misuse of THS 2.2. Of 985 participants, 47 (4.8%) reported using Heatsticks without the IQOS device; the majority (97.9%) lit the Heatstick like a CC, and one participant chewed the Heatstick on one occasion. The applicant evaluated the potential for consumers to attempt to re-use Heatsticks. When re-use is attempted, the Heatsticks deliver small amounts of aerosol with 17% of nicotine and 12% of TPM as a new Heatstick. The applicant did not provide additional data on consumer misuse of the Holder by attempting to use a combusted product (e.g., cigar, CC); however, heating a tobacco product will only generate an aerosol if there is enough of an "aerosol forming agent," such as glycerin. In addition, the tobacco in any conventional product inserted into the IQOS Holder would be heated only to a maximum of 350 °C - the maximum temperature of the heating blade. This temperature is much lower than the combustion threshold of tobacco (>400 °C). Furthermore, only products with a circumference of 22.9 mm or less would fit inside an IQOS Holder, which excludes most conventional US cigarettes.

On June 11, 2018, FDA received amendment MR0000117 to the MRTPAs. This amendment included the final study report for a randomized, controlled, open-label, two-arm, parallel group, multi-center clinical study of six months of *ad libitum* use of the non-menthol THS 2.2 compared to continued CC users in an ambulatory setting in the U.S. The primary study objective was to demonstrate favorable changes after six months across eight co-primary clinical risk endpoints (referred to by FDA as BOPH) for those switching from CC to THS as compared to continued CC use. Secondary objectives included self-reported product use, nicotine exposure levels, and evaluation of exposure reduction to selected HPHCs by measuring BOE in the THS group and the dual-use group.

Five of the eight BOPH endpoints showed a statistically significant change in smokers who switched (defined as $\geq$ 70% THS use) from CC smoking to THS use. All BOPH shifted in the same direction as when smokers quit, as described in literature. For the BOE, users who switched to THS (i.e., $\geq$70% THS use) had reduced levels for most measures. Users who met the applicants' criteria for dual use (1%-70% THS use) also had reduced BOE for most measures but the changes were smaller and not statistically significant. None of the BOE measures increased with THS use – even in those who were "dual-users" in the study.

There are limitations to the applicant's statistical approach that affect the reliability of the statistical conclusions of the study. However, the study does provide evidence of reduced exposures associated with switching completely from CC to THS. Additionally, there was a trend for BOE reduction in subjects who

dual-used CC and THS. The rate of self-reported dual use during this longer study was lower (~34%) than the considerably higher dual use rates in previous studies (~58% in the actual use study). The short-term and long-term effects of dual use remain unclear, but these data provide minimal evidence that short-term dual use of IQOS and cigarettes does not appear to increase exposures to the selected HPHCs.

Overall, the clinical studies show exclusive use of IQOS has potential for reduced adverse effects on individual health compared to CC smoking. Regular, Smooth Menthol, and Fresh Menthol Heatsticks provide nicotine at levels similar to CC which relieves nicotine cravings and withdrawal symptoms. The short (5-day) studies demonstrate improvement in BOE for complete switchers, which indicates reduced HPHC exposures. These trends in improvement persisted in the 90-day studies even though some participants had reduced compliance and were probably using other tobacco products in addition to IQOS. Although not demonstrated in the studies in the application, the reduced exposure to HPHCs is likely associated with reduced tobacco-related disease risk. There were some small (non-significant) improvements in BOPH that were in a positive direction. Although dual use was common in the U.S. studies, the clinical study submitted June 2018 showed less dual use over time (six months) and a trend (although not statistically significant) for improved measures of exposure to HPHCs. Product misuse is uncommon, and the product design makes misuse unsatisfying. The clinical studies and the literature searches did not identify specific short-term health-related issues uniquely associated with use of these products. The clinical studies did not demonstrate any difference in PK, PD, or adverse effects between the Marlboro, Smooth Menthol, and Fresh Menthol Heatsticks. The currently available evidence indicates CC smokers who switch completely to IQOS will have reduced toxic exposures and, although not demonstrated by the studies in the applications, consequently, are likely to have less risk of tobacco-related diseases. CC smokers who use IQOS while continuing to smoke (dual use) do not appear to experience increased HPHC exposures and the limited available information indicate they may also have reduced HPHC exposures.

The likelihood of IQOS use by current CC smokers was assessed in the perception study, the actual use study, and the WOT. The perception study, conducted in the U.S., indicated ~2/3 of current smokers expressed some interest in trying IQOS. The interest level increased to ~80-90% if IQOS was offered by a friend. Smokers expressed “intent to use IQOS regularly if they tried and liked it” and rates of ~55-70%. There was no significant difference in any of these scores for smokers intending to quit vs. those not intending to quit. Results from the actual use study, conducted in the U.S., and the WOT, conducted in five other countries where IQOS is currently marketed, were variable. Although the actual use and WOT studies are not generalizable to U.S. cigarette smokers, all study participants were CC smokers and the information gained from these studies provides useful trends for consideration in review of these applications for marketing in the U.S. In the U.S., 34% of cigarette smokers in the study initiated IQOS use, defined as using at least 100 Heatsticks. In the WOT, the prevalence of initiating IQOS use ranged from 36% in Italy to 76% in South Korea. Participants in both the actual use study and WOT had to express interest in using IQOS prior to study enrollment; however, the findings suggest that some smokers will find IQOS appealing and acceptable enough to initiate product use. In the U.S. study, daily cigarette consumption decreased between baseline and the observational period for all IQOS use groups, with the largest decrease occurring in participants who were predominant Heatstick users at Week 6 (average decrease of 7.6 CPD).

Dual use of IQOS and CC was common in all countries in the pre- and post-market studies. Among current smokers in the actual use study, a majority (57.6%) used the IQOS in addition to conventional cigarettes when dual use is defined as between 5% to 95% Heatsticks. The patterns of use overall are similar when considering the type of Heatstick ordered by the participant (Menthol, Regular, both); switching, dual use, and exclusive cigarette use did not differ by the type of Heatstick respondents requested at baseline. When using the applicant’s definition for switching (i.e., ≥95% Heatstick use), less than 8% of participants in the

actual use study met the criteria for switching from cigarettes to IQOS. Participants who became exclusive IQOS users, however, seemed less likely to return to using mostly CCs, indicated by the steady prevalence of exclusive IQOS use throughout the 6-week observational period. Although it is possible that with additional follow-up time more participants would become exclusive IQOS users, data from the actual use and the WOT studies show that most smokers become dual users during the initial period of IQOS use. This is a concern since there is limited evidence about the effects that dual use of IQOS and CC (compared to complete switching) will have on long-term reduction of HPHC exposures and the health risks for tobacco-related diseases. While results from the PBA-07 study showed that IQOS use was associated with reduction in cigarette consumption, the health benefits of reducing cigarette consumption instead of quitting completely are unclear. However, based on the currently available evidence, dual use is unlikely to pose increased health risks compared to continued exclusive CC use.

The applicant provided data from two Japanese on-line post-marketing surveys. In a 2016 Japanese online cross-sectional survey of 2000 adult smokers and nonsmokers, 3.7% of respondents reported using "heat-not-burn" (heated) tobacco products. The prevalence of heated tobacco product use was higher among those aged 20-39 (~4 %) than those aged $\geq$ 40 (~1 - 1.5%) and most (96.3%) were using "Marlboro Heatsticks with IQOS device." Among respondents currently using heated tobacco products, 84.9% also used CC, most of them daily. In the second Japanese marketing survey, data on self-reported use of IQOS and cigarettes were also collected from 14,999 adult IQOS purchasers who registered their device in an online market research database. (Since purchasing and registering IQOS were criteria of inclusion, this may not be a representative sample of all users.) The proportion of IQOS purchasers who were "exclusively" using IQOS (≥95%) increased from 52% in January 2016 to 65% in July 2016.

The U.S. perception study (PBS-05-NOC) assessed perceptions and intention to use IQOS among a sub-population of former smokers and never smokers, including a subgroup of young adult (aged 18-25 years) never smokers. In this study the applicant developed label/labeling/advertising (LLA) materials, including an IQOS brochure, Heatsticks pack, and direct mail communication. The LLA materials provided information intended by the applicant to distinguish IQOS from e-cigarettes, including statements about "real tobacco" and the similarity in appearance of IQOS Heatsticks and CC. Never smokers in this study, including young adults of legal age to 25 years, were only exposed to the Regular Heatsticks pack. This is a study limitation since menthol cigarette smokers comprise one-third of the U.S. market, and the study did not assess the response to menthol LLA materials in never smokers. Among never smokers and young adult never smokers, < 1% who viewed the LLA materials indicated they would *Definitely* or *Very Likely* use IQOS. The results for former smokers were slightly higher; of those who viewed LLA materials with no additional IQOS information, 5-6% indicated they would *Definitely* or *Very Likely* use IQOS though the positive intent to try IQOS was higher if 'offered by a friend.' For comparison, the applicant also asked former smokers about their intention to use e-cigarettes regularly and asked never smokers about their intention to try e-cigarettes. Former smokers' intention to use and never smokers' intention to try IQOS appeared to be similar to or somewhat lower than their intention to use or try e-cigarettes, although the applicant provided no statistical analysis of these differences. Hypothetical scenario studies with no actual consequences associated with the decisions are difficult to interpret. While these types of studies provide an indication of intent to try or use the product, they cannot be considered absolute signals of behavior when/if IQOS is a marketed product.

As noted above, the applicant provided results from internet market surveys conducted in Japan. During the first one to two years after IQOS went on the Japanese market in 2014, use by adult former and never smokers was low (1.5% among former smokers and 1.2% among never smokers). Among survey responders in 2017, there were 3.6% current IQOS users and 2.0% of those aged 15-19 years reported current use of

IQOS in 2017. Of the 2017 survey responders 1.3% were never smokers, 2.1% were former smokers, 18.8% were current smokers with intention to quit, and 10.3% were current smokers with no intention to quit. These results may not equate to the anticipated U.S. experience as e-cigarettes containing nicotine require a prescription in Japan and use patterns may differ in the U.S.

In 2017, a face-to-face survey was conducted in Italy among 3000+ participants aged ≥15 years selected from the general Italian population. Based on cigarette smoking status, 1.0% of never smokers, 0.8% of former smokers, and 3.1% of current smokers reported having ever tried IQOS. Among participants who reported that they had never tried IQOS but were intending to try it, 1.7% were never smokers, 0.5% were former smokers, and 5.0% were current smokers. In the Italian study, 0.9% of those aged 15-24 years reported having ever tried IQOS.

These Japanese and Italian studies suggest that the prevalence of IQOS use is lower in never and former smokers compared to current smokers and that fewer youth than adults currently use IQOS in Japan or Italy. These two published survey studies are the only data currently available on the prevalence of IQOS use in youth. The U.S. perception study suggests a low prevalence of intention to use IQOS among never and former smokers. In the U.S., most cigarette smokers begin trial and progression to regular use before age 18. Overall, the available information suggests the prevalence of IQOS use is lower in never smokers compared to current smokers and that fewer youth than adults currently use IQOS in Japan and Italy. Given that IQOS is still a relatively new product, the extent to which youth will initiate and use IQOS is unknown though the trend from other countries indicates that this is uncommon. The current evidence indicates IQOS uptake by youth and nonsmokers will be low. Furthermore, the limited flavor choices may reduce IQOS' appeal to youth. The social science reviewers have concerns that data regarding IQOS use in youth are limited; however, it could be difficult and impracticable to obtain data that would satisfy the reviewers' concerns in a pre-marketing environment.

Both the U.S. actual use and ex-U.S. WOT studies evaluated the likelihood of current cigarette smokers switching to IQOS. During the six-week observational period of the actual use study, 33.8% of current smokers initiated use of Heatsticks (defined as consuming ≥100 Heatsticks). Among those who started using Heatsticks, 16.3% were exclusively using Heatsticks (≥95% Heatstick use) during Week 6. In the WOT, exclusive Heatstick use among those who had used at least 100 Heatsticks ranged from 7.8% in Switzerland to 21.5% in Japan. Exclusive and predominant IQOS use was most common in Asia. More IQOS users may quit smoking over time, but data from the actual use and WOT studies suggest that most smokers become dual users or at least go through a "dual use" phase before quitting. Although less than 10% of cigarette smokers in the U.S. actual use study switched to exclusive IQOS use during the study, the proportion of exclusive IQOS users remained steady during the 6-week observational period. This suggests that individuals who initiate IQOS and use Heatsticks for at least 95% of their tobacco intake are able to maintain exclusive IQOS use over time and potentially replace their use of CC with Heatsticks long-term. The toxicological and clinical studies did not demonstrate an increase in HPHCs for users consuming IQOS and CC and, although not statistically significant, some HPHC exposures appear to decrease.

The applicant presented results from a Population Health Impact Model to assess the possible effects of the proposed new products on population health in the U.S. This is a computational and simulation model that tracks tobacco prevalence and deaths from four specific smoking-related diseases: lung cancer (LC), ischemic heart disease (IHD), stroke, and COPD on a hypothetical population exposed to two tobacco products - CC and THS 2.2. The applicant concludes that "introducing THS into the US population appears to lead to a sizeable public health benefit in terms of reduced cigarette smoking and tobacco-related mortality." FDA reviewers found no concerns with the statistical and computational aspects. However, there are limitations

to the modeling assumptions, e.g., the model only considers two products (cigarettes and IQOS), the population size does not change over time, there is no justification for the assumption that nonsmokers will not use IQOS, and the 20-year projection is relatively short for evaluating long-term health effects. Although the model is statistically valid, the overall analysis of the population model does not provide evidence to support the application.

The applicant provided sample labeling materials for the Heatstick packs, cartons, and the IQOS device package and printed film as well as the IQOS Tobacco Heating System User Guide and the IQOS Quick Start Guide. Apart from the warning information (discussed in more detail in section F.1), none of these materials raised concerns. The applicant conducted a study to evaluate the ability of prospective consumers to correctly understand and comply with THS Instructions for Use. Generally, most study participants were able to follow the instructions though there were some challenges with the cleaning instructions. The applicant notes these performances were scored based on participants' first attempt at the use tasks; thus, results may not be indicative of performance after users are familiarized with the product through repeated attempts. The applicant has stated (b) (4) The additional support along with the instructions that are included with the IQOS device should resolve most consumer issues related to product use. Overall, the results demonstrate sufficient consumer understanding of the products and their use.

At request of FDA, the applicant provided a summary of their marketing plan for the PMTAs in the U.S. The applicant plans to (b) (4) The applicant states (b) (4) . The applicant states they (b) (4) .

A. Recommendation for Marketing

As discussed in Sections III C, III D, and IV F of this review, I recommend the PMTAs be authorized subject to the following changes to the proposed product labeling and advertising for IQOS:

- Inclusion of the warning: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on the package labels of all Heatsticks packs and of all kits containing Heatsticks packs as well as in all advertisements for such products and kits. Data shows that consumers do not accurately perceive the addiction risks of IQOS. Permitting IQOS to be marketed without this warning would not be appropriate for protection of public health.
- Removal of the warning: "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide." from the required warnings to be displayed on the product package labels and advertisements under FCLAA. Based on a fair evaluation of all material facts, the warning is misleading with respect to these products which, although categorized as cigarettes, do not produce carbon monoxide above environmental levels and do not increase CO-related health risks.

None of the grounds specified in Section 910(c)(2) of the FD&C Act apply. Specifically, I find the following:

1. Permitting the marketing of the products is appropriate for the protection of the public health, as described in Section 910(c)(4) of the FD&C Act (subject to the labeling and advertising changes described above);

2. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in 906(e);[93]
3. Based on a fair evaluation of all material facts, the labeling (when subject to the changes described above) is not false or misleading in any particular; and
4. The products do not fail to conform to a tobacco product standard in effect under Section 907 of the FD&C Act.

I recommend FDA grant marketing authorization for the products described in the STNs, subject to the changes to the products' package labels and advertisements, as described above:

1. PM0000424: Marlboro Heatsticks
2. PM0000425: Marlboro Smooth Menthol Heatsticks
3. PM0000426: Marlboro Fresh Menthol Heatsticks
4. PM0000479: IQOS Holder and Charger

B. Postmarketing Recommendations

The applicant submitted information on the stability monitoring protocol that it intends to use post-approval of the new products. The applicant proposes to test the Heatsticks at (b) (4) (b) (4) (b) (4)) over a period of (b) (4) of product shelf life (b) (4) (b) (4) The applicant states that this storage condition was selected because of its much higher geographical relevance for the U.S. market and because the product is reasonably expected to be exposed to this condition. CTP recommends that the applicant adopt this post-approval stability protocol for Heatsticks.

C. Postmarketing Recordkeeping, Retention, Reporting and Marketing Requirements

The following language will be included in the marketing authorization:

The Food and Drug Administration (FDA) completed the review of your Premarket Tobacco Product Applications (PMTAs) submitted under section 910(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), specified in Appendix A.

Based on our review of your PMTAs, we find that the marketing of the new tobacco products specified in Appendix A is appropriate for the protection of public health, and that you have met the other requirements of section 910(c) of the FD&C Act. This marketing order is subject to marketing requirements under section 910(c)(1)(B) of the FD&C Act and record retention and reporting requirements under section 910(f) of the FD&C Act, as outlined in Appendix B. Additionally, this order is conditioned upon the products conforming with any applicable current or future tobacco product standards, unless specifically exempted under this order or the product standard(s). Under the provisions of section 910, you may introduce or deliver for introduction into interstate commerce the new tobacco products, in accordance with the order requirements outlined in Appendix B.

The requirements in this order are intended to help ensure that the marketing of your products will continue to be appropriate for the protection of the public health, taking into account initiation among non-users, particularly youth. However, compliance with these requirements alone is not a guarantee that the marketing of the products will remain appropriate for the protection of the public health, particularly if, despite these measures, there is a significant uptake in youth initiation, for example. FDA will continue to

[93] FDA has not yet promulgated any regulations under Section 906(e) of the FD&C Act.

monitor the marketing of your products.

This order does not constitute a finding that any of the products outside the scope of this authorization are in compliance with the FD&C Act and its implementing regulations. FDA has not evaluated other components or parts, or accessories that you may choose to market with the iQOS system, such as A/C power adapters, USB cables, charging docks, cleaners, disposal units, and pouches. To the extent that any premarket authorization requirements of section 910 of the FD&C Act apply, FDA does not intend to enforce them with respect to such products. However, it is your responsibility to ensure that these products comply with all other applicable laws and regulations. For example, if you choose to include the brand name "IQOS" on items other than the products authorized in these orders, you need to evaluate whether that would comply with 21 CFR 1140.34(a). In addition, we recommend you evaluate whether any of the branded accessories you plan to market would constitute advertising that requires the applicable warnings.

We note that, in your September 5, 2018 and March 25, 2019 amendments to your PMTAs, you include representations about your marketing plan for your products in the United States and indicate that you intend to focus marketing on adult cigarette smokers while limiting reach to unintended audiences. FDA encourages you to consider measures to limit youth-exposure to any of the products' labeling, advertising, marketing, and/or promotion appearing in print media publications. Limiting youth exposure and initiation and use of the products as you have indicated in your PMTAs (i.e., complete switching to IQOS by adult cigarette smokers) are important components of consideration for the marketing of these products to continue to be appropriate for protection of the public health.

Also, in accordance with 40 CFR 1506.6, we will make your environmental assessments publicly available.

This order authorizing the marketing of these new tobacco products does not mean FDA "approved" the new tobacco products specified in Appendix A; therefore, you may not make any express or implied statement or representation directed to consumers that conveys, or misleads or would mislead consumers into believing, among other things, that the new tobacco products specified in Appendix A are "approved" by FDA.[94] The products subject to this marketing order are subject to withdrawal or temporary suspension as described in section 910(d) of the FD&C Act.

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

1. Record Retention

Under section 910(f) of the FD&C Act, this order requires that you establish and maintain the records listed below. The records must be retained for a period of not less than four years from the date of distribution of the last batch of the new tobacco products listed in your marketing authorization. The records must be

[94] See Section 301(tt) of the FD&C Act.

legible, written in English, and available for inspection and copying by officers or employees duly designated by the Secretary upon request:

- The PMTA submitted prior to product order
- Periodic postmarket reports, as described below, and adverse experience reports, including all relevant documentation associated with the experience
- Records of all nonclinical or clinical studies, including:
  - Source data;
  - Study protocols (including statistical analysis plan);
  - Amendments showing the dates and reasons for any protocol revisions;
  - Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals or non-approvals;
  - Informed consent forms;
  - Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC;
  - Investigator financial disclosure statements;
  - Progress reports;
  - Monitoring reports;
  - Adverse experience reports;
  - Case report forms/subject diaries/medical records/laboratory reports;
  - Subject data line listings/observation records;
  - Test article accountability records;
  - Study results/protocol summaries/study reports; and
  - Certifications and amendments to certifications
- Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls), packaging, storage, and stability monitoring and testing (including protocol and results) of the products
- Records pertaining to the sale, distribution, or other disposition of the products, specifically:
  - A list of distributors and retailers of the products, including brick-and-mortar and digital[95];
  - Any available information (not to include personally identifiable information) about product purchases, such as purchasers' demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use);
  - Policies and procedures regarding verification of the age and identity of purchasers of the products; and
  - Policies and procedures regarding restrictions on youth access to the products
- Records pertaining to the products' labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
  - Specimens of all labeling, labels, inserts/onserts, instructions, and other accompanying information;
  - Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers;
  - Copies of any formative research studies conducted among any audiences in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;

[95] For the purposes of this order, here and throughout the document, "digital" includes internet/online and mobile.

- Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
- Copies of any contractual agreements regarding the creation and/or dissemination of the products' labeling, advertising, marketing, and/or promotional materials;
- Copies of all advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any:
  - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
  - Targeting of specific adult audiences by age-range(s), including young adult audiences, ages 18-24, and other demographic and/or psychographic characteristics that reflect your intended target audience;
  - Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
  - Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the products;
  - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
  - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated; and/or
  - Use of earned media and/or public-relations outreach to create labeling for, advertise, market, and/or promote the products
- Copies of all records pertaining to media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), and all post-launch delivery-verification reports submitted to you from an accredited source, by channel, by product, and by audience demographics; and
- Policies and procedures for real-time digital media monitoring to identify, correct, and prevent any delivery of advertising impressions to youth, ages 17 years and under, including documentation of such monitoring activities and implementation of corrective and preventive measures

- Health hazard analyses, if performed voluntarily or directed by FDA
- Records pertaining to any and all complaints associated with any of the products that you receive or of which you are aware

2. Serious and Unexpected Adverse Experiences Reporting

Under section 910(f) of the FD&C Act, this order requires that you report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and the tobacco product(s) within 15 calendar days after the report is received by you. These experiences may become known to you through any source including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT FOR STN(s) XXX.**

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

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

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

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as product labeling and postmarket reports;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

3. Manufacturing Deviations

Under section 910(f) of the FD&C Act, this order requires that you establish and maintain records and reports of all manufacturing deviations, investigations, and corrective and preventive actions including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution. For products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death you are required to report the deviation to FDA within 15 calendar days of identification.

4. Periodic Reporting

The information in the following postmarket periodic reports will help FDA determine whether continued marketing of your tobacco products is appropriate for the protection of public health and/or there are or may be other grounds for withdrawing or temporarily suspending the marketing authorization order.

Under section 910(f) of the FD&C Act, this order requires that you submit the following periodic reports to FDA **on a quarterly basis, for a period of two years**, beginning three months from the date of this order. For each three-month reporting period, these periodic reports must include:

- A cover letter that includes the following text in your subject line: **PERIODIC REPORT for PM0000424-PM0000426, PM0000479.** The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, reporting period.
- A summary of U.S. sales and distribution of the tobacco products, including total U.S. sales reported

in dollars, units, and volume, and broken down by U.S. census region, major retail markets, and channels where the products are sold (e.g., convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops, company-owned stores). This summary must also be broken down by product (e.g., specific HeatStick flavor).

- Data on product purchasers. Report any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results must be broken down by purchaser demographics (e.g., age, gender, race/ethnicity, geographic location) and must not include personally identifiable information.

Under section 910(f) of the FD&C Act, this order also requires that you also submit periodic reports to FDA **on a quarterly basis**, beginning three months from the date of this letter. For each three-month reporting period, these periodic reports must include:

- A cover letter that includes the following text in your subject line: **PERIODIC REPORT for PM0000424-PM0000426, PM0000479.** The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, reporting period.
- An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). This analysis must be verified against post-launch delivery-verification reports submitted to you from an accredited source.
- A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures.

Under section 910(f) of the FD&C Act, this order also requires that you submit the following periodic reports to FDA **on an annual basis**, beginning twelve months from the date of this order. For each twelve-month reporting period, these periodic reports must include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for PM0000424-PM0000426, PM0000479**. The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, reporting period.
- A summary of how the marketing of the tobacco products continues to be appropriate for the protection of public health, which includes:
    - A status report of ongoing studies and a summary of completed studies about the tobacco products conducted by you, or on your behalf.
    - A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.
    - A summary of reported adverse experiences for the tobacco products, which includes a listing of all adverse experiences, including the serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.
    - A summary of U.S. sales and distribution of the tobacco products, not previously submitted,

including total U.S. sales reported in dollars, units, and volume, and broken down by U.S. census region, major retail markets, and channels where the products are sold (e.g., convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops, company-owned stores). This summary must also be broken down by product (e.g., specific HeatStick flavor).

- Data on product purchasers not previously submitted. Report any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results must be broken down by purchaser demographics (e.g., age, gender, race/ethnicity, geographic location) and must not include personally identifiable information.
- A summary of the implementation and effectiveness of your policies and procedures regarding verification of the age and identity of purchasers of the products.
- A summary of the implementation and effectiveness of your policies and procedures regarding restrictions on youth access to the products.
- A description of each change made to the manufacturing process, facilities, or controls during the reporting period including:
  - A comparison of each change to what was described in the PMTAs;
  - The rationale for making each change; and
  - A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the tobacco products and the basis for concluding that each manufacturing change did not result in any modification to the products.
- A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution and indicate any deviation(s) that may affect the characteristics of the products.
- A summary of any stability monitoring and testing of the HeatSticks products, including monitoring and testing protocol (including batch/lot sampling) and results.
- All final printed labeling (including all labeling variations, such as those reflecting different required warnings) not previously submitted, including the date the labeling was first disseminated and the date when the labeling was discontinued, and a description of all changes to the labeling. The labeling must include all the panels and be presented in the actual size and color with legible text. The labeling must include labels, inserts/onserts, instructions, and any other accompanying information or materials for the products.
- All final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers not previously submitted, along with the original date such materials were first disseminated and the date they were discontinued, and a description of all changes to the materials. The materials must include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the text may be provided separately and referenced.
- A summary of all formative consumer research studies conducted – whether by you, on your behalf, or at your direction – among any audiences, in the formation of new labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions and behaviors toward using the products, and including the findings of these

studies and copies of the stimuli used in testing.

- A summary of all consumer evaluation research studies conducted – whether by you, on your behalf, or at your direction – among any audiences, to determine the effectiveness if labeling, advertising, marketing and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing.
- A summary of the creation and dissemination of the products' labeling, advertising, marketing, and/or promotional materials – whether conducted by you, on your behalf, or at your direction – including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities.
- A description of the implementation of all advertising and marketing plans, including strategic creative briefs and paid media plans – whether conducted by you, on your behalf, or at your direction – by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any:
  - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
  - Targeting of specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and/or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;
  - Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
  - Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the products;
  - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
  - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated; and/or
  - Use of earned media and/or public-relations outreach to create labeling for, advertise, market, and/or promote the products;

  including the original date such plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel and by product.
- An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under), not previously submitted. This analysis must be verified against post-launch delivery-verification reports submitted to you from an accredited source.
- A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures, not previously submitted.

Under sections 910(c)(1)(B) and 910(f) of the FD&C Act, this order also requires that you provide the following notifications to FDA. These notifications are not for pre-approval, but are required so that FDA can have timely access to your marketing plans and materials, and if needed, provide you advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and on the

finding that continued marketing of your products is appropriate for the protection of the public health. You may begin disseminating the materials 30 days after providing notification to FDA.

- Provide FDA notification of all labeling, advertising, marketing, and/or promotional materials for which you have not previously provided notification, **at least 30 days prior** to the initial publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials, and include in your notification:
  - Full-color copies of all such labeling, advertising, marketing, and/or promotional materials for the products. The materials must include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the text may be provided separately and referenced.
  - All advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any plans to:
    - Use competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
    - Target specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and/or psychographic characteristics that reflect your intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;
    - Restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
    - Use owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the products;
    - Use partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
    - Conduct any consumer engagements – whether by you, on your behalf, or at your direction – including events at which the products will be demonstrated; and/or
    - Use earned media and/or public-relations outreach to create labeling for, advertise, market, and/or promote the products.

5. Marketing Requirements

Under section 910(c)(1)(B) of the FD&C Act and in accordance with section 202(a) of the Family Smoking Prevention and Tobacco Control Act, this order requires:

- Inclusion of the warning statement: "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on the package labels of all HeatSticks packs and of all kits containing HeatSticks packs as well as in all advertisements for such products and kits.[96] Specifically, the warning statement must appear directly on the package and must be clearly visible underneath any

[96] This warning must appear on each package and each advertisement, in addition to the rotating Surgeon General warnings required under FCLAA (except the carbon monoxide warning, which is to be removed from the rotation of the Surgeon General warnings as described in this order). When FDA promulgates a final rule with respect to health warnings for cigarettes, FDA will reevaluate the conditions of marketing with respect to warnings for the products subject to this order.

cellophane or other clear wrapping as follows:
    - Be located in a conspicuous and prominent place on the two principal display panels of the package and the warning area must comprise at least 30 percent of each of the principal display panels;
    - Be printed in at least 12-point font size and the warning statement must occupy the greatest possible proportion of the warning area set aside for the required text;
    - Be printed in conspicuous and legible Helvetic bold or Arial bold type (or other sans serif fonts) and in black text on a white background or white text on a black background in a manner that contrasts by typography, layout, or color, with all other printed material on the package;
    - Be capitalized and punctuated as indicated in this order; and
    - Be centered in the warning area in which the text is required to be printed and positioned such that the text of the warning statement and the other information on the principal display panel have the same orientation.
- For print advertisements and other advertisements with a visual component (including, for example, advertisements on signs, shelf-talkers, websites, mobile applications, and e-mail), the warning statement must appear in the upper portion of the area of the advertisement within the trim area as follows:
    - Occupy at least 20 percent of the area of the advertisement;
    - Appear in at least 12-point font size and the warning statement must occupy the greatest possible proportion of the warning area set aside for the required text;
    - Appear in conspicuous and legible Helvetica bold or Arial bold type (or other similar sans serif fonts) and in black text on a white background or white text on a black background in a manner that contrasts by typography, layout, or color, with all other material on the advertisement;
    - Be capitalized and punctuated as indicated in this order;
    - Be centered in the warning area in which the text is required to appear and positioned such that the text of the warning statement and the other textual information in the advertisement have the same orientation; and
    - Be surrounded by a rectangular border that is the same color as the text of the warning statement and that is not less than 3 millimeters (mm) or more than 4 mm.
- Removal of the warning: "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide." from the required warnings to be displayed on the product package labels and advertisements under the Federal Cigarette, Labeling and Advertising Act (FCLAA).
- As a reminder, under section 4 of FCLAA (15 U.S.C. 1333), you must submit a warning plan to the United States Federal Trade Commission (FTC).

Under section 910(c)(1)(B) of the FD&C Act, this order requires you to:

- For any **digital sales** – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent the sale of the products to individuals who are under the federal minimum legal age to purchase tobacco products.
- For any of the products' labeling, advertising, marketing, and/or promotion appearing in your **owned digital properties** (e.g., your company-owned, consumer-directed, product-branded website(s) and/or mobile applications) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare consumer information against independent, competent, and reliable data sources, such as public records, at the first point of access to such properties, to restrict access to

such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in any **shared digital properties** (e.g., your product-branded social media accounts, pages and associated content; content promoting your products on your behalf disseminated through another entity's social media accounts) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of the available site-, platform- and content- (e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded account and all associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the products on your behalf through the influencer's account), at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.
- For any of the products' labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product(s) running on another company's website; paid advertising for the product(s) running in social media; paid distribution of influencer content) – whether conducted by you, on your behalf, or at your direction:
    - Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products. Such targeting must use only first- and/or second-party age-verified data, where:
        - "First-party" age-verified data is data owned by you (e.g., your customer registration data collected via site traffic to your company-owned website; data you use in direct marketing to your adult smoking customers) that you have age-verified through independent, competent, and reliable data sources; and
        - "Second-party" age-verified data is first-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data) to which you have access. Such data must be age-verified by the second party.
        - "First-party" and "second-party" data does not include data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles marketers may use to enhance audience targeting. Such data is not considered age-verified and can only be used in combination with first- and/or second-party age-verified data.
- Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) – whether conducted by you, on your behalf, or at your direction – to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to youth, ages 17 and under. Such monitoring also requires post-launch delivery verification reports be submitted to you from an accredited source.
- For any use of **partners, influencers, bloggers, and/or brand ambassadors** to create labeling for, advertise, market, and/or promote the products – whether conducted by you, on your behalf, or at your direction – disclose to consumers or viewers, via the use of statements such as "sponsored by [firm name]" in such labeling, advertising, marketing, and/or promotional materials, any

relationships between you and entities that create labeling for, advertise, market, and/or promote the products, on your behalf, or at your direction.

Appendix: The Public Health Rationale for Recommended Restrictions on New Tobacco Product Labeling, Advertising, Marketing, and Promotion

I. Background

Most tobacco use is established in adolescence and age of initiation plays a significant role in the progression from tobacco experimentation to regular use (HHS 2012). It is well established that industry practices, such as tobacco product labeling, advertising, marketing and promotion, substantially impact youth trial and uptake of tobacco product use. Part of FDA's premarket review under the PMTA pathway is aimed at determining if marketing a new tobacco product would increase or decrease the likelihood that those who do not currently use tobacco products, will start using them.

Firms seeking a marketing order for a new tobacco product not yet on the market may not have robust data on how U.S. consumers will perceive the specific product, including its risks, or the degree to which its labeling, advertising, marketing, and promotion may influence youth perception or appeal to youth. This memo describes FDA's authorities under the Family Smoking and Tobacco Control Act (Tobacco Control Act) to monitor and restrict tobacco product marketing and related activities in the context of premarket tobacco product application review and authorization. Given FDA's statutory mandate to protect young people from the dangers of tobacco use and ensure that the marketing of new tobacco products is appropriate for the protection of the public health, the agency can request and review labeling, advertising, marketing, and promotional materials and plans for new tobacco products that have received premarket authorization to ensure that there are no grounds for withdrawing authorization and restrict the marketing of such products as appropriate for the protection of public health. This will help FDA evaluate the potential impact of such materials on the likelihood of initiation and use of the new tobacco products by youth or others and provide the firm and/or the agency an opportunity to prevent or mitigate any related potential harms to the public health.

II. The Food, Drug, and Cosmetic Act, as Amended by the Tobacco Control Act: Congressional Findings and FDA Authorities Related to Tobacco Product Labeling, Advertising, Marketing, and Promotion

The Tobacco Control Act makes clear the harmful influence of tobacco product labeling, advertising, marketing and promotion on youth tobacco use, and the intent of Congress to give FDA the authority to restrict these activities. In the Tobacco Control Act, Congress finds that, "[t]obacco advertising and marketing contribute significantly to the use of nicotine-containing tobacco products by adolescents," and "[b]ecause past efforts to restrict advertising and marketing of tobacco products have failed adequately to curb tobacco use by adolescents, comprehensive restrictions on the sale, promotion, and distribution of such products are needed." TCA §2(5) and (6). Thus, Congress concludes, "[c]omprehensive advertising restrictions will have a positive effect on the smoking rates of young people," and "[r]estrictions on advertising are necessary to prevent unrestricted tobacco advertising from undermining legislation prohibiting access to young people and providing for education about tobacco use." TCA §2(25) and (26).

These findings are underscored by section 906(d) of the FD&C Act, which grants FDA the authority to "require restrictions on the sale and distribution of a tobacco product, including restrictions on the access to, and the advertising and promotion of, the tobacco product, if [...] such regulation would be appropriate for the protection of public health," and section 910(a)(2) of the FD&C Act, which grants FDA the authority

to require premarket review and authorization of a new tobacco product before such product may be legally marketed in the United States. Further, as part of premarket application review, FDA may require "information relevant to the subject matter of the application" to assist the agency in determining "whether the marketing of a tobacco product […] is appropriate for the protection of public health" (section 910(b)(1)(G) and 910(c)(4) of the FD&C Act). In an order authorizing the marketing of a new tobacco product, FDA may also restrict the sale and distribution of the tobacco product to the extent that the sale and distribution of a tobacco product may be restricted under section 906(d) of the FD&C Act. FD&C Act §910(c)(1)(B).

III. Effects of Youth-Exposure to Tobacco Product Labeling, Advertising, Marketing, and Promotion on Youth-Appeal, -Perception, and -Use of Tobacco Products

A. Influence of Tobacco Product Marketing on Youth Tobacco Use, in General

As noted in the FD&C Act, as amended by the Tobacco Control Act, a key consideration in determining whether the marketing of a tobacco product is appropriate for the protection of public health is whether the marketing of the product would increase or decrease the likelihood that those who do not use tobacco products, especially youth, will start using them. In addition to Congress' findings in the Tobacco Control Act, there is a large body of scientific evidence that documents the potential harm of tobacco product labeling, advertising, marketing and promotion on youth tobacco use.

In one of the first comprehensive reviews on the subject—the National Cancer Institute's (NCI) 19th monograph, *The Role of the Media in Promoting and Reducing Tobacco Use*—authors conclude that "the total weight of evidence—from multiple types of studies, conducted by investigators from different disciplines, and using data from many countries—demonstrates a causal relationship between tobacco advertising and promotion and increased tobacco use" (NCI 1998). As such, the direct role of tobacco product marketing and related activities in increasing tobacco use in the United States, especially among youth, and the high rates of youth-exposure to tobacco marketing due to its ubiquity, are two key rationales cited by NCI for restricting tobacco product marketing and related activities.

The 2012 Surgeon General's report, *Preventing Tobacco Use Among Youth and Young Adults,* synthesizes more than 30 years of research on the topic. This report outlines similar findings—tobacco product labeling, advertising, marketing, and promotion influence a wide range of established risk factors for youth tobacco use by shaping attitudes, beliefs, and risk perceptions, and promoting pro-tobacco social and cultural norms. The report states, "there is strong empirical evidence, along with the tobacco industry's own internal documents and trial testimony, as well as widely accepted principles of advertising and marketing that support the conclusion that tobacco manufacturers' advertising, marketing, and promotions recruit new users as youth and continue to reinforce use among young adults" (HHS 2012). This evidence is sufficient to conclude that "marketing efforts and promotion by tobacco companies show a consistent dose-response relationship in the initiation and progression of tobacco use among young people" (HHS 2012).

To illustrate these points, the report cites findings of studies that demonstrate "advertising and promotion by the tobacco industry are effective in raising awareness of smoking, increasing brand recognition, and creating favorable beliefs regarding tobacco use. There is strong and consistent evidence that marketing influences adolescent smoking behavior, including selection of brands, initiation of smoking, and overall consumption of cigarettes" (HHS 2012). Further, "research conducted by the tobacco industry consistently demonstrates that the brand imagery portrayed on packages is particularly influential during youth and young adulthood—the period in which smoking behavior and brand preferences develop," and "displays of packages in retail outlets, commonly referred to as 'powerwalls,' have high visibility among youth and help to establish brand imagery and social norms at an early age" (HHS 2012). "Young people who are more

familiar with tobacco advertising can identify specific advertisements, have a favorite tobacco advertisement, or possess cigarette promotional items are more likely to begin smoking than their peers who do not have these characteristics," and "adolescents who both owned cigarette promotional items and had a favorite cigarette advertisement" were more likely to progress from initiation of smoking to established smoking (HHS 2012).

Research has found that a key tactic of tobacco companies seeking to attract and recruit youth users is to use advertising with aspirational imagery and themes known to resonate with younger audiences, such as independence, popularity, rebelliousness, attractiveness, and being "cool" (HHS 2012). Even tobacco advertising that purportedly targets adult users can have a profound influence on adolescent tobacco use behaviors if it creates positive feelings in youth toward the product; pleasant feelings motivate actions that consumers anticipate will reproduce those feelings (Slovic & Peters 2006). As such, youth are more likely to mimic behavior portrayed as favorable in advertising, such as tobacco use. Furthermore, youth often misjudge the risks and benefits of advertised products based on how they feel about them (Slovic & Peters 2006). If youth feel positively toward a product, they are more likely to perceive it as having lower risks and higher benefits.

In addition, adolescents are "uniquely susceptible to social and environmental influences to use tobacco" given their developmental stage and are heavily influenced by peers, family members, prominent members of their community, celebrities, and other cultural icons and adult role models—especially those they perceive to be popular, attractive, and "cool" (HHS 2012). As such, images of tobacco use in various types of media are "a potentially powerful socializing force among adolescents, in part because they are communicated by people who are identified by youth as media stars," and "adolescents actively rely on external information as they seek to shape their own identities, often looking to media stars as models of what to wear and what to do" (HHS 2012). These marketing campaigns may be misleading in that they imply positive, pervasive and/or pro-tobacco social norms that are inaccurate or overstated. The misleading impression can be enhanced by failing to disclose a sponsor's relationship with a company or failing to reveal that the content was not organically generated independently of the sponsoring company. Because youth have a heightened sensitivity to normative influences, sponsored tobacco marketing content may encourage youth uptake of tobacco use (HHS 2012).

B. Influence of Tobacco Product Marketing on Youth Tobacco Use in the Context of Novel Tobacco Products

Much of the research spanning the past few decades has focused on the influence of tobacco product marketing on cigarette smoking in particular; however, companies that sell other types of tobacco products engage in the same labeling, advertising, marketing, and promotional practices used by cigarette companies. "[T]he traditional division of products, brand identities, and marketing between cigarette and smokeless tobacco companies has all but become nonexistent in recent years as major U.S. cigarette companies, including RJR and Altria, have acquired smokeless tobacco companies and have developed new smokeless tobacco products" (HHS 2012). Some of these products are even marketed with popular cigarette brand names (e.g., Camel Snus).

Beyond cigarette-specific marketing, research has found that youth exposed to in-store marketing of e-cigarettes, hookah, cigars, smokeless tobacco, and pipe tobacco were two to three times more likely to use those products as well as to initiate cigarette use (Cruz et al. 2018). Further, research exploring the influence of tobacco marketing on youth use of novel tobacco products, such as e-cigarettes, confirms that exposure and receptivity to tobacco advertising is significantly associated with tobacco initiation among adolescents. The 2016 Surgeon General's report, *E-cigarette Use Among Youth and Young Adults*, concluded "e-cigarette products are marketed in a wide variety of channels that have broad reach among youth and young adults,"

and themes in e-cigarette marketing are "parallel to the themes and techniques that have been found to be appealing to youth and young adults in conventional cigarette advertising and promotion" (HHS 2016).

The report also summarizes the results of several studies looking at the relationship between e-cigarette marketing and youth tobacco use. For example, an analysis of the 2011 National Youth Tobacco Survey (NYTS) found that "adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of marketing channels to which they were exposed and ever use" (HHS 2016; Agaku & Ayo-Yusuf 2014). Two analyses of 2014 NYTS data assessing exposure to e-cigarette advertising in different channels (i.e., internet, print, television and movies, retail stores) found that "exposure to each type of e-cigarette marketing was significantly associated with increased likelihood of ever having used and current use of e-cigarettes among middle and high school students. Exposure was also associated with susceptibility to use e-cigarettes among current nonusers. In multivariate models, as the number of channels of e-cigarette marketing exposure increased, the likelihood of use and susceptibility also increased" (HHS 2016; CDC 2016; Mantey et al. 2016). These findings are particularly relevant in the context of more recent NYTS data showing a substantial increase in youth use of e-cigarettes from 2017 to 2018 (Gentzke et al. 2019). This uptick in youth e-cigarette use also contributed significantly to the first increase in overall youth tobacco use in recent years (Gentzke et al. 2019).

Recent studies have also assessed the influence of e-cigarette marketing on youth use of conventional cigarettes. For example, an analysis of data collected between 2013-2015 via the Population Assessment of Tobacco and Health study found youth receptivity was highest for e-cigarette advertising (compared to conventional cigarette, cigar, and smokeless tobacco product advertising), and receptivity to e-cigarette advertising was also associated with initiation of conventional cigarette smoking (Pierce et al. 2018). Another study had similar findings concluding that exposure to any e-cigarette advertising may play a role in teens' decision to initiate e-cigarette and conventional cigarette use (Padon, Lochbuehler, et al. 2017). These findings further underscore the powerful influence of tobacco product labeling, advertising, marketing, and promotion within and between product types, and the need for marketing restrictions for novel tobacco products.

C. Influence of Digital Tobacco Marketing on Youth Tobacco Use

While all tobacco product labeling, advertising, marketing, and promotion has the potential to significantly influence youth tobacco use, digital[97] labeling, advertising, marketing, and promotion is particularly concerning given that it is transforming traditional marketing practices and is highly targeted to young people. The Pew Research Center reports that a vast majority of teens have access to a home computer or smartphone and nearly half of teens report using the internet "almost constantly" (2018), which means that many youth are constantly being exposed to marketing of a variety of different products, including tobacco products. While there is overwhelming evidence that children, teens, and young adults are exposed to and influenced by marketing of unhealthy products in traditional media, the internet provides marketers with new, relatively inexpensive channels and tools for disseminating their messages (Dunlap et al. 2016). Research examining online engagement with tobacco marketing among youth found a sizable increase of engagement over time (Soneji, Yang, Knutzen, et al. 2018) and that the number of engagements is associated with tobacco use initiation, frequency of use, and progression to poly-product use (Soneji, Yang, Moran, et al. 2018). According to the 2012 Surgeon General's report, "the techniques of digital marketing are part of sophisticated behavioral targeting in which the marketer collects data on the users' every move (e.g., every click of the mouse, sign-up for a contest, forwarding to a friend) to enable ever more precisely

[97] For the purposes of this appendix, here and throughout the document, "digital" includes internet/online and mobile.

targeted marketing" (HHS 2012). This precision marketing also represents an opportunity to limit youth-exposure to the digital marketing of tobacco products.

Via social media applications, marketers gain access to detailed profiles of users and their friends. Social media has fundamentally altered the marketing landscape by moving young audiences from passive recipients of advertising to active participants in the co-creation and dissemination of marketing messages (Dunlap et al. 2016). Corporate brands leverage the use of social media by adolescents and young adults to target and engage with young audiences (Dunlap et al. 2016). Unlike traditional forms of advertising that target potential customers with ads, companies that join in the "complex network of relations" of social media "befriend" their customers, which is a particularly appealing approach for companies wanting their consumers to express their personality through brand association (Dunlap et al. 2016). "Marketers seek to create 'brand ambassadors,' [i.e., social-media influencers] who promote the product in the context of their online communications, whether or not such promotions are recognized by the users or receivers as marketing. The effect is to blur the distinction between marketing communications and market research" (HHS 2012).

For example, a study examining message content on Twitter concluded that Twitter serves as an important platform for e-cigarette marketing (Chu et al. 2015). Whenever a message posted by an e-cigarette brand is "retweeted" by another user, the message has reached a new network of users. Additional retweets can provide a cascading spread within and outside an original poster's network and cause the message to go viral. This exposure through a retweeting network allows rapid diffusion of messages across groups (Chu et al. 2015). However, Twitter content often reaches unintended audiences, including youth and other vulnerable populations, due to the platform's exponential reach and relatively limited control over what types of people are exposed to specific messages (Chu et al. 2015). With more than 30% of today's youth reporting they use Twitter, marketing and promotion of tobacco products through Twitter can influence youth (Pew Research Center 2018). In addition, a recent study found that sales growth of JUUL was accompanied by a variety of innovative, engaging, and wide-reaching campaigns on social media platforms popular among youth, such as Twitter, Instagram, and YouTube (Huang et al. 2018).

IV. The Public Health Rationale for Requiring Submission of New Tobacco Product Labeling, Advertising, Marketing, and Promotional Materials and Plans and for Placing Restrictions on the Marketing of New Tobacco Products to Limit Youth-Exposure to Such Marketing

A. Purpose of Marketing Requirements and Restrictions for New Tobacco Products, in General

As noted in the introduction, FDA has a statutory mandate to ensure that the marketing of new tobacco products is appropriate for the protection of the public health. FDA's premarket review under the PMTA pathway is aimed, in part, at determining if marketing a new tobacco product would increase or decrease the likelihood that those who do not currently use tobacco products will start using them. Among non-users, youth are a significant population of concern as their current stage of brain development makes them especially susceptible to nicotine addiction (HHS 2012). Prior sections of this memo have illuminated the powerful impact of tobacco product labeling, advertising, marketing, and promotion on youth-perceptions of tobacco products, youth-appeal of tobacco products, the likelihood of youth initiation and use of tobacco products, even when said marketing is purportedly targeted or designed to appeal to adults. Thus, for FDA to help ensure that the continued marketing of a new tobacco product is appropriate for the protection of public health, it is critical for FDA to conduct ongoing review and evaluation of the product's labeling, advertising, marketing, and promotional materials and plans to assess any possible effects on perceptions, appeal, intentions, and behaviors among intended and unintended audiences, and to place appropriate restrictions on the product's marketing and related activities from the outset to limit youth-exposure to such marketing.

Additionally, requiring a firm that receives marketing authorization for its products to provide labeling, advertising, marketing, and promotional materials and plans in advance of their use on an ongoing basis is not for pre-approval, but will provide FDA timely access to such materials and plans and, if needed, allow FDA to provide advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and on the finding that continued marketing of the products is appropriate for the protection of the public health.

B. Reducing Youth-Appeal of Tobacco Product Marketing

Generally, firms receiving marketing authorization for a new tobacco product should seek to reduce the youth-appeal of the tobacco product's labeling, advertising, marketing, and promotional materials, including avoiding the use of imagery and themes known to resonate with youth, such as aspirational content depicting tobacco use as "cool," attractive, rebellious, and/or risky, or as a means to make one more popular, desirable, or independent (HHS 2012). Other potential strategies for limiting youth-appeal of labeling, advertising, marketing, and promotional materials include focusing marketing content on instructional demonstrations and product comparisons and avoiding bright, bold, cheerful designs and colors, which can influence youths' product choices because these characteristics affect their perception of the products, draw attention to them, and influence purchase decisions (Padon, Mahoney, et al. 2017; Akcay 2012; Lempert & Glantz 2016).

Instead, labeling, advertising, marketing, and promotional materials should be clearly tailored to appeal to adults by using personalization strategies that make the content relevant and meaningful to adult recipients and should depict individuals who are similar to the target audience in terms of attributes, beliefs, and interests, in relatable situations that make it easier for adult viewers to engage with and connect to the advertising (Hawkins et al. 2008; Nielsen 2014). For example, advertising tailored to adult tobacco users would likely use headline and body copy that is relevant only to adults who might be considering switching products; would use models that are obviously older adults (ages 35-54) who look like and/or explicitly state they are tobacco users; and would portray people in realistic situations for tobacco users without making them look highly appealing or aspirational to other non-targeted populations, such as youth.

C. Limiting Youth-Exposure to Tobacco Product Marketing

Given the association between tobacco product marketing and youth initiation of tobacco use detailed in Section III, to help ensure the marketing of the products receiving marketing authorization under the PMTA pathway remains appropriate for the protection of public health, it is critical to limit youth-exposure to the products' marketing, advertising, labeling, and promotion. Placing certain marketing restrictions[98] on the newly authorized tobacco products from the outset, such as the media channels through which the firm markets its products, are essential components of limiting youth-exposure, and are thus appropriate for the protection of public health.

1. Restrictions on Paid Digital Tobacco Product Marketing

The rise of digital marketing has changed media consumption habits over the past decade and created an increasingly complex media landscape where it is not yet possible to completely eliminate youth-exposure to tobacco marketing. However, the data sources, methodologies, and technologies used to deliver and track digital media consumption have also evolved, enabling product marketers to create sophisticated, highly targeted digital marketing plans and paid media buys designed to reach their intended audiences based on specific demographics, psychographics, and media passion-points while also limiting reach or

[98] For the purposes of this appendix, this section focuses on restrictions related to digital tobacco product marketing. Considerations for other types of marketing restrictions may be addressed in the future, and the contents of this appendix should not be viewed as an exhaustive list.

"spill" to unintended audiences. Thus, it is possible, efficient, and necessary for firms to take advantage of these technologies to help ensure that tobacco product marketing is targeted to adults and that "spill" to youth audiences is minimal.

For example, paid digital advertising targeting capabilities have evolved such that it is possible, if not standard practice, to target paid advertising using sophisticated data management systems and algorithms connecting individuals to a range of data points, including their demographic characteristics, purchase behaviors, preferences, political opinions, internet search terms, browsing history, interactions with digital content (e.g., liking a social media post, following a specific influencer, sharing a video), digital accounts, connected devices, physical location, and information about other members of their household. Consumers are also increasingly digitizing and sharing detailed information about their personal beliefs, experiences, and behaviors, giving marketers ever-growing capabilities to track and target individuals who meet the exact demographic and psychographic profiles of their ideal consumers. As a result, targeting advertising based on a "digital destination," such as placing advertising on a specific website, is becoming largely obsolete and economically inefficient in comparison to targeting advertising based on specific digital profiles connected to actual consumers who can thus be reached in almost any digital location and time (IAB 2018).

This is especially significant when considering the need to limit youth-exposure to tobacco marketing appearing in the digital environment, which is exponentially more vast, ever-changing, and difficult to categorize than more traditional media channels like broadcast television and radio and print, making it difficult to accurately determine the audience composition of a specific digital property (i.e., what percent of visitors to a specific website are within a certain age-range), or even assess where one digital property ends and another begins. Fortunately, paid digital advertising targeting capabilities offer tobacco marketers the ability to target adults who meet specific age criteria through the use of first- and/or second-party age-verified data (see table) on any digital property accepting paid tobacco advertising, while also restricting youth-access to such advertising. Marketers can also layer on additional demographic and psychographic data (e.g., tobacco product purchase behaviors) to further enhance the efficiency of their paid digital media buys.[99]

Table. Definitions of first- and second-party age-verified data

First-party age-verified data	Data owned by a firm (e.g., a firm's customer registration data collected via site traffic to the firm's company-owned website; data the firm uses in direct marketing to its adult smoking customers) that the firm has age-verified through independent, competent, and reliable data sources.
Second-party age-verified data	First-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data) to which a firm has access. This data must be age-verified by the second party and not through data aggregators.

[99] In addition to first- and second-party age-verified data, firms can use data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles to enhance first- and second-party age-verified audience targeting data. However, such data is not considered age-verified and should only be used in combination with first- and/or second-party age-verified data.

Using targeting through the use of first- and/or second-party age-verified data (see table) does not mean that a firm will not be able to advertise at all in certain digital platforms, for example on certain websites that do not have age-restriction measures in place. Rather, even if a website does not have its own first-party age-verified data, tobacco advertising could still show up on that site. For example, if an adult that a tobacco marketer has age- and identity-verified as meeting the federal minimum legal age to purchase tobacco products through independent, competent, and reliable data sources visits TeenVogue.com, that adult could be delivered a tobacco ad on the site using the marketer's first-party age-verified targeting data (regardless of whether TeenVogue.com has its own first-party age-verified data to share with the tobacco marketer), but an age-verified teen on TeenVogue.com would not be delivered the same tobacco ad as a result of this targeting. Therefore, through the use of targeting data, different individuals can see different ads when visiting the same website at the same time. This allows for a highly targeted approach to tobacco advertising delivery, which can help ensure that youth exposure is minimized, while at the same time not restricting access to adults.

2. Restrictions on Tobacco Product Social Media Marketing and the Use of Influencers, Bloggers, Brand Ambassadors, etc.

Although paid digital advertising can be effectively targeted using first- and second-party age-verified data to reach adults, there are other types of digital marketing cannot be targeted using this approach. For example, product-branded social media accounts essentially operate as both mini websites and "free" advertising channels offering a range of effective means of directly reaching and engaging consumers. In fact, "the ability to influence a large number of individuals, the minimal effort required to make influence attempts, and the flexibility to deploy a variety of influence strategies through information technologies are a potent combination making influence in online social networks considerably more compelling and pervasive than in conventional interpersonal interactions," highlighting the need for close scrutiny of these methods (Subramani & Rajagopalan 2003). Further, one of the most effective digital marketing practices today—especially among youth who are particularly susceptible to social influences—is the use of "organic" depictions of tobacco use and endorsements of tobacco products by cultural icons and other influencers through their own social media accounts (HHS 2012).

Thus, as part of ensuring digital media plans and buys for tobacco products are highly targeted to adults while limiting spill to youth, it is critical to mitigate against the incredible reach and influence of social media, including "organic" influencer promotion. Currently, there are no universal age-restriction controls on social media platforms and some do not offer any age-restriction options; however, many social media platforms are beginning to offer branded-account owners the option to age-restrict some or all of their account pages, followers, and content, including even specific posts, photos, videos, events, etc. These options still face a few additional limitations; for example, most social media platforms allow users to establish their own account profile settings, including self-reported age, and users are not age- or identity-verified. However, users are increasingly prompted to "link" digital profiles and accounts (e.g., option to sign-up for a new account using an existing email account or social media account), increasing the likelihood of more accurate self-reporting.

As part of these restrictions, firms must ensure that their own social media accounts as well as those of any influencers promoting a tobacco product on a firm's behalf use the available age-restriction controls to restrict youth access to any product promotion disseminated through social media accounts. Firms must also ensure the disclosure to consumers or viewers, via the use of statements such as "sponsored by [firm name]," of any relationships between the firm and entities that creating labeling for, advertise, marketing

and/or promote the product on the firm's behalf to help prevent misleading marketing, which is especially likely to influence youth.

V. Proposed Marketing Restrictions in PMTA Authorization Orders

In this context, FDA should consider including detailed marketing restrictions and requirements, in addition to other requirements, for any new tobacco product receiving market authorization under sections 910(c)(1)(B) and 910(f) of the FD&C Act. FDA should determine such marketing restrictions and requirements on a case-by-case basis when issuing an order that the marketing of a tobacco product is appropriate for the protection of public health. Information that should be considered in these determinations includes, but is not limited to, information submitted to FDA by a firm seeking pre-market tobacco authorization regarding the firm's intended labeling, advertising, marketing, and promotion of the products; use of industry practices known to substantially impact youth trial and uptake of tobacco product use; new and emerging technologies, media, and marketing practices; and existing applicable laws and legal agreements affecting the sales, distribution, marketing, advertising, labeling, and/or promotion of certain tobacco products.

Generally, firms seeking marketing authorization for new tobacco products should seek to limit youth-exposure to the products' labeling, advertising, marketing, and promotion. Restrictions in a marketing order should be aimed at the following with respect to advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product:

- Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
- Targeting of specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and/or psychographic characteristics that reflect the intended target audience;
- Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
- Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the products;
- Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
- Consumer engagements, including events at which the products were demonstrated; and/or
- Use of earned media and/or public-relations outreach to create labeling for, advertise, market, and/or promote the products.

Firms should establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent **digital sales** of the products to individuals who are under the federal minimum legal age to purchase tobacco products.

Firms should establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare consumer information against independent, competent, and reliable data sources, such as public records, at the first point of access to any **owned digital properties** (e.g., the firm's company-owned, consumer-directed, product-branded website(s) and/or mobile applications), to restrict access to any of the products' labeling, advertising, marketing, and/or promotion appearing in such properties to only individuals who are at least of federal minimum legal age to purchase tobacco products.

Firms should establish, maintain, and monitor use of the available site-, platform- and content- (e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded account and all

associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the products on the firm's behalf through the influencer's account), at the first point of access to any **shared digital properties** (e.g., the firm's product-branded social media accounts, pages and associated content; content promoting the products on the firm's behalf disseminated through another entity's social media accounts), to restrict access to any of the products' labeling, advertising, marketing, and/or promotion appearing in such properties to only individuals who are at least of federal minimum legal age to purchase tobacco products.

Firms should establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of any of the products' labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product(s) running on another company's website; paid advertising for the product(s) running in social media; paid distribution of influencer content), to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products. Such targeting must use only first- and/or second-party age-verified data (see table). Firms should restrict advertising practices that are not and/or cannot be targeted using such data (e.g., tactics like "Run-of-Site," "homepage takeovers," "splashy buys").

Firms should establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). Such monitoring should require real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to youth, ages 17 and under. Such monitoring also should require post-launch delivery verification reports be submitted to the firm from an accredited source (e.g., Media Ratings Council).

Firms should **disclose to consumers or viewers any relationships between the firm and entities** that create labeling for, advertise, market, and/or promote the products, on the firm's behalf or at the firm's direction, via the use of statements such as "sponsored by [firm name]" in any such labeling, advertising, marketing, and/or promotional materials.

It is vital to the continued protection of public health that FDA take these and other marketing-related considerations seriously when evaluating marketing plans to ensure they are sufficiently targeted to limit youth-exposure to tobacco product labeling, advertising, marketing, and promotion. The evaluation of these marketing plans, including evaluation of their potential impact on youth tobacco use, will help FDA determine whether the marketing, and continued marketing, of the products is appropriate for the protection of the public health.

VI. Conclusion

Given the level of evidence indicating the direct and powerful impact of tobacco marketing on youth tobacco use, and FDA's statutory mandate to protect young people from the dangers of tobacco use, it is both reasonable and critical for firms to submit planned labeling, advertising, marketing, and promotional materials and plans for new tobacco products that are seeking or have received premarket authorization, and for FDA to place restrictions on the marketing of such products. This important safeguard will help FDA ensure, on an ongoing basis, that the continued marketing of new tobacco products remains appropriate for the protection of public health.

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