Module 6 : Research

6.3 Effect on Tobacco Use Initiation Among Non-Users

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1. INFORMATION ON TOBACCO USE INITIATION AMONG NON-USERS

To measure the potential benefit of marketing an MRTP to the public, the FDA Modified Risk Tobacco Product Applications Guidance recommended investigating several areas, including the effect on tobacco use initiation among non-users[1]. In this section, we provide data from both pre-market studies included in the original MRTPA[2], and postmarket studies conducted both within the U.S. and internationally, on the effect of *IQOS* on tobacco use initiation among non-users. In addition, we cross-reference Module 7 of the initial MRTPA for the Authorized *IQOS* products with related appendices and data, and with subsequent amendments, and Module 7 of the supplemental PMTA for the Authorized *IQOS* 3 System (PM0000634), as well as Module 7 of the supplemental MRPTA for the *IQOS* 3 System (MR0000192).

1.1. Premarket U.S. data

1.1.1. Background

To provide data on the effect on tobacco use initiation among non-users, PMI conducted a U.S. premarket quantitative study (THS-PBA-05-REC-US) to assess the effect of the authorized reduced exposure claim, included as part of the THS Label, Labeling and Marketing Materials (LLM), on behavioral intentions among adult tobacco non-users. A summary of the methodology of this study is presented in section 6-2 (Table 1).

Below, we provide a brief summary of previously submitted evidence from this U.S. pre-market quantitative study on behavioral intentions among adult tobacco non-users.

1.1.2. Effect of THS Label, Labeling and Marketing Material on Behavioral Intentions among Adult Non-Smokers

Positive Intention to Try and positive Intention to Use[3] THS among Adult Former Smokers and Adult Never Smokers were low. Among Adult Former Smokers for the LLM tested and including Surgeon General's warnings[4], Positive Intention to Try ranged from 4.2% to 6.3%;

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[1] FDA. Modified Risk Tobacco Product Applications. Guidance for Industry. Rockville, MD: U.S. Department of Health and Human Services. March 2012. https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM297751.pdf.

[2] MRTPA Modified Risk Granted Order - Exposure Modification of December 12, 2019, authorizing the marketing of the modified risk product *IQOS* 2.4 System Holder and Charger (STN: MR0000133).

[3] Positive Intention to Try (operationalized as the sum of % Very Likely and % Definitely responses to the item on Intention to Try) and positive Intention to Use (operationalized as the sum of % Very Likely and % Definitely responses to the item on Intention to Use Regularly).

[4] Results for PMI warnings are not presented herein and have been described in more details in sections 6.2.2, 6.3.1, 6.4 and 7.3.2 of the original MRTPA.

positive Intention to Use ranged from 3.1% to 5.2%. For Adult Never Smokers, very few subjects expressed an *Intent to Use* (between 0% and 2.1% for positive Intention to Try and 0% for positive Intention to Use. Similarly for the LA-25 Adult Never Smokers group (between 0% and 1.0% for positive Intention to Try and 0% for positive Intention to Use. These low levels of *Intent to Use* THS were consistent with the low levels of *Intent to Use* CC and E-Cigarettes.

1.1.3. Conclusion of U.S. Pre-market Studies

Based on the above data that was previously submitted to the FDA as part of the original MRTPA (MR0000059-MR0000061, MR0000133), the FDA TPL review[5] determined that

- *Among former smokers: the results suggest some interest in trying the product among former smokers, but the addition of the claim did not appear to increase interest among this group. Accordingly, the results do not suggest that the products, if marketed with a reduced exposure claim, would generate a high level of interest among former smokers. This finding is consistent with a potential benefit to population health.*
- *Among adult never smokers: the results suggest almost no interest in trying the product among adult never smokers, and the addition of the reduced exposure claim did not appear to increase interest among this group. Accordingly, the results do not raise concerns that the proposed MRTP would generate a high level of interest among never smokers. This finding is consistent with a potential benefit to population health.*
- *Among young adult never smokers: the evidence related to young adult never smokers suggests low interest in trying the product. In the applicant's studies, the addition of the claim did not appear to increase interest in trying IQOS. Accordingly, the results do not raise concerns that the proposed MRTP would generate a high level of interest among young adult never smokers. This finding is consistent with a potential benefit to population health.*

Although PMP S.A. has not conducted any new Tobacco Product Perception and Intention (TPPI) studies for the Authorized System in the U.S., the results and conclusions from the THS-PBA-05-REC-US study remain valid and relevant as further confirmed by postmarket study data from U.S. and international markets. Specifically, the evidence demonstrates that

[5] Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911(d) of the FD&C Act – Technical Project Lead, p. 62, July 6, 2020.

there is a low likelihood of starting using *IQOS* among non-smokers, including former and never smokers.

1.2. Postmarket U.S. Data

1.2.1. Background

As part of the PMSS program for *IQOS* pursuant to the MRGOs orders from the FDA, PMP S.A. has developed a comprehensive post-market surveillance program within the United State that permits evaluation of the impact of the marketing of the *IQOS* System on tobacco or nicotine-containing product initiation, relapse, and reinitiation among tobacco non-users, including youth and young adults. A summary of each study that was included in the latest version of our approved PMSS program is provided in Section 8.1. However, as explained in the same section 8.1, the cessation of sales of *IQOS* due to the ITC order has limited our ability to study and surveil *IQOS* use. As such, timing and plans for PMSS have been adjusted as documented in the letter sent to FDA on January 14, 2022[6]. Changes include pausing *IQOS* Cross-sectional PACS Study and, while the Underage Tobacco Use Survey (UTUS) data collection continued, the oversample in Atlanta, GA, Charlotte, NC and Richmond, VA starting in the second quarter of 2022 was halted.

1.2.2. U.S. Postmarket Data among Tobacco Non-Users from IQOS Cross-sectional PACS

ALCS, on behalf of PMP S.A. conducted the *IQOS* cross-sectional Postmarket Adult Consumer Study (PACS) among qualified adult ever established *IQOS* users aged 21 years of age or older. Part of the objectives of this survey included collection of data on initiation with *IQOS*. A summary of the *IQOS* Cross-sectional PACS methods is presented in section 6-2 (Table 1).

In relation to initiation, as shown in Table 1, all current established *IQOS* users had ever tried at least one tobacco product and almost all had ever used at least one product to the lifetime criterion at the time of the survey (98.18%) or prior to *IQOS* initiation (96.13%). When asked about ever tobacco usage on a consistent basis, the vast majority of current *IQOS* users stated that they had used cigarettes (96.58%), followed by e-vapor products (44.65%), cigars (20.73%), and smokeless tobacco (15.03%). The proportions of tobacco products ever tried or used on a consistent basis prior to trying *IQOS* were similar in all categories, indicating that the vast majority of users tried or used these products before trying *IQOS*.

[6] Letter « Adjustment to the Postmarket Surveillance and Studies (PMSS) Plan forMR0000059 - MR000061 and MR0000133 » dated January14, 2022.

Table 1 Types of tobacco products ever tried, used to lifetime criterion, and currently using, among current *IQOS* users

Measure	Types of tobacco products ever tried, used, and currently using **at the time of the survey** % (95% CI)	Types of tobacco products tried, used, and currently using **30 days prior to trying *IQOS*** % (95% CI)
Base (Total Participants)	n = 439	n = 439
Ever Tried		
Cigarettes	99.32 (98.02; 99.86)	99.32 (98.02; 99.86)
Cigars*	63.78 (59.29; 68.28)	60.36 (55.79; 64.94)
Pipe filled with tobacco	20.73 (16.94; 24.52)	19.82 (16.09; 23.55)
Hookah	31.89 (27.53; 36.25)	30.07 (25.78; 34.36)
E-vapor products	72.21 (68.02; 76.40)	69.70 (65.41; 74.00)
Smokeless tobacco	25.74 (21.65; 29.83)	24.83 (20.79; 28.87)
Oral tobacco-derived nicotine products	20.05 (16.30; 23.79)	18.45 (14.82; 22.08)
Any tobacco**	100.00 (99.16; 100.00)	99.77 (98.74; 99.99)
Used to Lifetime Criterion (numeric criterion or consistent basis, as applicable)		
Cigarettes	96.58 (94.88; 98.28)	93.39 (91.07; 95.72)
Cigars*	20.73 (16.94; 24.52)	17.31 (13.77; 20.85)
Pipe filled with tobacco	5.01 (2.97; 7.05)	4.78 (2.79; 6.78)
Hookah	4.33 (2.42; 6.23)	3.19 (1.55; 4.83)
E-vapor products	44.65 (40.00; 49.30)	40.77 (36.18; 45.37)
Smokeless tobacco	15.03 (11.69; 18.38)	14.12 (10.87; 17.38)
Oral tobacco-derived nicotine products	5.47 (3.34; 7.59)	4.10 (2.25; 5.96)
Any tobacco**	98.18 (96.44; 99.21)	96.13 (94.32; 97.93)
Current Use		
Cigarettes	48.75 (44.07; 53.42)	91.57 (88.97; 94.17)
Cigars*	13.90 (10.66; 17.13)	15.72 (12.31; 19.12)
Pipe filled with tobacco	2.51 (1.04; 3.97)	2.96 (1.38; 4.55)
Hookah	4.10 (2.25; 5.96)	4.78 (2.79; 6.78)
E-vapor products	20.05 (16.30; 23.79)	29.61 (25.34; 33.88)
Smokeless tobacco	3.42 (1.72; 5.12)	5.01 (2.97; 7.05)
Oral tobacco-derived nicotine products	3.42 (1.72; 5.12)	5.01 (2.97; 7.05)
Any tobacco**	64.92 (60.46; 69.38)	95.22 (93.22; 97.21)

* This includes regular cigars, cigarillos, and little filtered cigars
** This refers to any tobacco product other than *IQOS*
CI: Confidence Interval, n: Number of observations
Source: "IQOS® Cross-sectional PACS" - Final Study Report - Wave 1[7]: Table 3

[7] 2022 Annual report and PMSS plan submitted on April 29, 2022, P01-1_-_IQOS_Cross-Sectional_PACS_-_Wave_1_Final_Study_Report

In relation to re-initiation (see Table 2), only a small proportion (2.16%) of ever established *IQOS* users reported that they first tried *IQOS* after not using any tobacco products for 12 months or longer, and 5.83% first tried *IQOS* after not smoking cigarettes 12 months or longer. These proportions of re-initiation were similar for users of menthol *HeatSticks* compared to users of non-menthol *HeatSticks*.

Table 2 Initiation with *IQOS* among Long-Term Former Established Smokers and Long-Term Former Established Users of All Tobacco Products

Measure	Ever Established *IQOS* Users % (CI)	Ever Established *IQOS* Users Who Prefer Menthol *HeatSticks* % (CI)	Ever Established *IQOS* Users Who Prefer non-Menthol *HeatSticks* % (CI)
Base (Total Participants)	n = 463	n = 242	n = 221
First trial of *IQOS* after not using any tobacco products for 12 months or longer	2.16 (0.84; 3.48) (P)	2.07 (0.67; 4.76) (P)	2.26 (0.74; 5.20) (P)
First trial of *IQOS* after not smoking cigarettes for 12 months or longer	5.83 (3.70; 7.97)	6.61 (3.48; 9.74)	4.98 (2.11; 7.84)
First trial of *IQOS* after not smoking cigarettes for 12 months or longer who prefer/preferred menthol cigarettes	2.16 (0.84; 3.48) (P)	4.13 (1.62; 6.64) (P)	0.00 (0.00; 1.66)
First trial of *IQOS* after not smoking cigarettes for 12 months or longer who prefer/preferred non-menthol cigarettes	3.46 (1.79; 5.12)	2.48 (0.92; 5.32) (P)	4.52 (1.78; 7.27) (P)

(P): Low Statistical Precision
Source: "IQOS Cross-sectional PACS" - Final Study Report - Wave 1[8]: Table 13

[8] 2022 Annual report and PMSS plan submitted on April 29, 2022, P01-1_-_IQOS_Cross-Sectional_PACS_-_Wave_1_Final_Study_Report

1.2.3. U.S. Postmarket Data on Underage Awareness, Ever Use, And Past 30-Day Use of the IQOS System from UTUS analysis

In the MRGO (July 7, 2020)[9], FDA indicated that *"..., given the novelty of these products and the uncertainty related to the impact of modified risk information on youth, your studies must be designed to monitor individuals under the age of 18 to assess: (a) youth awareness of IQOS, to evaluate how effectively your marketing is limiting unintended exposure to youth, and (b) youth use of the IQOS system, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. Your surveys must also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20)."*

Therefore, on behalf of PMP S.A., ALCS conducted an analysis of U.S. post-market data relevant to *IQOS* collected through its Underage Tobacco Use Survey (UTUS)[10].

The UTUS is a nationally representative survey of U.S. household-dwelling individuals 13-20 years of age. A summary of the UTUS study is provided in Table 3.

Detailed results of the UTUS Survey were provided as part of the 2023 Annual Reporting[11].

[9] Modified Risk Granted Order (MRGO) authorizing the *IQOS* 2.4 System Holder and Charger (MR0000133) and associated Marlboro *HeatSticks* (MR0000059-61).

[10] Update PMSS plan submitted on April 7, 2022; Response to Deficiency letter submitted on June 27, 2022, Proceed Letter dated January 10, 2023 (PS0000169, PS0000194, PS0000231 and PS0000268).

[11] 2023 Annual report and PMSS plan submitted on April 28, 2023, Appendix 2023-pmss-a03-utus-analysis-rep-for-iqos-pmss and 2023-pmss-a01-mrtp-use-behavior.

Table 3 Methodology of Analysis of Relevant Data from the ALCS Underage Tobacco Use Survey

Study Title: Estimation of Awareness and Use of *IQOS* among Underage Individuals 13-20 Years of Age. Analysis of Relevant Data from the ALCS Underage Tobacco Use Survey

(Short Title: Analysis of UTUS)

Study design: The UTUS is designed to draw nationally representative samples of underage individuals 13-20 years of age using a probability-based sampling method. The UTUS uses a repeated cross-sectional study design to draw probability samples of non-institutionalized, household-dwelling individuals 13-20 years of age living in the U.S. Study samples are drawn using a list-assisted, address-based-sampling approach utilizing housing unit addresses from the United States Postal Service. The UTUS *IQOS* module includes questions about awareness, usage, and consumption specific to *IQOS*.

Subjects: A total of 5,753 individuals completed the survey between quarter 2 of 2022 and quarter 1 of 2023.

Main criteria for inclusion: To qualify for study participation, individuals had to meet the following study eligibility criteria:

- Identify as English or Spanish speaking persons living in the United States;
- Have access to internet and/or telephone;
- 13 to 20 years of age;
- Have sufficient abilities to complete the questionnaire (i.e., reading/responding to online survey instrument or listening/speaking to interviewer over the telephone);
- 13-17-year-old individuals have received consent from their parent/legal guardian to participate and themselves assent to participate; and
- 18-20-year-old individuals consent to participate.

Objectives and Outcome Measures:

Objective 1: Estimate awareness and source of awareness of *IQOS* among underage individuals

Objective 2: Estimate ever and past 30-day *IQOS* use among underage individuals

Objective 3: Estimate lifetime use behavior among underage ever users of *IQOS*

Objective 4: Estimate past 30-day use behavior among underage past 30-day *IQOS* users

UTUS is fielded on a quarterly basis. For the current analysis, data from quarter 2 of 2022 to quarter 1 of 2023 were aggregated to comprise the most recent four-quarter period.

The UTUS results are based on a sample of 5,753 underage individuals in the United States; aggregated from quarters 2, 3, and 4 surveys conducted in 2022 and quarter 1 survey conducted in 2023. About one in five participants replied they were "not sure" whether they had ever seen or heard of *IQOS* and hence were removed from further analysis.

In the remaining sample of 4,629 participants an estimated 4.8% of youth (13-17 years) and 8.3% of young adults (18-20 years) reported having ever seen or heard of *IQOS*. An estimated 0.5% of youth and 0.8% of young adults reported ever use of *IQOS*. 0.12% of youth and young adults reported past 30-day use of *IQOS* (Table 4).

Among the 21 individuals who had indicated use of *IQOS*, but not within the past 30 days (i.e., *IQOS* ever-users), five correctly identified that *IQOS* "only uses sticks containing actual tobacco,"[12] while two did not know. Of the six individuals who reported use of *IQOS* in the 30 days prior to taking the survey, three correctly identified *IQOS*. Together this evidence shows a certain level of confusion about *IQOS*, and that self-reported use may be overestimated among underage individuals.

Nevertheless, results of the UTUS show that underage awareness, ever use, and past 30-day use of *IQOS* is very low.

[12] Correct identification of *IQOS* was defined as selecting "*This device only uses sticks containing actual tobacco*" to the survey question "*Which of the following best describes IQOS?"*.

Table 4 UTUS 2022 to 2023 Estimates: Awareness, Ever Use, and Past 30-Day Use of *IQOS*

Measure	Awareness % (95% CI)	Ever *IQOS* Use % (95% CI)	Past 30-Day *IQOS* Use % (95% CI)
Overall, *N*=4629, (13-20 Years)	n = 271	n = 27	n = 6
	5.96 (5.19, 7.0)	0.57 (0.36, 0.91)	0.12 (0.05, 0.34)
Youth, *N*=2697, (13-17 Years)	n = 118	n = 11	n = 4
	4.81 (3.93, 5.87)	0.47 (0.23, 0.96)	0.15 (0.05, 0.47)
Young Adults, *N*=1932, (18-20 Years)	n = 153	n = 16	n = 2
	8.25 (6.96, 9.76)	0.79 (0.46, 1.33)	0.07 (0.02, 0.28)

Sources: UTUS data collected from April 2022 to February 2023[13].
Percentages are derived from weighted data. *N*'s are derived from unweighted data. Sample sizes may vary in each subgroup due to missing responses.
Abbreviations: UTUS = Altria Client Services Underage Tobacco Use Survey; CI = Confidence Interval.

1.2.1. Conclusion of U.S. Postmarket studies

During the limited duration when *IQOS* was marketed in the U.S, postmarket studies showed i) low prevalence of *IQOS* use among youth ii) low initiation among tobacco never users, including youth, iii) low relapse, and re-initiation of tobacco use with *IQOS* among former tobacco users, and iv) that the majority of *IQOS* users were adult cigarette smokers when they started using *IQOS*. On the balance of this evidence, it can be concluded that U.S. postmarket studies support that *IQOS* continues to satisfy MRTP requirements and will continue benefit the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

1.3. PMP S.A. International Postmarket Data: Repeated Cross-sectional Post-Market Surveys (PMX studies)

1.3.1. Background

Since the submission of the original MRTPA, PMP S.A. has continued to conduct repeated cross-sectional post-market studies (PMX studies) in several countries. These studies have been conducted in nationally representative random samples of legal age adult participants from the general population (n > 5,000; 4-6 waves distributed over the year)

[13] 2023 Annual report and PMSS plan submitted on April 28, 2023, Annex 2023-pmss-a01-mrtp-use-behavior.

coupled with surveys in large samples of *IQOS* users (n > 1,400; 4 waves distributed over the year) randomly selected from registered *IQOS* owners of PMI's country-associated *IQOS* Owner databases. Key findings from some of the surveys have been published in scientific peer-reviewed journals (Fischer et al., 2022; Afolalu et al., 2021).

1.3.2. PMP S.A. International Postmarket Data on initiation, relapse and re-initiation

Results from these repeated cross-sectional post-market surveys in Japan and Italy, of both the representative samples of the general adult populations and the random samples of registered *IQOS* owners, show that the introduction of *IQOS* with *HEETS/HeatSticks* do not lead to significant levels of uptake among adult TNP non-users, *i.e.*, initiation, relapse, and reinitiation of tobacco use with *IQOS* are very low across different countries and years. In addition, data from the *IQOS* user samples in Japan and Italy show that nearly all current *IQOS* users were adult cigarette smokers when they started using *IQOS*.[14] (see Table 5).

The cross-sectional study reports for Japan and Italy can be found in Appendix 7-a03-P1-PMX-01-JP-study-report-year-5, and Appendix 7-a04-P1-PMX-02-IT-study-report-year-2 respectively.

[14] In Italy, due to the COVID-19 pandemic, the study had to be suspended for two years because the face-to-face mode of administration of the interviews was not feasible.

Table 5 Initiation, Relapse rate, and Re-initiation rate with *IQOS* among adult TNP non-users in representative samples of the cross-sectional general adult population and *IQOS* Owners' surveys in Japan and Italy

	Japan					Italy	
	Year 1 2016/2017	**Year 2 2017/2018**	**Year 3 2018/2019**	**Year 4 2020/2021**	**Year 5 2021/2022**	**Year 1 2018/2019**	**Year 2 2019/2020**
General Population Sample	N=4,878	N=4,791	N=7,236	N=7,132	N=7,140	N=6,095	N=6,118
Initiation rate (among adult never TNP users 1 year ago)							
IQOS with *HEETS*	0.03% (n=1 of 3,066)	0.13% (n=4 of 3,109)	0.11% (n=5 of 4,685)	0.02% (n=1 of 4,705)	0.08% (n=4 of 4,800)	0.03% (n=1 of 3,811)	0.05% (n=2 of 3,900)
Cigarettes*	0.23% (n=7 of 3,066)	0.29% (n=9 of 3,109)	0.21% (n=10 of 4,685)	0.13% (n=6 of 4,705)	0.19% (n=9 of 4,800)	0.5% (n=19 of 3,811)	0.41% (n=16 of 3,900)
Relapse rate (in past 12 months among adult current TNP users)							
IQOS with *HEETS*	0.00% (n=0 of 894)	0.00% (n=0 of 900)	0.00% (n=0 of 1,304)	0.00% (n=0 of 1,129)	0.00% (n=0 of 1,094)	0.00% (n=0 of 1,568)	0.06% (n=1 of 1,636)
Cigarettes	---	---	---	---	---	1.08% (n=17 of 1,568)	0.92% (n=15 of 1,636)
Reinitiation rate (among adult current TNP users)							
IQOS with *HEETS*	0.11% (n=1 of 894)	0.11% (n=1 of 900)	0.08% (n=1 of 1,304)	0.09% (n=1 of 1,129)	0.09% (n=1 of 1,094)	0.06% (n=1 of 1,568)	0.06% (n=1 of 1,636)
Cigarettes	---	---	---	---	---	0.13% (n=2 of 1,568)	0.00% (n=0 of 1,636)
***IQOS* Owner Sample**	N=2,000	N=2,044	N=2,013	N=2,000	N=1,999	N=1,371	N=1,401
Initiation of tobacco use with *IQOS* (among adult current *IQOS* users)	2.0% (n=40 of 2,000)	1.3% (n=27 of 2,044)	0.7% (n=13 of 1,971)	1.9% (n=39 of 2,000)	2.6% (n=51 of 1,999)	0.66% ** (n=9 of 1,371)	0.48% (n=6 of 1,249)

Data from PMX Study reports for Japan[15] (year 1-5), and Italy (year 1-2).
TNP, tobacco or nicotine-containing product
* Cigarettes include hand-rolled cigarettes
** Based on full-year post-hoc analysis. The corresponding value for wave 4 [N=304] that was for Italy conducted in year 1 only, is 0.30% [n=1 of 304].

[15] In previous submissions, the initiation rates for Japan year 1-2 were based on adult current never users

1.3.3. Conclusion of International Postmarket studies

Results from international post-market surveys show that the introduction of *IQOS* with *HEETS* did not lead to significant levels of uptake among adult TNP non-users. Specifically, international post-market studies show i) low initiation among tobacco never users, ii) low relapse, and re-initiation of tobacco use with *IQOS* among former tobacco users, and that iii) the majority of *IQOS* users were adult cigarette smokers when they started using *IQOS*.

On the balance of the evidence and given the consistency of the findings across the different countries, it can be concluded that results in the U.S. are unlikely to differ from those consistently observed in international countries. This was further supported by the U.S. postmarket studies data gathered during the limited time when *IQOS* was commercialized in the United States.

1.4. Independent Studies

1.4.1. Background

PMP S.A. literature review of independent studies submitted as part of PMP S.A. Annual Reporting[16] also show that (i) the prevalence of *IQOS* use among youth, and/or (ii) the initiation of *IQOS* use among never smokers, and/or (iii) the re-initiation of *IQOS* use among former smokers is very low both in the U.S. and in international countries. Since PMP S.A.'s 2023 Annual Reporting, PMP S.A. has not identified any further relevant independent studies in the context of information on prevalence of HTP or *IQOS* use among youth or tobacco use initiation or re-initiation with HTPs and/or *IQOS* among tobacco non-users. The results of some of the key previously submitted independent U.S. studies are summarized below.

In the U.S. for heated tobacco products in general, an estimated 1.0% of middle and high school students were current users of heated tobacco in 2022 based on the National Youth Tobacco Survey (NYTS) results.[17] We consider that the estimated 1.0% of current HTP use may be an overestimate for the following reasons. First, prior research indicated a proportion of participants reporting awareness and use of HTPs when these products were in very limited distribution in the U.S. For example, based on NYTS data collected during early 2019, an estimated 1.6% of middle-school and high-school students used HTPs during the 30 days prior

[16] For the list of Annual Reports see section 4.2 Marketing Plan.

[17] Park-Lee, E., Ren, C., Cooper, M., Cornelius, M., Jamal, A., & Cullen, K. A. (2022). Tobacco Product Use Among Middle and High School Students—United States, 2022. *Morbidity and Mortality Weekly Report*, *71*(45), 1429-1435.

to the assessment.[18] Another study conducted in 2017 showed that an estimated 9.1% of 16- to 19-year-olds were aware of *IQOS*, a HTP brand.[19] Both studies were conducted before *IQOS* was authorized and available for sale in the U.S. in late 2019 and while other HTPs were also in very limited distribution in the U.S. Similarly, the most recent NYTS study had been conducted between January and May 2022, i.e., after the removal of *IQOS* products from the U.S. markets. Second, based on results from UTUS, only about one in four underage individuals who indicated they had ever used the product were able to identify *IQOS* correctly. Among the six individuals in the UTUS who reported current use of *IQOS*, three identified the product correctly. These results suggest possible misreporting of HTP use, a relatively new product category. Moreover, since NYTS began to assess HTPs in 2019, the estimated past 30-day use of HTPs was 1.6%, 1.4%, 0.7% and 1.0% in 2019, 2020, 2021 and 2022, showing no increase since *IQOS* was authorized in late 2019.[20] (Wang et al., 2019, Zhang and al., 2022, Gentzke et al., 2020, Gentzke and al., 2021, Park-Lee et al., 2022).

1.5. Conclusion

Based on the above pre-market and post-market data collected from both the United States and international markets, we believe that current adult cigarette smokers will continue to represent the segment of the U.S. population that is most likely to use *IQOS*.

Specifically, pre-market and post-market data as well as independent studies from both the U.S. and international markets consistently show low prevalence of *IQOS* use among youth, low initiation of *IQOS* use among never smokers, and low re-initiation and relapse of *IQOS* use among former smokers. Those findings are observed regardless of the *IQOS* Systems and the flavors currently commercialized.

Therefore, it is expected that *IQOS* associated with the authorized reduced exposure claim will continue to benefit the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products and will continue to satisfy MRTP requirements in accordance with section 911(g)(2)(B) of the FD&C Act.

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[18] Dai, H. Heated tobacco product use and associated factors among U.S. youth, 2019. Drug Alcohol Depend. 2020;214:108150.

[19] Czoli, CD; White, CM; Reid, JL, et al. Awareness and interest in *IQOS* heated tobacco products among youth in Canada, England and the USA. Tob Control. 2019;29(1):89-95.

[20] Gentzke et al., Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2020 MMWR Morb Mortal Wkly Rep.2020; 69(50): 1881-1888.

2. REFERENCES

Afolalu, E.F., Langer, P., Fischer, K., Roulet, S. and Magnani, P., 2021. Prevalence and patterns of tobacco and/or nicotine product use in Japan (2017) after the launch of a heated tobacco product (IQOS®): a cross-sectional study. F1000Research, 10.

Fischer, K., Bajec, M., Mainy, N., AlMoosawi, S., Sieverding, M., Zwisele, B., Camille, N., Magnani, P. and Roulet, S., 2022. Trends in prevalence and patterns of use of a heated tobacco product (IQOS TM) in Japan: A three-year repeated cross-sectional study. F1000Research, 11(720), p.720.

Gentzke et al., Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2020 MMWR Morb Mortal Wkly Rep.2020; 69(50): 1881-1888.

Gentzke, A.S., Wang, T.W., Cornelius, M., Park-Lee, E., Ren, C., Sawdey, M.D., Cullen, K.A., Loretan, C., Jamal, A. and Homa, D.M., 2022. Tobacco product use and associated factors among middle and high school students—National Youth Tobacco Survey, United States, 2021. MMWR Surveillance Summaries, 71(5), p.1.

Park-Lee et al. Tobacco Product Use Among Middle and High School Students — United States, 2022 MMWR Morb Mortal Wkly Rep 2022;71(45): 1429-1435.

Wang TW, Gentzke AS, Creamer MR, Cullen KA, Holder-Hayes E, Sawdey MD, Anic GM, Portnoy DB, Hu S, Homa DM, Jamal A, Neff LJ. Tobacco Product Use and Associated Factors Among Middle and High School Students - United States, 2019. MMWR Surveill Summ. 2019 Nov 6;68(12):1-22. doi: 10.15585/mmwr.ss6812a1. PMID: 31805035; PMCID: PMC6903396.

Zhang, L., Gentzke, A., Trivers, K.F. and VanFrank, B., 2022. Tobacco cessation behaviors among US middle and high school students, 2020. Journal of Adolescent Health, 70(1), pp.147-154.