

## Module 6.1: Clinical Population Health Studies

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## 1. INTRODUCTION

Data in Module 3 demonstrate the similarities in product design and manner of use between the *proposed MRTPs* and *authorized MRTPs*. Data in Modules 4 and 5 demonstrate the toxicological risk profile and individual health outcomes observed and expected for the *proposed MRTPs* are the same or improved compared to the *authorized MRTPs* and significantly improved compared to cigarettes. This module will demonstrate the similarities in user populations and user behaviors between the *proposed MRTPs* and *authorized MRTPs*.

Because of the similarities between the *proposed MRTPs* and *authorized MRTPs* demonstrated in the previous modules, data from submissions for the *authorized MRTPs* is bridged here to the *proposed MRTPs*. This module provides a summary of behavioral study data submitted with the original PMTAs, which is further supported by new study data discussed in Module 6.2 of these MRTPA's investigating the perceptions and intentions to use the *proposed MRTPs* among participants exposed to the reduced risk claim language. This module also provides a summary of our population health impact model, population health literature, and the post-market surveillance and studies plan we propose should the FDA authorize use of the reduced risk claim with the *proposed MRTPs*.

Collectively, these data demonstrate the similarities in user behavior and user populations between the *proposed MRTPs* and *authorized MRTPs*. Critically, the *proposed MRTPs* and *authorized MRTPs* appeal to the intended users and can successfully switch adults away from cigarettes, while posing minimal risk to unintended users (i.e., initiation or re-initiation among non-users, particularly youth and underage young adults). Combined with the data from Modules 3–5, the data demonstrate the *proposed MRTPs*, when marketed with the reduced risk claim, meet the standard for authorization under section 911(g)(1) of the FD&C Act. As actually used by consumers, the *proposed MRTPs* will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and
- Benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

## 2. TABULAR LISTING OF POPULATION HEALTH STUDIES

A tabular listing of cross-referenced population health studies in these MRTPA's can be found in Module 1, [Attachment 1-3-1](#).

## 3. DATA FROM AUTHORIZED MRTPA's

### 3.1. Swedish Experience

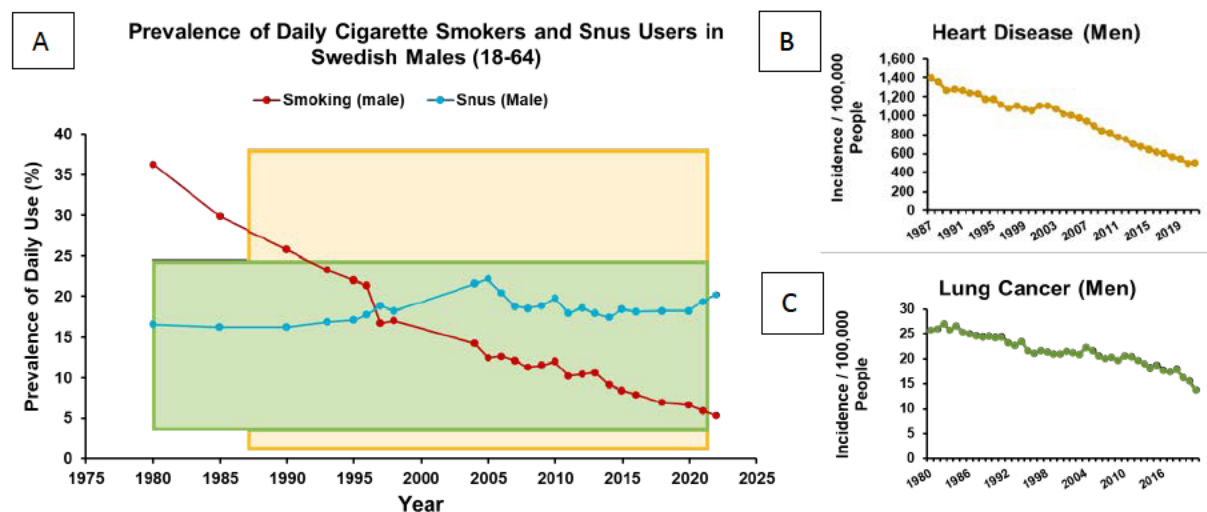
In their decision to authorize use of the reduced risk claim in marketing of the *authorized MRTPs*,<sup>1</sup> FDA noted the importance of the more than three decades of epidemiological data from Sweden demonstrating reduced rates of tobacco-related disease (e.g., lung cancer, heart disease) observed over time with the uptake of snus and associated decreased combusted cigarette use ('Swedish experience' data, see representative data in [Figure 1](#)). Even if such longitudinal data does not yet exist for the *proposed MRTPs*, the 'Swedish experience' is relevant to the *proposed MRTPs* due to the similarities in product design, manner of use, user behavior, and user populations. The toxicological safety profile of the *proposed MRTPs* is improved compared to the *authorized MRTPs*<sup>2</sup> and thus, compared to

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<sup>1</sup> Scientific Review of MRTPA under Section 911(d) of the FD&C Act – Technical Project Lead, available at: <https://www.fda.gov/media/131923/download>.

<sup>2</sup> See Module 4 of these MRTPA's.

combusted cigarettes. Clinical data further supports the reduced risk potential of the *proposed MRTPs*.<sup>3</sup> Users of the *proposed MRTPs* have a comparable or lower risk of developing serious health conditions compared to the users of the *authorized MRTPs* and a lower risk of developing serious health conditions compared to cigarette smokers. Therefore, increased uptake of the *proposed MRTPs* and associated decreased cigarette consumption in the United States is highly likely to lead to a similar observed decline in U.S. smoking-related disease rates, as observed in Sweden and as expected for the *authorized MRTPs*.



**Figure 1. Prevalence of Daily Cigarette and Snus use in Swedish Males 18-64 after 1980 (A), Incidence of heart disease (B) and Lung Cancer (C) in Swedish Men.**<sup>4</sup>

The yellow box in Figure 1A corresponds to the data represented in Figure 1B and the green box in Figure 1B corresponds to the data in Figure 1C.

### 3.2. Post Market Surveillance and Studies (PMSS)

As a function of receiving marketing granted orders (MGOs) and modified risk granted orders (MRGOs) for the *authorized MRTPs*, we conduct PMSS to continuously monitor, amongst other things, the effect these orders have on consumer perception (absolute and relative risk perceptions) and use behavior of the *authorized MRTPs*. The General Snus Patterns of Use (POU) Study is a longitudinal prospective study conducted over four waves, with data on perceptions and use behavior collected at baseline (wave 1), six months (wave 2), one year (wave 3), and two years (wave 4). The respondents self-reported use behavior of all tobacco and nicotine products (TNPs) at each wave and were asked to report their perceptions of the risk of developing health conditions (mouth cancer, heart disease, lung cancer) when using different TNPs or not using TNPs. Complete study information can be found in the PMSS reports submitted for the *authorized MRTPs*.<sup>5</sup>

Results over all waves demonstrate a high level of understanding among respondents that never using TNPs carries the lowest risks of developing health conditions like mouth cancer, heart disease, and lung cancer. Respondents perceive using the *authorized MRTPs* alone as carrying a lower risk of developing

<sup>3</sup> See Module 5 of these MRTPAs.

<sup>4</sup> Source: Incidence Data - Swedish National Board of Health and Welfare, Statistical Database (Accessed 5/2023); Prevalence Data: 1980-1998 - Henningfield J, Fagerstrom K Tobacco Control 2001;10:253-257; 2004-2022 - National Public Health Survey/Living Habits/ Tobacco and Nicotine (Accessed 6/2023)

<sup>5</sup> Data and information from the General Snus POU study are found in Attachment C of the January 30, 2024 amendment to the MRTPA renewal for the *authorized MRTPs* (MR0000256).

health conditions than continuing to smoke combusted cigarettes or dual use of the *authorized MRTPs* and cigarettes but comprehend the *authorized MRTPs* are not without risk entirely. Additionally, *authorized MRTp* usage generally declined over time, with some respondents who were regular users in Wave 1 quitting the product entirely by Wave 4. The decline in *authorized MRTp* use correlated with an increase in nicotine pouch use. Of *authorized MRTp* users, (b) (4) reported use of nicotine pouches at Wave 4, with (b) (4) reporting everyday use and (b) (4) reporting use on some days. Additionally, among participants completing all four waves of the study, use of cigarettes remained low throughout. Based on both self-reported use behavior and risk perception data collected from the POU, users generally understand continued use of cigarettes poses the greatest risk to their health, and switching completely away from combusted cigarettes reduces the risk to their health, while understanding using any TNP is not free of risk.

Though this study only focused on the risk perceptions of the *authorized MRTPs* compared to cigarettes and to using no TNPs, the study also captured data on users transitioning away from not only combusted products, but also away from the *authorized MRTPs* over the course of the two-year study. Some users who transitioned away from using the *authorized MRTPs* transitioned to using nicotine pouches, such as the *proposed MRTPs*, demonstrating they have a high understanding of the continuum of risk. As shown in Modules 4 and 5 of these MRTPA's, making such a transition from a product containing tobacco leaf (*authorized MRTPs*) to a product with similar nicotine content, but no tobacco leaf (*proposed MRTPs*), can provide benefit to individuals by further lowering exposure to potentially carcinogenic compounds compared to combusted cigarettes, and thus reducing risk of developing serious health conditions.

#### 4. BEHAVIORAL STUDY DATA FROM PRIOR SUBMISSIONS FOR THE *PROPOSED MRTPs*

Complete information related to consumer research and behavioral studies conducted for the *proposed MRTPs* was submitted in the original PMTAs<sup>6</sup> or in subsequent amendments to the original PMTAs.<sup>7</sup> Additional behavioral study information can be found (b) (4).<sup>8</sup> Below is a summary of the data and information from some of these studies. Further discussion is in the cross-referenced locations.

##### 4.1. *Patterns of Use Study* (b) (4)

The Patterns of Use (POU) study for the *proposed MRTPs* was a (b) (4) study investigating various aspects of product use behavior, including reasons for use, amongst both users and non-users of the *proposed MRTPs*. Those who used the *proposed MRTPs* during the study reported using an average of (b) (4). The number of people who used cigarettes or moist snuff every day or some days at week 1 decreased by the end of the study, while the number of people reporting using only the *proposed MRTPs* increased over the course of the study. Use of all other tobacco or nicotine products (TNPs) decreased. (b) (4) of *proposed modified risk product* users reported complete substitution (defined as starting the study using the *proposed MRTPs* and another TNP, but only using the *proposed MRTPs* (b) (4) with the *proposed MRTPs*, while (b) (4) of *proposed MRTp* users

<sup>6</sup> These data are in the cross-referenced (b) (4)

<sup>7</sup> Relevant data and information from (b) (4)

and (b) (4)

<sup>8</sup> Additional data and information (b) (4)

and (b) (4)

and (b) (4) of (b) (4) reported quitting all TNPs (defined as recording zero TNP use in (b) (4)). This study shows the *proposed MRTPA's* can help users transition away from using more harmful products, like cigarettes, (b) (4). Additionally, (b) (4) of respondents said they use the *proposed MRTPA's* to help reduce cigarette smoking, (b) (4) said to help quit smoking, and (b) (4) said the products are less harmful to their health compared to cigarettes. These data demonstrate users understand the continuum of risk and using an oral nicotine product may reduce their risk of developing serious health conditions like mouth cancer, lung cancer, and heart disease.

#### 4.2. Likelihood of Use Study (b) (4)

The Likelihood of Use (LOU) study investigated label comprehension, risk perceptions, and intentions to buy the *proposed MRTPA's* after exposure to stimuli in both users and non-users of TNP. Results showed a high level of label comprehension across all populations, including understanding the product contains nicotine and nicotine is an addictive chemical. Generally, intentions to buy the *proposed MRTPA's* was low in both the 21-24 and 24+ age groups of non-users, but intentions to buy were the lowest amongst former TNP users, suggesting former and non-users of TNPs are unlikely to initiate or re-initiate use of TNPs after being exposed to the *proposed MRTPA's*. Observed intentions to buy were highest amongst the cohorts of current cigarette smokers with the intention to quit smoking, suggesting smokers understand using non-combusted TNPs, like the *proposed MRTPA's*, may provide a benefit to their overall health by reducing their risk of developing serious diseases.

#### 4.3. (b) (4) ZYN User Profile Study

The ZYN user profile study collected information on the use behavior of light, medium, and heavy users of the *proposed MRTPA's*, including changes in dual use behavior, and investigated if there were any major differences in use behavior amongst users of 3 mg pouches and 6 mg pouches. In general, the study found dual users reported decreased usage of other TNPs, including cigarettes, once starting to use ZYN. (b) (4) of *proposed MRTPA* users who smoke combusted cigarettes at the time they began using the *proposed MRTPA's*, reported not having smoked in the past 30 days. The (b) (4) of the population (b) (4) who continued to smoke while using the *proposed MRTPA's* reported reducing their cigarette consumption over the study and most had reduced overall cigarette consumption (b) (4). (b) (4) The study also found (b) (4) (b) (4) when comparing across nicotine strengths (3 mg or 6 mg users) and across flavor varieties, indicating the major use behavior changes caused by beginning use of the *proposed MRTPA's* are a reduction in the number of combusted products consumed over time.

#### 4.4. Conclusions based on previous data for *proposed MRTPA's*

Respondents in the LOU and POU studies conveyed an understanding of the continuum of risk when considering use of TNP, *proposed MRTPA's*, and cigarettes. Across all health conditions (adult tooth loss, mouth cancer, gum disease, and serious health problems), most respondents perceived low/minimal absolute risk to human health for never using TNPs, low-to-moderate absolute risks to human health for using only the *proposed MRTPA's*, and moderate-to-very high absolute risks for continuing to smoke cigarettes. Users in the POU study and the ZYN user profile study demonstrated a continued decrease in use of other TNPs, including cigarettes, when using the *proposed MRTPA's*, with some demonstrating completely quitting cigarettes or all TNPs across the studies. Data from the LOU study shows the highest intentions to buy, and thus likelihood to use, the *proposed MRTPA's* were found amongst current adult cigarette smokers with the intention to quit smoking. These data demonstrate a clear benefit to users and the population as a whole, as using the *proposed MRTPA's* allowed current adult TNP consumers to decrease their consumption of combusted cigarettes, and there was minimal to no risk of uptake of the *proposed MRTPA's* or any TNPs observed amongst non-users and former TNP users. While these studies

did not investigate the proposed reduced risk claim specifically, they demonstrate a high level of understanding amongst both users and non-users of TNPs that cigarettes pose a higher risk to health, and switching completely to the *proposed MRTPs* presents a much lower risk to their health, compared to cigarettes.

## 5. TOBACCO PRODUCT PERCEPTIONS AND INTENTIONS TO USE STUDY

SMNA 5240072 is a survey study to assess perceptions of and likelihood to use the *proposed MRTPs* with the proposed reduced risk claim among 3400 U.S. adults (21+) in five cohorts: current combusted cigarette smokers, former users of TNPs other than combusted cigarettes or smokeless tobacco, non-established<sup>9</sup> users (b) (4),<sup>10</sup> non-established users from (b) (4), current smokeless users. Complete method information and results are in Module 6.2 of these MRTPAs. Briefly, results show the claim is well-understood among current, former, and non-established TNP users, and the claim language raised awareness of the lower risks of developing seven critical health conditions (i.e., lung cancer, heart disease, mouth cancer, throat cancer, emphysema, stroke, and chronic bronchitis) when using the *proposed MRTPs* compared to continued cigarette use. The results show this increased awareness of lower risk potential after using the *proposed MRTPs* did not result in increased likelihood to initiate or reinstate TNP use or uptake among vulnerable populations, including former and non-established TNP users. Additionally, respondents perceived highest absolute risks for daily use of cigarettes and lowest absolute risks for NRTs and cessation; respondents generally perceived use of the *proposed MRTPs* as a low-to-moderate risk for developing the majority of these health conditions.

## 6. PUBLIC HEALTH IMPACT MODEL (PHIM)

Complete data and summary information related to the PHIM developed for nicotine pouches, including the *proposed MRTPs* can be found (b) (4).<sup>11</sup> Further summary of the PHIM data can be found in the (b) (4).<sup>12</sup> Briefly, even under the most pessimistic assumptions, the PHIM shows uptake of the *proposed MRTPs* and associated decline in smoking, (b) (4)

## 7. USER POPULATIONS AND MARKETING CONTROLS

The intended user populations for the *proposed MRTPs* and *authorized MRTPs* are current adult tobacco or nicotine product users. Our extensive behavioral data summarized in sections 3 through 5 above demonstrate both product lines are used primarily by the same user population (current adult TNP users), while posing minimal risk of product uptake by unintended user populations (i.e., former and never TNP users). These data are further supported by the literature summarized in section 8 below. Most importantly, marketing of the *proposed MRTPs*, similar to that of the *authorized MRTPs*, has not resulted in significant use by youth and young adults under the age of 21.

To limit underage exposure to the *proposed MRTPs*, we have very robust marketing controls in place, including:

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<sup>9</sup> Non-established is defined as using < 100 tobacco product units in lifetime and not using any in last 30 days.

<sup>10</sup> Users between 21-24 years old were oversampled in this study. We do not recruit underage youth and young adults for our studies due to ethical concerns. Therefore, we oversample in the 21-24 age group as a way to bridge to assessment of risk perceptions and use intentions among underage youth and young adults.

<sup>11</sup> PHIM data and information are (b) (4)

<sup>12</sup> Referenced information is (b) (4)



- Prohibition on the use of social media influencers.
- Refusal of all requests for influencer partnerships.
- Use of third-party age verification mechanisms for access to our owned digital platforms and for sales made online.
- Support of development of age verification technology at point-of-sale.
- Use of independent age verification systems to restrict access to digital advertising from anyone under 21 years of age.
- Advertisements featuring only individuals who are, and appear to be, at least 35 years old.

(b) (4)

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The effectiveness of our marketing controls is confirmed by results of the independent research and analyses. Data for nicotine pouch use has only been tracked in the National Youth Tobacco Survey (NYTS) since 2021; however, reporting shows consistently low youth use of nicotine pouches across all three years (1–1.5%), especially in comparison to youth use of e-cigarettes (7.6–9.4% over the same time period)<sup>14,15,16</sup>, which remain the most popular tobacco product amongst youth. Despite the popularity of these products among youth, FDA has granted marketing orders for several e-cigarette products.<sup>17,18,19,20</sup> Additionally, nicotine pouch youth use rates are comparable to those observed for smokeless tobacco, which includes snus, across the same three-year time period (0.96%–1.5%). Results from the Altria Client Services Underage Tobacco Use Study (UTUS), a repeated cross-sectional survey collecting data on underage tobacco use on a quarterly basis, were similar to those based on NYTS data.<sup>21</sup> Nicotine pouch use estimates remained low throughout the May 2020 – August 2022 UTUS study period, at less than 0.5% among youth (ages 13–17) and 1.7% or less among

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(b) (4)

<sup>14</sup> Gentzke AS, Wang TW, Cornelius M, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students — National Youth Tobacco Survey, United States, 2021. *MMWR Surveill Summ* 2022;71(No. SS-5):1–29. DOI: <http://dx.doi.org/10.15585/mmwr.ss7105a1> external icon.

<sup>15</sup> Park-Lee E, Ren C, Cooper M, Cornelius M, Jamal A, Cullen KA. Tobacco Product Use Among Middle and High School Students — United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1429–1435. DOI: <http://dx.doi.org/10.15585/mmwr.mm7145a1>.

<sup>16</sup> Birdsey J, Cornelius M, Jamal A, et al. Tobacco Product Use Among U.S. Middle and High School Students — National Youth Tobacco Survey, 2023. *MMWR Morb Mortal Wkly Rep* 2023;72:1173–1182. DOI: <http://dx.doi.org/10.15585/mmwr.mm7244a1>.

<sup>17</sup> Scientific Review of PMTA under Section 910(c) of the FD&C Act — Technical Project Lead, available at: <https://www.fda.gov/media/169527/download>.

<sup>18</sup> Scientific Review of PMTA under Section 910(c) of the FD&C Act — Technical Project Lead, available at: <https://www.fda.gov/media/164458/download>.

<sup>19</sup> Scientific Review of PMTA under Section 910(c) of the FD&C Act — Technical Project Lead, available at: <https://www.fda.gov/media/165236/download>.

<sup>20</sup> Scientific Review of PMTA under Section 910(c) of the FD&C Act — Technical Project Lead, available at: <https://www.fda.gov/media/165234/download>.

<sup>21</sup> Cheng, H.G., Vansickel, A.R. & Largo, E.G. Awareness and use of tobacco products among underage individuals: findings from the Altria Client Services underage tobacco use survey 2020–2022. *BMC Public Health* 23, 662 (2023). <https://doi.org/10.1186/s12889-023-15610-1>.

underage young adults (ages 18–20). The most recent Monitoring the Future (MTF) data<sup>22</sup> shows nicotine pouch use is as low as 0.4% among 8<sup>th</sup> graders, and 1.4% among 12<sup>th</sup> graders. Of the nine other similar substances tracked in MTF, eight had higher use prevalence amongst 8<sup>th</sup> through 12<sup>th</sup> graders than nicotine pouches, including both “vaping nicotine” and “cigarettes.” In comparison, MTF data from 2017 was provided in the MRTPA for Copenhagen Snuff Fine Cut, a recently FDA-authorized MRTP, showing use prevalence of smokeless tobacco products was at 3.5% among 8<sup>th</sup> through 12<sup>th</sup> graders. Therefore, current youth use of the nicotine pouch category is even lower than for the smokeless tobacco product category when FDA authorized Copenhagen® Snuff Fine Cut as an MRTP.

Thus, multiple years of U.S. survey data from multiple sources demonstrate the *proposed MRTPs* are not being used by youth based, in part, on our robust marketing controls to restrict youth access to our products. Additionally, our behavioral study data demonstrates the products are being used by the intended population – current adult TNP users – and this evidence shows a willingness for adults to switch from cigarettes to the *proposed MRTPs*. This evidence also further demonstrates their understanding of the potential benefits to their health if they switch away from cigarettes to the *proposed MRTPs*.

## 8. POPULATION HEALTH LITERATURE

A systematic literature review conducted on the published population health literature related to nicotine pouches can be found in the (b) (4).<sup>23</sup> Additionally, several publications especially relevant to this application are highlighted below.

The Centers for Disease Control and Prevention (CDC) published a summary of data and results from the 2023 NYTS in the Morbidity and Mortality Weekly Report (MMWR) on November 3, 2023.<sup>16</sup> Discussion of the nicotine pouch data, including year to year comparisons since 2021 (the first year nicotine pouch use was individually tracked), is in the (b) (4).<sup>24</sup> Additional discussion of these data are in section 7 above.

A 2023 Vogel, et al.<sup>25</sup> study published randomized controlled trial results investigating the effect of the proposed modified risk claim on perceptions and intentions to use the 3 mg *proposed MRTPs* among young adults (defined as ages 21-34 in this study; average = 24.5) who use inhalable nicotine and tobacco products (e.g., e-cigarettes, cigarettes). This independent study found use of the claim increased intentions to use the *proposed MRTPs* and increased perceptions the *proposed MRTPs* are less harmful than cigarettes. The authors hypothesized flavored nicotine pouches would be perceived as less harmful than Smooth pouches (unflavored); however, results showed flavor did not impact harm perceptions of the *proposed MRTPs*. The authors also noted the appealing flavors and use of the MRTP claim could “facilitate transition to [oral nicotine products] among those unready to quit nicotine/tobacco use, potentially conferring a harm reduction benefit.” A notable limitation of the study

<sup>22</sup> Miech, R. A., Johnston, L. D., Patrick, M. E., O’Malley, P. M., & Bachman, J. G. (2023). Monitoring the Future national survey results on drug use, 1975–2023: Secondary school students. Monitoring the Future Monograph Series. Ann Arbor, MI: Institute for Social Research, University of Michigan. Available at <https://monitoringthefuture.org/results/annual-reports/>

<sup>23</sup> (b) (4)

<sup>24</sup> Relevant information is in (b) (4)

<sup>25</sup> Vogel, E. A., Tackett, A. P., Unger, J. B., Gonzalez, M. J., Peraza, N., Jafarzadeh, N. S., Page, M. K., Goniewicz, M. L., Wong, M., & Leventhal, A. M. (2023). Effects of flavour and modified risk claims on nicotine pouch perceptions and use intentions among young adults who use inhalable nicotine and tobacco products: a randomised controlled trial. Tobacco control, tc-2023-058382. Advance online publication. <https://doi.org/10.1136/tc-2023-058382>



is the small sample size ( $n = 47$ ) and only four flavor varieties and one nicotine strength of the *proposed MRTPs* in plain packaging, were tested in this study. While the strength of results is limited due to the small sample size, the study demonstrated young adults understand the claim language and perceive the *proposed MRTPs* as less harmful than cigarettes. Additionally, intentions to switch completely away from inhalable nicotine products to nicotine pouches were higher amongst those exposed to the claim language, demonstrating the reduced risk claim can help inform users of the potential benefit to their health if they switch completely away from combusted products.

A review by Grandolfo, et al.<sup>26</sup> discusses nicotine pouches in the context of tobacco harm reduction, comparing available data between nicotine pouches, snus, and cigarettes. In regard to population health benefits of nicotine pouches, the review demonstrated nicotine pouches appeal most to and are used most often by adult consumers of tobacco and nicotine and are not frequently used by youth or young adults. The review concludes current patterns demonstrate nicotine pouches are reaching current adult consumers, while posing minimal risk for youth appeal and youth uptake of the products. Combined with the extensive non-clinical and clinical evidence demonstrating lower toxicants from nicotine pouches compared to snus and cigarettes, the review concludes nicotine pouches are a strong tobacco harm reduction candidate.

#### 9. POST-MARKET SURVEILLANCE STUDIES (PMSS) PLAN FOR *PROPOSED MRTPs*

(b) (4)

Namely, (b) (4)

Additionally, we will regularly report sales and distribution data, product safety information (including AE reporting), and relevant marketing materials to FDA. Due to the similarities between the *proposed MRTPs* and *authorized MRTPs*, (b) (4)

to comply with the requirements and submit the protocol to FDA for approval before beginning studies.

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<sup>26</sup> Grandolfo E, Ogden H, Fearon I M, et al. (February 15, 2024) Tobacco-Free Nicotine Pouches and Their Potential Contribution to Tobacco Harm Reduction: A Scoping Review. *Cureus* 16(2): e54228. doi:10.7759/cureus.54228