RESEARCH ANALYSIS REPORT
ESTIMATION OF PREVALENCE OF IQOS USE

Secondary Analysis of Relevant Data from the ALCS Adult Tobacco Consumer Tracking Study

(Short Title: Secondary Analysis of ATCT)

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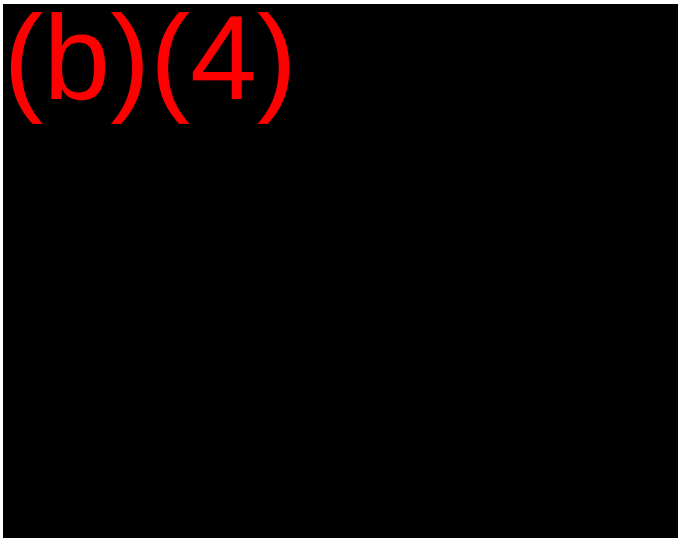

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1. INTRODUCTION

1.1. Background

Philip Morris Products S.A. (PMP S.A.) developed the IQOS Tobacco Heating System and Marlboro HeatSticks (hereinafter referred to as IQOS) as novel tobacco and nicotine-containing products with the potential to reduce harm or the risk of tobacco-related disease associated with smoking cigarettes. PMP S.A. submitted Modified Risk Tobacco Product Applications for IQOS to the U.S. Food and Drug Administration (FDA) seeking authorization to market the products as modified risk tobacco products. On July 7, 2020, FDA issued "Modified Risk Granted Orders – Exposure Modification" authorizing IQOS to be marketed with a reduced exposure claim. The Orders are conditioned upon agreement to conduct postmarket surveillance and studies (PMSS) in accordance with protocols approved by FDA. This document is prepared as part of the PMSS program for IQOS pursuant to the Orders.

1.2. Rationale

The Federal Food, Drug and Cosmetic Act (FDCA) directs the Food and Drug Administration (FDA) to condition an exposure modification order received under FDCA § 911(g)(2) on the MRTP applicants' agreement to conduct PMSS (FDCA §§ 911(g)(2)(C)(ii)). "The outcomes evaluated in postmarket surveillance and studies should focus on the effect of the MRTP on consumer perception, behavior and health under real world conditions of use" (Food and Drug Administration, 2012). For this reason, ALCS[1] on behalf of the applicant, PMP S.A., plans to conduct certain components of PMSS to assess the effect of the MRTP among U.S. consumers. The program will consist of a collection of data over time that supports an assessment of IQOS in the postmarket setting. This Estimation of Prevalence of IQOS Use Research Analysis is one component of the postmarket surveillance program. Specifically, it describes the analyses we conducted using data relevant to IQOS from ALCS's ongoing Adult Tobacco Consumer Tracking Study (ATCT).

2. PURPOSE AND OBJECTIVES

2.1. Purpose

The purpose of this secondary analysis is to estimate IQOS prevalence among adults 21 years of age or older based on relevant data from a population-based consumer survey (i.e. ATCT).

[1] Altria Client Services (ALCS) and the parent of PMP S.A., Philip Morris International Management S.A., have entered into a distribution agreement by which ALCS and its affiliates have exclusive rights to distribute and sell IQOS in the U.S. after FDA authorization. ALCS affiliate PM USA markets IQOS in the U.S. Therefore, PMSS that involves the study of consumers and consumption in the U.S. will be conducted by ALCS to be submitted as part of PMSS reporting by PMP S.A.

2.2. Objectives

The objectives of the original analysis plan are to:

1) Estimate prevalence of IQOS use, in total and by demographic characteristics

2) Estimate prevalence of exclusive, dual and poly tobacco use with IQOS

3) Estimate the number of days and amount of tobacco product usage among current IQOS users

4) Describe initiation, quitting and complete switching behaviors relative to IQOS use

However, as stated in the original analysis plan, we are implementing a stepwise reporting process (described in Section 4). Before the number of current IQOS users reaches 20, only the raw count of current IQOS users will be reported. Based on the number of current IQOS users observed in ATCT from March 2021 to February 2022, we will only report the raw count of number of current IQOS users.

3. OVERVIEW OF THE ADULT TOBACCO CONSUMER TRACKING STUDY

We analyzed data from the ALCS Adult Tobacco Consumer Tracking Study, an on-going cross-sectional computer assisted random-digit dialing telephone interview administered to a nationally representative sample drawn from the U.S. adult civilian non-institutionalized population.

The ATCT annual sample includes approximately 28,800 U.S. adults 21 years or older. The sample is based on a sampling approach that utilizes Random Digit Dial (RDD) landline and cell phone interviewing frames following an equal probability selection method (EPSEM) design. The composition of the sample is 50% cell phone and 50% landline.

For any research that will have results projected to the overall population, and prevalence research in particular, probability samples (e.g., RDD telephone) are preferable to non-probability (e.g., internet-based). In probability samples, persons in the population have a known chance of being selected in the sample, margin of error is universally recognized and accepted, and results can be projected to the population at large with a known level of precision. In non-probability samples, some people in the population have no chance (or an unknown chance) of being selected in the sample (coverage bias). The amount of coverage bias and the exact nature of the bias will vary depending on the source (e.g., various online panels).

Quota controls for geography, sex, and other demographic characteristics are used to reduce the reliance on data weighting. It is important to have a demographically/geographically representative sample for the ATCT study, as tobacco usage behavior can vary greatly across different types of adult respondents. Accordingly, the weighting design for ATCT calls for the nesting of certain weighting variables (for example, race/ethnicity within region); however, these data "nests" can potentially include small sample sizes within a subgroup. In order to weight the data successfully, an adequate number of adult respondents are needed in all weighting subgroups, including those that are hardest to reach. This will ensure that the weighting will bring the data into better alignment with reality, rather than distort it from reality.

While data weighting is a common practice, excessive data weighting is not ideal (for example, heavy lifting of underrepresented subgroups and/or extreme reductions to overrepresented subgroups). Additionally, (as mentioned above), adequate numbers of adult respondents are needed within all weighting sub-groups. Therefore, the ATCT study includes quota controls to both reduce the reliance on weighting, as well as to ensure the success of the weighting.

The quota controls are as follows:

- Hard quota controls for region, sex, and mode (landline/cell)
- Soft quota "guardrails" for age, education, and race/ethnicity. These guardrails are not strict quotas for each sub-group, but rather loose guidelines of ±13 percentage points (pp).

These controls are in place to prevent extreme oversampling of the easiest to reach adult respondents. These quota controls also assure that adequate numbers of adult respondents are available within the nested weighting subgroups, thereby assuring the overall success of the data weighting. In an effort to minimize reliance on these controls, those households reached on landline are asked first for the youngest aged adult male (the hardest population to reach) followed by the youngest aged adult female. However, the need for these controls introduces the possibility of selection bias. While it is impossible to measure selection bias, demographic metrics that are *not* controlled for (such as income) are frequently compared with other statistics reported by federal agencies to ensure consistency and that selection bias is in fact minimal.

3.1. ATCT Tobacco Categories

ATCT is a study designed to measure tobacco prevalence. Eligible adult respondents are asked if they have used any of the following products:

- Cigarettes
- Cigars
- Pipe tobacco
- E-Vapor
- Snus
- Chewing tobacco
- Moist smokeless tobacco or dip
- Oral nicotine products
- Hookah
- Heated tobacco products
- Any Other Tobacco Products not already mentioned.

"Heated tobacco products", the category to which IQOS belongs, was added as a new category to ATCT in October 2019. For each of the above products that the adult respondent has used, additional questions are asked to measure amount of usage and consumption. The usual brand within categories used by consumers is also assessed in ATCT. The categories mentioned above will be combined into the following categories for data analysis:

- Cigarettes
- Cigars
- Pipe tobacco
- E-Vapor

- Smokeless tobacco (snus, chewing tobacco, moist smokeless tobacco or dip)
- Oral nicotine products
- Hookah
- Heated tobacco products

Note: Any other tobacco products not already mentioned will not be considered in the analysis.

3.2. ATCT Study Duration

ATCT is fielded on a continuous basis. Data will be analyzed across the most recent 12 month period for the purpose of reporting.

3.3. ATCT Recruitment

A nationally representative sample is drawn from the US adult population through a computer assisted random-digit dialing telephone interview. The sample is based on a probability sampling approach that utilizes landline and cell phone interviewing frames following an equal probability selection method design. The composition of the sample is 50% cell phone and 50% landline. Quota controls for geography, sex, and other demographic characteristics are used to reduce the reliance on data weighting.

3.4. ATCT Inclusion and Exclusion Criteria

Participants must satisfy the following criteria at the time of screening to be enrolled into the ATCT study: civilian, non-institutionalized population of the United States, 21 years or older, including residents of non-institutional group quarters such as college dormitories, group homes, shelters, rooming houses, and civilians dwelling on military installations.

Respondents who meet any of the following exclusion criteria are excluded from participation in the ATCT study:

1. Unable to read, speak or understand English;
2. Under the age of 21
3. Potential participant is identified as being a non-civilian or member of an institutionalized population
4. Adults on active duty in any branch of the US armed forces

4. SECONDARY ANALYSIS PROCEDURES

Our analysis and reporting of IQOS-relevant information from ATCT for postmarket surveillance purposes will follow a step-wise process based on the number of current IQOS users (used IQOS brand of heated tobacco product in the past 30 days) identified within the ATCT dataset[2].

The process will unfold as follows:

- Step 1 Reporting. The number of current IQOS users in the ATCT dataset is reported when the MTRPA was granted for IQOS. The count will be based on data from the most recent 12 moving-month. We will only report counts if the number of current IQOS users in the ATCT dataset is less than 20.
- Step 2 Reporting. When the number of current IQOS users in the ATCT dataset reaches 20, we will start to report prevalence at the national level. The reported results include the count and percentage of total current IQOS users with 95% confidence interval. The results will be based on either the most recent 12 moving-month if we have reported IQOS use in all 12 months, or the months when ATCT starts to capture current IQOS users if it is less than 12 months.
- Step 3 Reporting. When the number of current IQOS users in the ATCT dataset reaches 100, we will start to report all other outcome measures as stated in this analysis plan. Based on sample size calculations, we need at least 100 current IQOS users in the ATCT data set to start reporting outcome measures for the four objectives.

5. OUTCOME MEASURES AND DATA ANALYSIS

As described in Section 4, when the number of current IQOS users in the ATCT dataset is less than 20, we will only report the number of current IQOS users in the ATCT dataset (i.e., Step 1 Reporting).

Objective 1: Report the number of current IQOS users in ATCT

Definitions of current use of IQOS:

- Selected 'Yes' to (b)(4) (b)(4)

And

- Selected 'IQOS' to '(b)(4) (b)(4)

Note: For PMTA Quarterly Reports, the participants also need to select 'Marlboro' to the question (b)(4) (b)(4)

[2] ALCS currently has a process in place to report IQOS-relevant information from ATCT for the purpose of the IQOS PMTA authorization. When fully executed, this analysis plan will extend beyond the reporting plan devised for the PMTA.

6. RESULTS

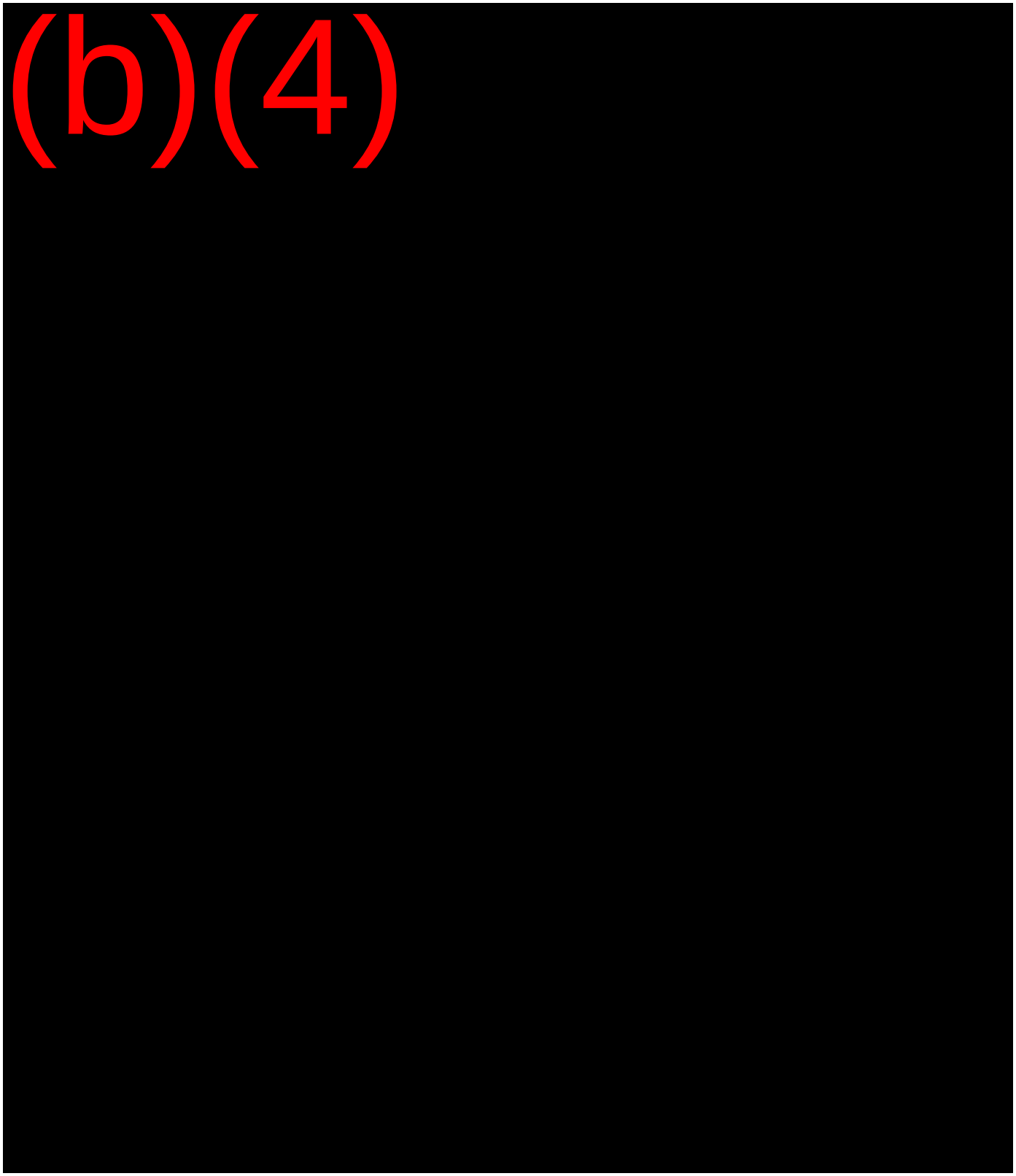
As stated in Sections 4 and 5, before the number of current IQOS users reaches 20, only the raw count of current IQOS users will be reported. Table 1 displays ATCT sample sizes with the raw count of current IQOS users in ATCT for each reporting month and in total (from March 2021 to February 2022).

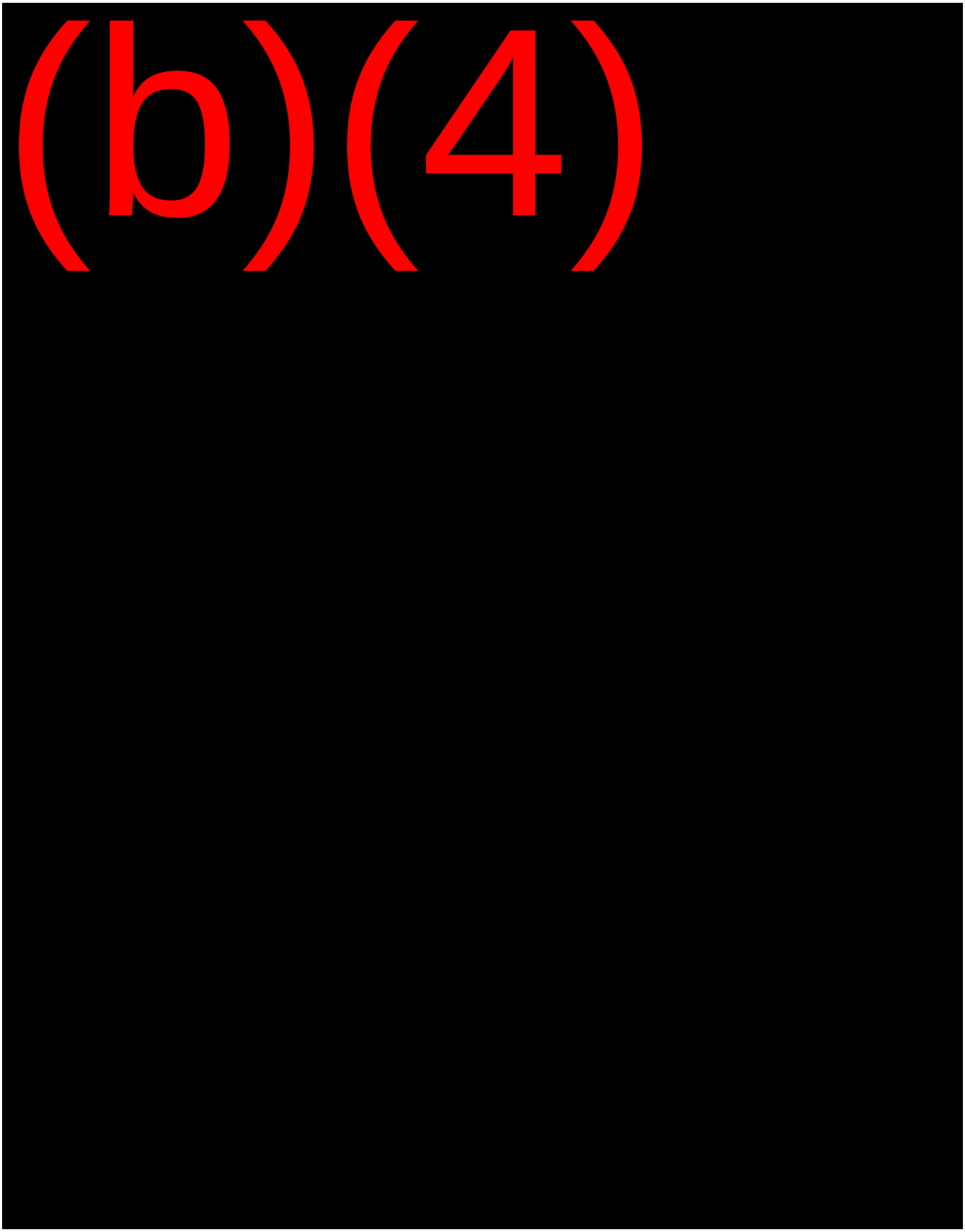
Table 1: Raw Count of Current IQOS Users in ATCT by Survey Month

Survey Month	Monthly Sample Size	Raw Count of Current IQOS Users	Raw Count of Current IQOS Users who reported Marlboro as regular HeatStick brand[1]
March 2021	2,403	(b)(4)	(b)(4)
April 2021	2,407		
May 2021	2,401		
June 2021	2,410		
July 2021	2,407		
August 2021	2,405		
September 2021	2,403		
October 2021	2,405		
November 2021	2,402		
December 2021	2,407		
January 2022	2,404		
February 2022	2,402		
Total	28,856		

[1]Reported in IQOS PMTA June to August 2021 Quarterly Report.

7. APPENDIX 1 – SELECTED ATCT QUESTIONS RELATED TO IQOS AND RELEVANT TO THIS ANALYSIS PLAN

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