January 22, 2026
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Modified Risk Tobacco Product Applications (MRTPAs)
MR0000268
Swedish Match USA, Inc.

Office of Science
Center for Tobacco Products
Food and Drug Administration

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Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Benjamin Apelberg, Ph.D., M.H.S., Deputy Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for January 26, 2026, discussion of Swedish Match USA, Inc. MRTPAs for 20 ZYN nicotine pouch products (FDA Submission Tracking Number MR0000268)

1. Introduction

1.1. Regulatory Background

We would like to thank the TPSAC members in advance for their efforts to provide recommendations to FDA on the modified risk tobacco product applications (MRTPAs) submitted by Swedish Match USA, Inc.

On April 5, 2024, FDA received MRTPAs from Swedish Match USA Inc. for 20 of its ZYN nicotine pouch products, which state that the company is seeking risk modification orders under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to market their ZYN products, hereafter referred to as ZYN, with the following modified risk claim: "Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." See Appendix A for information on the statutory requirements for modified risk tobacco products (MRTPs). These products received marketing authorizations through the premarket tobacco product application (PMTA) pathway on January 16, 2025.

The applicant describes ZYN as 400 mg sealed pouches containing tobacco-derived nicotine in a salt formulation, along with flavor ingredients, an artificial sweetener, stabilizers, fillers, and pH adjusters, and without any whole, cut, or ground tobacco. The products come in two nicotine levels, 3 mg and 6 mg. The applicant states ZYN has the same intended use as General Snus, which received MRGOs with the same modified risk claim; the product is held between the lip and gum for a period of use and then discarded.

FDA evaluates all information and statements on the proposed label, labeling, and advertising submitted by the applicant as part of the Agency's scientific review. In addition to determining whether the proposed modified risk claim is scientifically accurate and consumers understand it, FDA must assess, when determining whether to issue an order under 911(g)(1) of the FD&C Act, whether the product, as it is actually used, will significantly reduce harm and the risk of tobacco-related disease to individual users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

FDA is reviewing the scientific information submitted in the MRTPA to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met (Appendix A).

The evidence submitted by the applicant includes data from chemical analyses of the product; clinical and epidemiological evidence; a study of consumer understanding, perception, and behavioral intentions; and other scientific information. FDA also takes relevant public comments into consideration in accordance with Section 911(e).

1.2. Draft Topics for TPSAC Discussion

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

Discussion 1: Discuss whether the proposed modified risk claim is substantiated by scientific evidence.

Discussion 2: Discuss the available evidence about consumers' understanding of the proposed modified risk claim and their perceptions of ZYN.

Discussion 3: If ZYN is marketed with the proposed claim, discuss the evidence regarding the likelihood that people who currently use combusted cigarettes will completely switch to ZYN and/or will dual use ZYN and combusted cigarettes long-term.

Discussion 4: If ZYN is marketed with the proposed claim, discuss the evidence regarding the likelihood that persons who do not use tobacco products will start using ZYN.

The following sections provide a summary and preliminary evaluation of the evidence provided in the MRTPA relevant to the foregoing topics.

2. Preliminary FDA Review Findings

2.1. Relative Health Risks to Individuals

This section describes and assesses the evidence submitted related to the relative health risks of ZYN to individuals who use tobacco. The constituent profile of the product is presented, followed by clinical and epidemiological evidence of potential health risks associated with product use.

2.1.1. Harmful and Potentially Harmful Constituents (HPHCs) and Biomarker Data

2.1.1.1. HPHCs

In 2012, FDA published a preliminary list of Harmful and Potentially Harmful Constituents (HPHCs),[1] which are chemicals or chemical compounds in tobacco products or tobacco smoke or emissions that are or potentially are inhaled, ingested, or absorbed into the body as an aerosol or any other emission, and that cause or could cause direct or indirect harm to users or nonusers of tobacco products. In the PMTA decision summary supporting the Marketing Granted Orders (MGOs) for ZYN (January 16, 2025), testing results showed that levels of 36 of the 42 HPHCs reported for ZYN are below the limit of quantification. The chemistry review of the PMTAs concluded that all testing methods used to measure HPHCs were validated and fit for purpose. The HPHCs that were quantifiable in at least one of the products were acetaldehyde, coumarin, formaldehyde, naphthalene, nicotine, and nornicotine. However, from a toxicological perspective, the levels of these HPHCs were below the level that would be expected to pose a health risk. Levels of nearly all HPHCs reported were lower in ZYN than in the comparison products, including General Snus. Notably, General Snus products contain quantifiable levels of N'-

[1] https://www.fda.gov/tobacco-products/products-ingredients-components/harmful-and-potentially-harmful-constituents-hphcs

nitrosonornicotine (NNN), nicotine-derived nitrosamine ketone (NNK) and higher levels of nitrite (a precursor of tobacco-specific nitrosamines [TSNAs]) and nornicotine (a precursor of NNN) compared to ZYN (2025 PMTA decision summary). The main comparator is combusted cigarettes based on the proposed modified risk claim. However, the applicant did not provide a direct HPHC comparison between ZYN and any comparator combusted cigarette product. Therefore, FDA compared the constituent data, including HPHC data, in ZYN to those in the mainstream smoke (MSS) of the 1R6F reference combusted cigarette generated under both the International Organization for Standardization (ISO) non-intense (ISO 3308, 2012) and ISO intense (ISO 20778, 2018) smoking regimens. The constituent data for 1R6F MSS were obtained from its certificate of analysis[2] and from two scientific publications (Forster et al., 2018; Jaccard et al., 2019). A direct comparison of the HPHCs measured in Zyn filler and 1R6F combusted cigarette MSS indicates that with limited exceptions (i.e., nicotine, coumarin), all HPHCs were lower in ZYN.

2.1.1.2. Cross-sectional biomarker study (SM22-03)

The cross-sectional biomarker study (SM22-03) was a non-randomized, multi-center investigation conducted in Sweden in January-March 2023 to assess biomarkers of exposure and biomarkers of potential harm among different tobacco use groups. The study enrolled 198 healthy adults ages 25-45 across four groups: exclusive Swedish Match-brand nicotine pouch use (50 participants), exclusive Swedish snus use (48 participants), exclusive combusted cigarette use (50 participants), and no tobacco use (50 participants). Participants used their selected products exclusively for 14 days while recording usage patterns, with blood and urine samples collected (at Day 1 for the no tobacco use group and Days 1 and 14 for the tobacco use groups) for biomarker analysis. Key findings revealed that the Swedish Match-brand nicotine pouch group had biomarker profiles similar to the group that did not use tobacco and consistently lower than the combusted cigarette group. Specifically, biomarkers of the TSNAs 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and NNN, were often below quantifiable limits for nicotine pouch use, comparable to no tobacco use, and higher for both snus and combusted cigarette use. Additionally, 3-OH-B[a]P, the biomarker of the carcinogenic benzo[a]pyrene, was lower among adults who use nicotine pouches compared with those who use combusted cigarettes. Moreover, biomarkers of potential harm, including those related to inflammation and oxidative stress, were generally lower for nicotine pouch use compared to combusted cigarette use and often comparable to no tobacco use. Nicotine-related biomarker concentrations in the Swedish Match-brand nicotine pouch group were similar to the snus use group but higher than cigarette use group.

However, the study's interpretability is limited. It was conducted in Sweden with Swedish brand nicotine pouch products. While the majority using nicotine pouch products used ZYN brand products (~65%), the products differed from the proposed MRTPs in terms of the variety of flavor and nicotine concentrations. Factors limiting generalizability include usage patterns in Sweden that may differ from those in the U.S. and a relatively young and healthy study population. The cross-sectional design prevents establishing causal relationships. Additionally there were no adjustments for potentially confounding sociodemographic or behavioral variables that may explain group differences.

Nevertheless, the results of this biomarker study align with the recently published cross-sectional study by Azzopardi et al. (2023) and sponsored by British American Tobacco, which documented substantially lower TSNAs, polycyclic aromatic hydrocarbons (PAHs), and other biomarkers in adults using the Velo pouch compared to those smoking combusted cigarettes. Another recently published paper by Dai et al. (2025) based on Population Assessment of Tobacco and Health Study (PATH) Wave 7 (2022-2023) data

[2] Certificate of Analysis for 1R6F Certified Reference Cigarette.
https://ctrp.uky.edu/assets/pdf/webdocs/1R6F%20Certificate%20of%20Analysis.pdf. Accessed May 15, 2025.

also observed higher cotinine concentrations in adults using nicotine pouches compared to those smoking combusted cigarettes, corroborating the nicotine biomarker patterns observed in the SM22-03 analysis. Together, this biomarker evidence is consistent with HPHC data indicating that nicotine pouches present lower toxicant exposure than combusted cigarettes while delivering comparable amounts of nicotine.

2.1.2. Evidence of Potential Health Risks

Nicotine pouches are a novel type of oral tobacco product, and as such, long-term health data specific to these products remain limited. The applicant did not submit any observational or clinical studies directly evaluating health outcomes associated with ZYN use. Instead, the applicant referenced data pertaining to snus, a smokeless tobacco product. As described in the 2025 PMTA decision summary supporting the MGOs for ZYN, the applicant's justification for applying the published literature on the long-term health effects of Swedish snus use to ZYN use was based on similarities in use topography and systemic nicotine exposure. The applicant lists the following similarities between Swedish snus and ZYN:

Product characteristics

- Both products are pouched and thus have a similar appearance.
- Both are manufactured by the applicant under similar quality management systems.
- Both have similar types of flavors.
- Nicotine content, pH, route of exposure, and exposure levels are comparable.

Use patterns

- Both Swedish snus and ZYN products are non-combusted and used by placing them in the oral cavity where nicotine dissolves in saliva and is absorbed through the mouth's mucous membrane.
- Both have similar use patterns such as frequency of use, duration of use, and amount used.

Consumer characteristics

- Many consumers who use ZYN previously used moist snuff.

As mentioned above, however, product testing showed that levels of nearly all HPHCs reported were lower in ZYN than in Swedish snus. The biomarker study SM22-03 further supports that using ZYN exposes individuals who use the product to lower levels of HPHCs than using Swedish snus.

As concluded in the 2019 General Snus MRTPA decision summary, issued on October 22, 2019, the available epidemiological evidence on Swedish snus demonstrates that, compared to combusted cigarette smoking, exclusive Swedish snus use is associated with significantly lower risks of several smoking-related diseases, including oral cancer, lung cancer, heart disease, stroke, and chronic obstructive pulmonary disease (COPD) . Since the ZYN products have similar use patterns but lower HPHC levels compared to Swedish snus, the applicant reasoned that the long-term health effects of the ZYN products are likely to be lower than the health effects of Swedish snus.

2.1.2.1. Mouth Cancer

FDA concluded in the 2016 and 2019 General Snus MRTPA decision summaries (November 2, 2016 and October 22, 2019, respectively) and the 2024 General Snus MRTPA renewal decision summary (November 7, 2024) that the risk of developing oral cancer is substantially lower in adults who exclusively use Swedish snus than in adults who smoke combusted cigarettes. The applicant submitted a

2020 pooled analysis of nine Swedish cohort studies, which found that ever snus use was not associated with oral cancer when compared to never snus use (adjusted hazards ratio [aHR] 0.90; 95% CI: 0.74–1.09), including adults who never smoked (HR 0.87; 95% CI: 0.57–1.32) (Araghi et al., 2021) (2024 MRTPA renewal decision summary). The results align with previous epidemiological reviews of Swedish data indicating no clear association between Swedish snus use and oral or pharyngeal cancer risk. In comparison, combusted cigarette smoking is associated with about 11 times the risk of oral cancer than that in adults who never smoked (2019 MRTPA decision summary).

2.1.2.2. Heart Disease

The 2016 and 2019 General Snus MRTPA decision summaries and the 2024 General Snus MRTPA renewal decision summary reported that adults who use snus may have elevated cardiovascular risk compared to those who do not use tobacco; however, the risk was substantially lower than that of adults who smoke. Most recently, a meta-analysis found no significant increase in the risk of ischemic heart disease or acute myocardial infarction among adults who currently use Swedish snus and never smoked (Lee et al., 2022). A prospective cohort study (Yuan et al., 2022) found that Swedish snus use was not associated with peripheral artery disease (HR 0.88; 95% CI: 0.66–1.17) while combusted cigarette smoking was strongly associated (HR 4.01; 95% CI: 3.17–5.08). The study also showed that adults who formerly smoked and adults who currently smoked combusted cigarettes remained at elevated risk of peripheral artery disease compared to adults who never smoked. A pooled analysis found that among adults who never smoked combusted cigarettes, exclusive current snus use compared to never tobacco use was associated with increased cardiovascular disease (CVD) mortality (aHR 1.27, 95% CI: 1.15-1.41) (Byhamre et al., 2021). In comparison, combusted cigarette smoking is associated with 2.5 to 3 times the risk of dying from CVD compared to adults who never smoked combusted cigarettes (Thun et al., 2013).

By activating the sympathetic nervous system, nicotine causes acute cardiovascular effects such as increased heart rate and blood pressure, but there is currently no consistent evidence to suggest these changes lead to long-term cardiovascular risk (Dennison Himmelfarb et al., 2025). In a recent analysis of PATH biomarker data, adults who use smokeless tobacco had higher nicotine biomarker concentrations but lower inflammatory and oxidative stress biomarker concentrations compared with adults who smoke combusted cigarettes, suggesting that CVD risk may be driven by tobacco constituents other than nicotine (Rezk-Hanna et al., 2022).

2.1.2.3. Stroke

An FDA-led systematic review and meta-analysis (Rostron et al., 2018) found that in Swedish studies of adults who never smoked combusted cigarettes, current snus use was not linked to increased stroke risk (RR = 1.04; 95% CI: 0.92–1.17; n = 1). In contrast, U.S. studies of smokeless tobacco use in people who never smoked showed a higher stroke risk (RR = 1.28; 95% CI: 1.01–1.62; n = 3). In comparison, the risk of dying from stroke is twice as high among people who smoke combusted cigarettes compared to those who never smoked (Thun et al., 2013). While evidence is mixed, the totality of the evidence together suggests the risk of stroke is lower in adults who use snus than in those who smoke combusted cigarettes.

2.1.2.4. Lung Cancer

The 2016 and 2019 General Snus MRTPA decision summaries concluded that Swedish snus use does not significantly increase the risk of lung cancer. In a cohort of never-smoking Swedish construction workers, Luo et al. (2007) reported a relative risk of 0.8 (95% CI: 0.5–1.3) for lung cancer among adults who use snus compared with those who do not use tobacco. Earlier work by Bolinder et al. (1994) also found no

excess lung cancer risk among adults who use snus. In contrast, the risk of dying from lung cancer is 25 times higher among adults who smoke combusted cigarettes than those who do not smoke (Thun et al., 2013). Collectively, these findings demonstrate that exclusive Swedish snus use is not associated with increased lung cancer risk and that the risk is substantially lower than with combusted cigarette smoking. Given that nicotine pouches likewise do not involve inhalation or combustion, the risk of lung cancer is also expected to be lower for nicotine pouch use relative to combusted cigarette use.

2.1.2.5. Emphysema and Chronic Bronchitis

As summarized in the 2016 and 2019 General Snus MRTPA decision summaries, use of smokeless tobacco products like snus is not expected to cause respiratory disease, including emphysema and chronic bronchitis, which is associated with inhaled toxicants. Literature submitted in support of the General Snus MRTPAs (Schivo et al., 2014; Stevenson et al., 2006) indicates no association between smokeless tobacco product use and chronic respiratory disease. In contrast, combusted cigarette smoking is associated with 22-25 times the risk of dying from COPD as having never smoked (Thun 2013).

2.1.2.6. Adverse Experiences

The authorized products are packaged in polypropylene cans, consistent with 21 Code of Federal Regulations (CFR) 177.1520(c), with certified child-resistant safety lids to reduce risk of accidental exposure in children. The applicant states that the primary container is designed to be child-resistant: the consumer opens the can by breaking the label perforation and twisting the lid to align the top and bottom arrows on the can to lift the lid. Child-resistant packaging testing was performed and certified by Institut für Kindersicherheit im in Hamburg, Germany according to the requirements of 16 CFR 1700.20 (Test procedure for special packaging), certifying that the 195-1 CR Snuff Containers for the authorized products are child-resistant. In the 2025 ZYN PMTA decision summary, the TPL concluded that based on summative information from the toxicology, engineering, and medical reviews, the new products have lower HPHC levels compared to General Snus; hence, the potential adverse experiences from product misuse were not expected to be greater than those produced by similar smokeless tobacco products.

America's Poison Centers National Poison Data System (NPDS) is a data repository containing case information collected from contact to regional poison control centers serving all 50 states and U.S. territories. All interactions with poison control centers are managed by trained and certified specialists. Information on nicotine pouch exposure cases (reports or reported incidents by persons who contact poison centers regarding an exposure to a substance) is recorded based on product codes, which are available for several nicotine pouch brands. During the three-year period from April 1, 2022, to March 31, 2025, the number of reported U.S. nicotine pouch exposure cases steadily increased from 181 cases in the second quarter of 2022 to 906 cases in the first quarter of 2025. Among cases including age information, 74.2% occurred among children ages <5, 3.0% among youth ages 5-11, 1.7% among adolescents ages 12-17, 6.34% among adults ages 18-24, and 14.8% among adults ages 25+.[3] Ingestion was the reported route of exposure for almost all cases involving nicotine pouch products (98.6%). Overall, 1.0% of nicotine pouch exposure cases resulted in hospital admissions, 14.4% were treated/evaluated and released at a healthcare facility, and the majority (79.9%) were not referred to a healthcare facility. Regarding medical outcome, approximately half of cases resulted in either a minor

[3] Missing or incomplete data are excluded in the percentage values for age. Data are considered missing or incomplete when no information is provided for the variable or when listed as an estimated age such as age ≤5 years, teen (ages 13-19), unknown child (≤19), 20s, and Unknown Adult (age ≥20). Four persons listed as being in their 30s and 40s are categorized as age ≥25.

effect[4] (19.0%) or no reported effect (28.1%); 50.6% of cases were not followed or unable to be followed. A major effect was experienced in three (0.06%) exposure cases. No cases of death were reported.

A recent publication also presented NPDS data from 2010-2023 and found that the rate of nicotine pouch ingestions increased by 763.1% from 2020 to 2023 among children younger than age 6. The same study found that ingestion of nicotine pouches, compared to other nicotine product types, was more likely to be associated with a serious medical outcome (OR 1.53, 95% CI 1.10-2.13) or medical admission (OR 2.03, 95% CI: 1.31-3.15) (Olivas et al., 2025). The increased rate of pediatric exposures of this category of product raises concerns about the growing potential for unintentional misuse.

2.1.3. Summary

2.1.3.1. Relative Health Risks and Scientific Accuracy of Modified Risk Claim

The majority of the 42 HPHCs reported for ZYN are below the limit of quantification. Consistent with the HPHC testing, the biomarker study (SM22-03) found that the level of the biomarker of the carcinogenic benzo[a]pyrene was lower among adults who use Swedish Match-brand nicotine pouches and those who use Swedish snus use compared with those who use combusted cigarettes. Additionally, biomarkers of the TSNAs NNAL and NNN are much lower among adults who use Swedish Match nicotine pouches compared with those who use combusted cigarettes or Swedish snus.

Nicotine pouches are relatively newer than other well-established tobacco product categories and there are currently no long-term epidemiological studies pertaining specifically to ZYN or nicotine pouch use. Thus, the applicant used the epidemiological evidence of the health effects associated with Swedish snus use to support its proposed claim, citing the many similarities such as use topography between the two types of products. In the 2025 ZYN PMTA decision summary, FDA reviewers concluded that the Swedish snus epidemiological studies were applicable to the health risks of ZYN. The published literature on the health risks of Swedish snus use relative to combusted cigarette smoking was summarized in the 2016 and 2019 General Snus MRTPA decision summaries. As concluded in the 2019 decision summary, the scientific evidence supported that compared to combusted cigarette smoking, exclusive snus use is associated with lower risk of the following health outcomes: mouth cancer, heart disease, stroke, lung cancer, emphysema, and chronic bronchitis. FDA's preliminary evaluation of the totality of the evidence described above suggests that the proposed modified risk claim "Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis" is scientifically accurate.

2.2. Consumer Understanding and Perceptions

This section presents the applicant's proposed communication of the modified risk information through the product's label, labeling, and advertising and assesses the applicant-submitted evidence to demonstrate consumer understanding of the proposed modified risk statement and the effect of the statement on risk perceptions of ZYN.

[4] On the basis of definitions provided by NPDS, patients experiencing a minor effect exhibit some signs and symptoms from the exposure, which would usually resolve rapidly, such as mild, self-limited gastrointestinal symptoms, without dehydration or transient cough. Persons experiencing a moderate effect exhibit more pronounced and prolonged signs and symptoms for which some form of treatment would be indicated, such as a high fever, disorientation, or gastrointestinal symptoms causing dehydration. Major effects from exposure are life-threatening or might result in severe signs and symptoms (e.g., repeated seizures, cardiac arrest, or respiratory arrest), severe disability, or disfigurement.

2.2.1. Labels, Labeling, and Advertising (LLA)

The applicant is proposing to use the modified risk claim: "Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." If it receives a modified risk granted order, the applicant indicated it intends to include the modified risk claim in product promotional material when appropriate, but not on the product labels or labeling. The applicant submitted a single example of an advertisement with the claim, a product concept used as stimuli in the applicant's Consumer Perceptions and Likelihood of Use study:

Figure 1. Sample advertising submitted by Swedish Match USA (Source: MRTPA Module 6.2.4).

2.2.2. Summary of SMNA 5240072 "Quantitative Study to Assess Perceptions of and Likelihood of Use of ZYN® with Modified Risk Claims Among US Adults"

2.2.2.1. Methods: design, sample, stimuli, measures, analyses

2.2.2.1.1. Study design

The applicant submitted a study titled SMNA 5240072 "Quantitative Study to Assess Perceptions of and Likelihood of Use of ZYN® with Modified Risk Claims Among US Adults," hereafter referred to as the Consumer Perceptions and Likelihood of Use study. This study was a web-based, quasi-experimental, pre-post test in which consumers were assigned to one of two study conditions based on which condition was "least-filled," resulting in non-random assignments. The two conditions involved viewing an advertisement with (test) or without (control) the modified risk claim. Respondents were assigned to a study condition, completed a pre-test, viewed their assigned advertisement, and completed a post-test. This study examined the following outcomes: intentions to use tobacco products, intentions to use ZYN (measured at post-test only) and nicotine pouches (measured at pre-test only), intentions to quit smoking, absolute and relative risk perceptions, and understanding of aspects of ZYN (e.g., minimum legal age for purchase, flavors, nicotine concentrations available).

2.2.2.1.2. Sample

The applicant drew the sample from unspecified consumer panels, with a final sample of 3,450 respondents. The applicant divided respondents into a test and a control group using a least-fill method based on quotas of tobacco product use and demographic characteristics. The applicant indicated it chose the least-fill method to ensure that the test and control conditions were demographically balanced. Table 1 in Appendix B provides information about the demographic profile of the treatment and control groups. The applicant created five respondent groups based on self-reported tobacco product use:

1. Combusted cigarette use (N=1,010)
    a. Smoked 100+ combusted cigarettes in lifetime and currently smoke every day or some days.
2. Former combusted cigarette use and/or current use of other tobacco products (N=610)
    a. Formerly used combusted cigarettes and now either do not use any tobacco products or use tobacco products other than combusted cigarettes or smokeless tobacco products.
    b. Never used combusted cigarettes and currently uses tobacco products other than combusted cigarettes or smokeless tobacco products.
3. Current smokeless tobacco use (N=610)
    a. Currently uses any type of smokeless tobacco product every day or some days and has not smoked 100+ combusted cigarettes in their lifetime.
4. Never regularly used tobacco in the general population (ages 21+) (N=610)
    a. Have used fewer than 100 tobacco product units in their lifetime and have not used any in the past 30 days.
5. Oversampling of young adults who never regularly used tobacco (ages 21-24) (N=610)
    a. Have used fewer than 100 tobacco product units in their lifetime and have not used any in the past 30 days.

Both the combusted cigarettes and current smokeless tobacco use groups included respondents who were currently using nicotine pouches. Almost 20% of adults who used combusted cigarettes and more than half of adults who currently used smokeless tobacco in the study reported using nicotine pouches every day or some days. Table 2 in Appendix B provides information about the rates of tobacco product use by these two groups. The former combusted cigarette use and/or current other tobacco product use group included both respondents currently using tobacco products and respondents not currently using tobacco products. The applicant did not provide any information about the type or frequency of tobacco product use in this group.

The applicant stratified its sample by these groups and used post-stratification weighting based on demographic characteristics of the U.S. adult population from the 2022 National Health Interview Survey (NHIS).

2.2.2.1.3. Stimuli

The study exposed respondents to two stimuli: a “shelf set” image of a retailer display of various tobacco products (including ZYN) and a “product concept” one-page marketing piece akin to a counter mat/point-of-sale display with a picture of the product, details about the product and different varieties available, strengths and flavors, as well as the required warning that nicotine is an addictive chemical.

The applicant exposed both the test and control groups to the same shelf set, but the test group version of the product concept included the proposed claim while the control group version did not.

2.2.2.1.4. Measures

The applicant conducted a total of 10 cognitive testing interviews of the instrument with respondents from the five respondent groups before fielding the study. The applicant did not provide results nor indicate whether or how the instrument was modified in response to cognitive testing findings.

The instrument included measures of the following: demographics, label comprehension, health literacy, relative risk perceptions, absolute risk perceptions, intentions to use nicotine pouches, intentions to use ZYN, and intentions to quit. Of note, the label comprehension questions included true/false items regarding nicotine strength variants of ZYN and whether ZYN is risk-free, meant to be used for more than one hour, and contains nicotine salts. Next, respondents answered multiple-choice questions assessing understanding of nicotine, its addictiveness and minimum legal age of purchase. The instrument did not include questions assessing comprehension of claim language directly (e.g., asking respondents who saw the claim what the language in the claim means).

2.2.2.1.5. Analyses

The applicant provided summary statistics for the primary variables of interest. These included counts and proportions for categorical variables and means, standard deviations, and 95% confidence intervals (95% CI) for ordinal and continuous variables. The applicant did not conduct any tests of statistical significance.

2.2.2.2. Understanding of the Risk Reduction Described in the Claim

Compared to those who did not view the claim, respondents who use combusted cigarettes who viewed the claim perceived ZYN to be less risky than combusted cigarettes for the health conditions mentioned in the claim, though the impact appeared to be modest. For example, Figures 2 and 3 below present the percentage of adults who use cigarettes and young adults (ages 21-23) who never regularly used tobacco who believe ZYN poses a higher, same amount, lower, or no risk of lung cancer and mouth cancer compared to cigarettes. Among adults who use combusted cigarettes, nearly 48% who saw the proposed claim (vs. 44% who did not) perceived ZYN to confer lower lung cancer risk than combusted cigarettes. Similarly, among young adults who never regularly used tobacco, 39% who saw the claim (vs. 35% who did not) perceived ZYN to carry lower lung cancer risk than combusted cigarettes. Among adults who were using cigarettes, 38.8% of the test group (vs. 35.1% of the control group) perceived ZYN to confer lower mouth cancer risk than cigarettes. Similarly, among young adults who never regularly used tobacco, 31.5% of the test group (vs. 21% of the control group) perceived ZYN to confer lower mouth cancer risk than cigarettes. The study yielded similar findings for the remaining five health conditions referenced in the proposed claim among both respondent groups that used and never regularly used tobacco.

Figure 2: Assessments of the relative lung and mouth cancer risk of ZYN compared to cigarettes among adults who currently use combusted cigarettes.

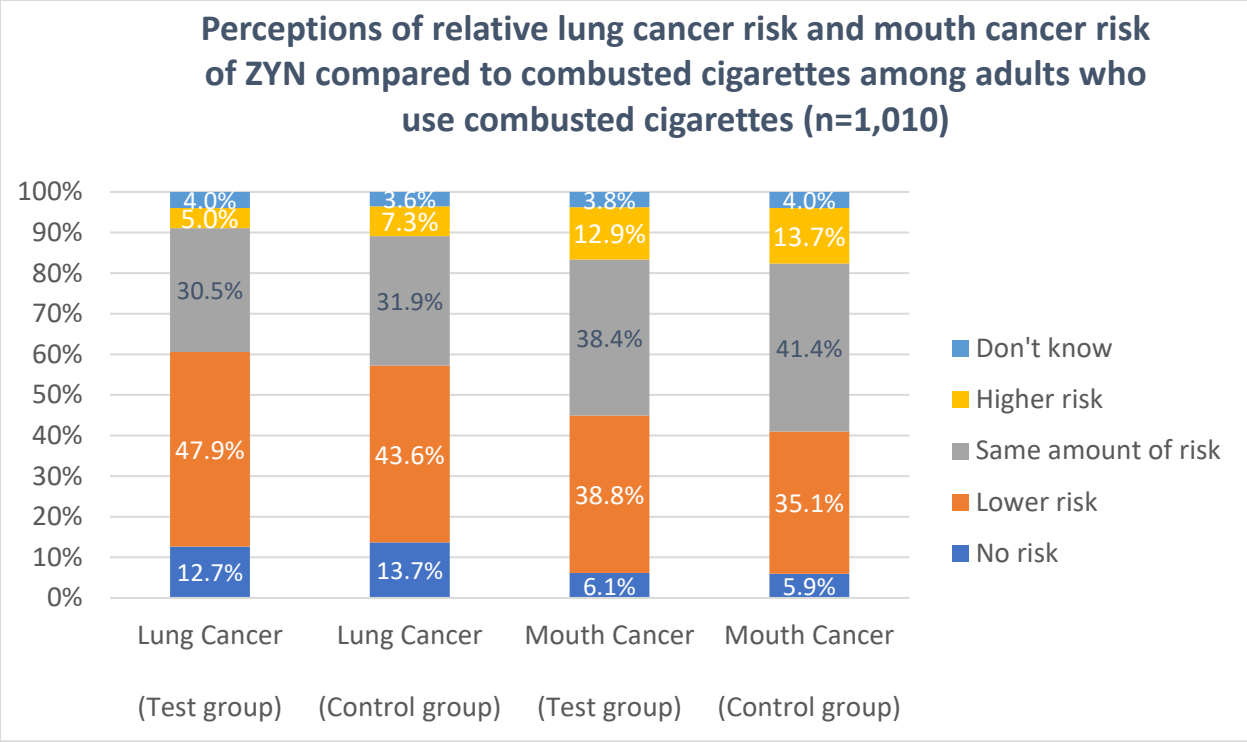
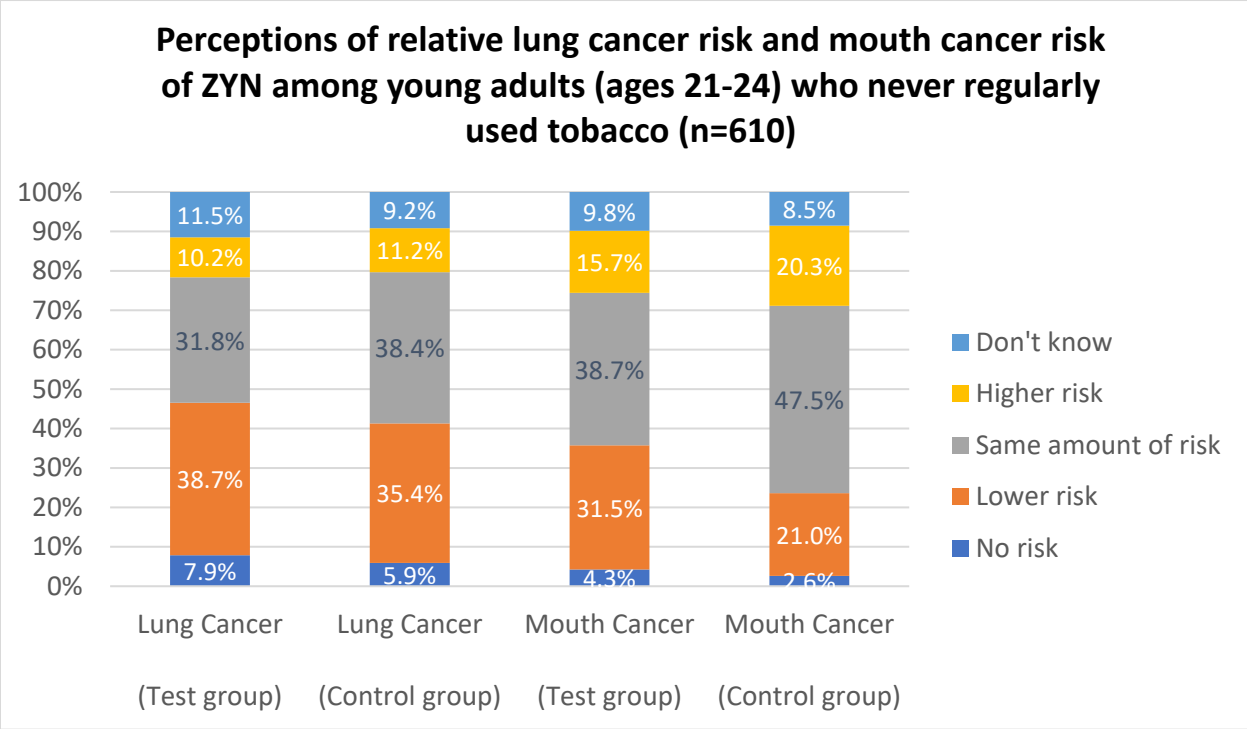


Figure 3: Assessments of the relative lung and mouth cancer risk of ZYN compared to cigarettes among young adults (ages 21-24) who never regularly used tobacco.



The applicant did not provide 95% CIs or other estimates of statistical variance that would have allowed FDA to determine whether relative risk perceptions of ZYN compared to combusted cigarettes statistically significantly differed between the test condition and the control condition.

The applicant's findings align with the broader research on perceptions of the relative risk of nicotine pouches. For example, a recent study tested the exact proposed claim on a blinded product: ZYN pouches were provided to respondents in a container with no product name or branded imagery on the label. This study found that, compared to respondents who did not see the claim, those who did see the proposed claim believed that using the nicotine pouch product was less likely to cause the health conditions in the claim compared to combusted cigarettes (Vogel et al., 2025).

2.2.2.3. Understanding that using ZYN still poses health risks

Although risk perceptions associated with ZYN were lower among respondents who viewed vs. did not view the proposed claim, the applicant's findings indicate consumers correctly understood that ZYN is not risk-free. Following exposure to the stimuli, the applicant measured absolute risk perceptions of ZYN for twelve health outcomes on a 5-point scale (ranging from 1 = "No Risk" to 5 = "Very High Risk"). Overall, regardless of health outcome and across all tobacco use groups and study conditions, respondents on average perceived ZYN to confer health risk (*M* = 2.6-3.9). The claim did not impact absolute risk perceptions of ZYN for any health condition among adults who use combusted cigarettes. Among young adults who never regularly used tobacco, the claim impacted absolute risk perceptions only for mouth cancer, with those who viewed (vs. did not view) the proposed claim perceiving ZYN to confer lower mouth cancer risk (*M* = 3.4, 95% CI: 3.3-3.5 vs. *M* = 3.7, 95% CI: 3.6-3.9). Additionally, respondents answered a true/false question that asked "Would you say ZYN is…" followed by four statements. The second statement was "is risk free". Across both the test and control groups, 82% of adults who use combusted cigarettes, 92% of young adults who never regularly used tobacco, and more than 76% of the other respondent groups answered "false" to this statement, indicating they perceived ZYN to confer health risk.

2.2.2.4. Understanding how to use ZYN to reduce risk

Examining whether consumers understand how to use ZYN to receive the health benefits described in the claim (i.e., that they need to completely switch from combusted cigarettes to ZYN) helps FDA evaluate whether the applicant has demonstrated that the proposed claim will enable the public to comprehend the information concerning modified risk. Of note, dual use of nicotine pouches and combusted cigarettes is fairly common: approximately one quarter of adults who currently use nicotine pouches also currently use combusted cigarettes (Reyes-Guzman et al., 2025; Palmer et al., 2025).

The applicant did not test whether consumers understood how to use ZYN to receive the health benefits described in the claim (i.e., complete switching from combusted cigarettes to ZYN). The applicant also did not assess how consumers perceive the health risks associated with incomplete switching from combusted cigarettes to ZYN. The proposed claim appears to specify how to use ZYN to confer lower risk of specific health conditions using the phrase "…instead of cigarettes".

However, as part of the current applications, the applicant cited the Perceptions and Behavioral Intentions (PBI) study submitted in the MRTPA for Swedish Match's General Snus products and evaluated by FDA in the 2019 General Snus MRTPA decision summary. Except for the product name, the proposed claim language for ZYN is identical to the claim tested in the PBI study and is currently in use as the General Snus modified risk claim. The General Snus PBI study included an item that asked adults who use combusted cigarettes how many combusted cigarettes they could smoke per day while also using

General Snus and still achieve lower disease risk. Findings indicated that a considerable proportion of consumers understood that they would need to switch completely to confer lower disease risk. Viewing the proposed claim increased the proportion of adults who smoke that responded "Zero (0) cigarettes," which the applicant defined as correct (young adults who smoke: 56% with the claim, 45% without the claim; older adults who smoke: 44% with the claim, 34% without the claim). At the same time, adding the proposed claim did not increase the proportion of adults who smoke who responded "Up to 5 cigarettes," "Up to 20 cigarettes," or "As many as you want to smoke." These findings suggest that, for General Snus, consumers demonstrated adequate understanding of what they need to do (i.e., completely switch) to receive the health benefits specified by the proposed claim. FDA expects the level of understanding of the clause "instead of" would remain the same in this context. Thus, FDA's preliminary evaluation of the evidence suggests the language "instead of cigarettes" used in the proposed claim for ZYN is adequately understood by consumers to indicate complete switching.

2.2.3. Summary

The applicant intends to market ZYN with the claim "Using ZYN instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis" on advertising, but not on labels or labeling.

The applicant conducted an online, quasi-experimental study of adults who use or do not use tobacco to assess consumer understanding of an advertisement and impact of the claim on risk perceptions. The instrument did not include direct questions about consumer understanding of the claim itself. Viewing the claim appeared to reduce relative risk perceptions of ZYN compared to combusted cigarettes for the health conditions mentioned in the claim, though the effect appeared to be small, and no tests of statistical significance were reported. Study findings also suggest that, even with these slight reductions in perceived relative risks, consumers appeared to understand that using ZYN poses some risk to health. Findings indicate, however, that regardless of claim exposure, many consumers still appeared to overestimate health risks associated with ZYN. Therefore, misunderstanding of the claim was not in the direction of underestimating the risks associated with ZYN.

The applicant did not test whether consumers understood how to use ZYN to receive the health benefits described in the claim (i.e., switch completely). The applicant also did not assess consumers' perceptions of the health risks associated with incomplete switching from combusted cigarettes to ZYN. However, the applicant cited a study of the same claim, in which consumers appear to have demonstrated adequate understanding of what they need to do (i.e., to completely switch) to receive the health benefits specified by the proposed claim.

2.3. Likelihood of Use and Impacts to the Population

This section uses estimates from national surveys and the applicant's own study to describe patterns of use of ZYN and nicotine pouches in the absence of modified risk information. The section then presents and assesses findings from the applicant's Consumer Perceptions and Likelihood of Use study designed to examine changes in intentions to use ZYN when respondents are presented with the proposed modified risk claim.

2.3.1. Use of ZYN without Modified Risk Information

2.3.1.1. Impacts on Those Currently Using Tobacco Products

2.3.1.1.1. National Surveys

Estimates from national surveys indicate that adult nicotine pouch use prevalence is currently relatively low. Data from the September 2022 Tobacco Use Supplement to the Current Population Survey (TUS-CPS) show that 0.4% of U.S. adults reported current use of nicotine pouches; among those, 24.8% reported current smoking, 33.8% reported former smoking, and 41.4% reported never smoking, but may have used other tobacco products. Current nicotine pouch use was most commonly reported among males, adults ages 18-34, non-Hispanic White individuals, people living in urban areas, and people with a household income of at least $75,000 a year (Reyes-Guzman et al., 2025). While the TUS-CPS does not include questions about brand preferences, ZYN was the most popular nicotine pouch brand in the U.S. at that time, during which nicotine pouch sales were increasing (Majmudar et al., 2022). More recently, Nielsen data show that monthly nicotine pouch sales more than tripled from 2021 to 2024 (He et al., 2025).

Another study using the September 2022 TUS-CPS data found that, among adults reporting current smoking, those who attempted to quit in the last year (vs. those who did not) were more likely to report current nicotine pouch use (1.6% vs 0.6%; adjusted OR, 3.2 [95% CI, 1.8-5.7], $P < 0.001$) (Dai & Leventhal, 2024). Similarly, another study using 2022-2023 TUS-CPS data found that, among adults who had ever used nicotine pouches, very few (1.8%) had never used tobacco before, suggesting that ZYN is not a product of tobacco initiation among adults. Daily nicotine pouch use was more common among adults who recently quit smoking cigarettes and ever used smokeless tobacco (Delnevo et al., 2025).

2.3.1.1.2. Patterns of Use Study

As part of this application, the applicant cross-referenced the Patterns of Use study submitted in its PMTA for ZYN. This study examined patterns of ZYN use, including likelihood of cessation of combusted cigarette use among adults who use ZYN, without the presence of the proposed modified risk claim. The Patterns of Use study consisted of a cross-sectional retrospective survey, a 10-week prospective study, and a post-hoc flavor analysis.

In the retrospective survey, participants were asked to recall tobacco product use over the preceding 30-day period, reasons for using ZYN, and intentions to quit using specific types of tobacco products. Participants included 1,266 adults who use ZYN and 733 participants who only used other tobacco products. Among participants using ZYN, 42% reported smoking combusted cigarettes during the weeks prior to using ZYN. In the time period between initiating use of ZYN and completing the survey (median time = 5-6 months; range ≤1 month-24 months), the prevalence of combusted cigarette use decreased from 42.0% to 15.1%. Among adults who smoke, those who also used ZYN vs. those who did not reported a greater intention to quit smoking (mean values of 4.98 and 3.18, respectively, on a 7-point scale).

The 10-week-long prospective study evaluated patterns of use among adults using ZYN (n = 346) and adults using tobacco products other than ZYN (n = 196). Among participants using ZYN, the proportion who also used combusted cigarettes declined from 15.9% to 8.1% over the course of the 10-week study. This finding suggests that approximately half of participants who dual-used combusted cigarettes and ZYN completely switched to ZYN by the end of the study period. Nearly one quarter of participants (24%, 83/346) who used ZYN completely switched from other tobacco products (such as combusted cigarettes,

moist snuff, snus, e-cigarettes, cigars, or cigarillos) and reported exclusive use of ZYN by end of the 10-week prospective study period. Of note, there was significant loss to follow-up: a large portion of participants using ZYN (49%) and participants using tobacco products other than ZYN (54%) left the Patterns of Use study before it was completed and were not replaced. The applicant reported switching data only for participants who completed the 10-week prospective study. Since these participants may have been the most committed to using ZYN, in a real-world scenario, rates of complete switching from combusted cigarettes to ZYN may be lower than those observed in the study.

2.3.1.2. Impacts on Those Not Using Tobacco Products, Including Youth

2.3.1.2.1. National Surveys

Estimates from national surveys and other published findings indicate that prevalence of nicotine pouch use among youth is currently relatively low. Data from the 2024 National Youth Tobacco Survey (NYTS) show that 1.0% (110,000) of U.S. middle school and 2.4% (360,000) of U.S. high school students reported currently using nicotine pouches. NYTS data indicate that ZYN is the most popular nicotine pouch brand among youth: 33.5% (30,000) of middle school students and 72.0% (250,000) of high school students who reported current nicotine pouch use reported that ZYN is their usual brand (Jamal et al., 2024). Results from a recently published study using Monitoring the Future (MTF) Study data found that 2.6% of grade 10 and grade 12 students reported current nicotine pouch use in 2024, consistent with the NYTS 2024 estimate for high school students. An analysis of these MTF data showed a statistically significant increase in current nicotine pouch use among students in grades 10 and 12 between 2023 to 2024 (1.3% to 2.6%) (Han et al., 2025).

2.3.2. Potential Impact of Modified Risk Claim on Intention to Use

2.3.2.1. Impacts on Those Currently Using Tobacco Products

2.3.2.1.1. Intentions to Use ZYN

In addition to assessing consumer understanding and risk perceptions, the applicant's Consumer Perceptions and Likelihood of Use study assessed the effect of the proposed modified risk claim on consumers' intentions to use nicotine pouches, intentions to use ZYN, and, among respondents who reported current smoking, intentions to quit combusted cigarettes. Intentions were measured using the 11-point Juster scale in which those who selected 0 report no or almost no chance that they will use ZYN or nicotine pouches on a regular, ongoing basis, and those who selected 10 report they are certain or practically certain to use ZYN or nicotine pouches on a regular, ongoing basis (Juster, 1966).

Viewing the stimuli with the proposed claim did not impact intentions to use ZYN relative to viewing the stimuli without the claim. Intentions to use nicotine pouches (measured pre-exposure) and ZYN (measured post-exposure) were generally higher among respondents using smokeless tobacco (*M* = 4.2-5.1) than among respondents using combusted cigarettes (*M* = 2.5-3.8). As noted in section 2.2.2.1.2, the combusted cigarette use and current smokeless tobacco use groups in this study included respondents who currently use nicotine pouches (19.4% currently using combusted cigarettes and 52.6% currently using smokeless tobacco). This may have caused ceiling effects (i.e., limited the ability to detect any impact of the proposed claim because intentions to use nicotine pouches in this subgroup were likely already high and thus could not increase much further after claim exposure) .

2.3.2.1.2. Intentions to Quit Smoking Combusted Cigarettes

The proposed claim had no effect on intentions to quit among respondents currently using combusted cigarettes. Prior to exposure to the stimuli, respondents currently using combusted cigarettes had some motivation to quit smoking as measured by the Motivation to Stop Scale (MTSS), which uses a 7-point

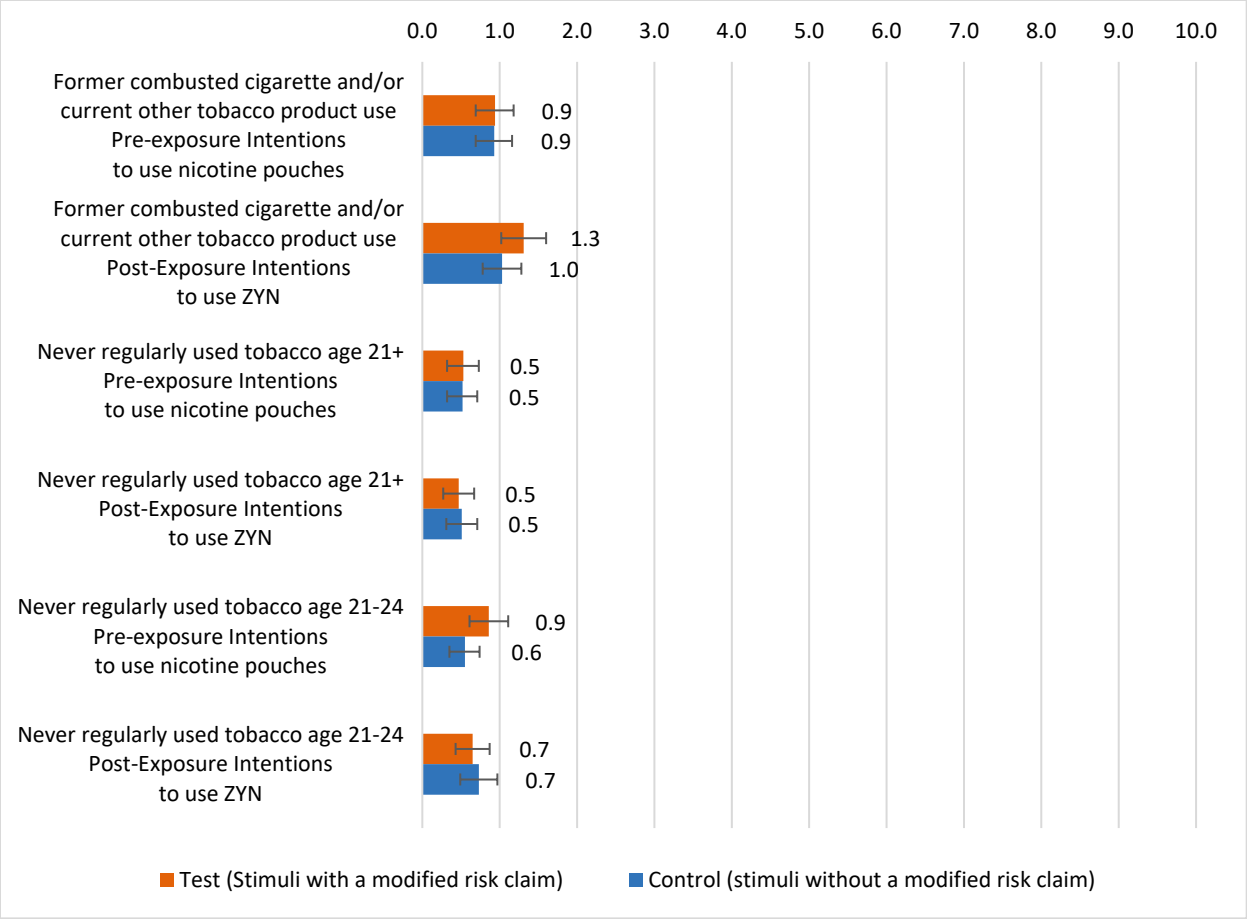
response scale (Kotz et al., 2013). Pre-exposure averages on the MTSS did not vary between the test and control groups (*M* test = 3.3, 95% CI: 3.2-3.5; *M* control = 3.6, 95% CI: 3.4-3.7). After exposure to the stimuli, there continued to be no difference in average MTSS scores between the test and control groups. The average MTSS score increased a small amount in both the test and control groups and this increase was statistically significant, as indicated by non-overlapping confidence intervals, in the test group (pre-exposure *M* = 3.3, 95% CI: 3.2-3.5; post-exposure *M* = 3.6, 95% CI: 3.56-3.8). T

2.3.2.2. Impacts on Those not Currently Using Tobacco Products

Overall, the proposed claim had no impact on intentions to use ZYN among adults who formerly used combusted cigarettes, adults using other tobacco products, and adults who never regularly used tobacco products (general population and young adults). Intentions to use nicotine pouches (pre-exposure) and ZYN (post-exposure) were low across these three groups. Figure 4 presents the average pre-exposure intentions to use nicotine pouch scores and the average post-exposure intentions to use ZYN scores (ranging from 0-10) across these three groups. Across all three groups, the average post-exposure intentions to use ZYN were similar between the test group exposed to the proposed claim and the control (unexposed) group. There were also no within-group differences between the pre-exposure average intentions to use nicotine pouch scores and the post-exposure average intentions to use ZYN scores across these three groups.

Youth and young adults who do not use tobacco are among the populations that would not stand to benefit from the use of a lower risk alternative to cigarettes. The applicant's Consumer Perceptions and Likelihood of Use study oversampled young adults as a proxy for youth and found that intentions to use ZYN among young adults who do not use tobacco were low and not impacted by exposure to the proposed claim. The applicant's Consumer Perceptions and Likelihood of Use study and the published literature suggest that the modified risk claims that have been studied to date generally do not have a direct impact on the tobacco initiation intentions of youth and young adults who do not use tobacco (Chaffee et al., 2023; Chen-Sankey et al., 2023; El-Toukhy et al., 2018; Fix et al., 2017; Mays et al., 2015; McKelvey et al., 2020; O'Brien et al., 2022; Wackowski et al., 2020; Wagoner et al., 2022; Whaley et al., 2024; Yang et al., 2022). However, perceptions of the risk of tobacco products can influence future tobacco product use among youth (Buta et al., 2024; Li et al., 2023; Strong et al., 2019) and adults (Brose et al., 2015; Elton-Marshall et al., 2020; Li et al., 2023). Therefore, it is possible that exposing youth to the proposed claim could influence future behavior indirectly if the claim reduces perceived risk of the products. Given that youth are at increased risk, generally, for initiating tobacco use, it is critical that any marketing plans be designed to prevent youth exposure, should a modified risk order be granted.

Figure 4: Intentions to use nicotine pouches and ZYN among adults who formerly used combusted cigarettes and/or currently use other tobacco products and adults who have never regularly used tobacco



Consumer Perception and Likelihood of Use Study respondents' mean self-reported likelihood to use nicotine pouches (pre-exposure) and ZYN (post-exposure). The item asked, "How likely or unlikely are you, yourself, to use each of the following products on a regular, ongoing basis?" Response options ranged from 0= "No chance, almost none [0 in 100]" to 10= "Certain, practically certain [99+ in 100]" Error bars: 95% CIs

2.3.3. Summary: Likelihood of Use and Impacts to the Population

Adult nicotine pouch use prevalence is currently relatively low, with 0.4% of U.S. adults reporting current nicotine pouch use. Use is highest among young adults ages 18-34 (Reyes-Guzman et al., 2025), and evidence suggests nicotine pouch sales are increasing (Majmudar et al., 2022; He et al., 2025). About a quarter (24.8%) of adults who use nicotine pouches also smoke cigarettes, while 33.8% formerly smoked, and 41.4% never smoked but may have used other tobacco products (Reyes-Guzman et al., 2025). Among adults who smoke, those who attempted to quit smoking in the last year vs. those who did not were more likely to report current nicotine pouch use (Dai & Leventhal, 2024). Among adults who had ever used nicotine pouches, very few (1.8%) had never used tobacco before, suggesting that ZYN is not a product of tobacco initiation among adults. Daily nicotine pouch use was most common among adults who recently quit smoking cigarettes and ever used smokeless tobacco (Delnevo et al., 2025).

Youth nicotine pouch use prevalence is currently relatively low, with 2024 NYTS data showing that 1.0% of U.S. middle school and 2.4% of U.S. high school students report current nicotine pouch use (Park-Lee et al, 2024). Results from a recently published study using 2024 MTF Study data for students in grades 10

and 12 reported similar findings (Han et al., 2025). The 2024 NYTS data show that ZYN is the most popular nicotine pouch brand among youth (Park-Lee et al., 2024).

In the applicant's Patterns of Use study submitted as part of its PMTA for ZYN and cross-referenced in this application, the proportion of participants who used ZYN in addition to combusted cigarettes declined from 15.9% to 8.1% over the 10-week prospective study. Nearly one quarter of participants (24%, 83/346) who used ZYN completely switched from other tobacco products and reported exclusive use of ZYN by end of the study period. However, there was significant loss to follow up, and complete switching from combusted cigarettes to ZYN in a real-world scenario may be more modest.

The applicant's Consumer Perceptions and Likelihood of Use study found that intentions to use ZYN among adults who currently use combusted cigarettes and adults who currently use smokeless tobacco were low to moderate (at or below the midpoint on the 11-point Juster scale) and did not appear to be impacted by the proposed claim. Exposure to the proposed claim also did not appear to impact the intentions of adults who smoke to quit combusted cigarettes.

While the Consumer Perceptions and Likelihood of Use study did not include youth, existing literature suggests that the claim is not anticipated to have a direct impact on the intentions of youth to use ZYN.

Overall, national surveys and applicant-submitted data suggest that nicotine pouch use is currently relatively low among both youth and adults, though use appears to be increasing. Among adults, nicotine pouch use is most common among individuals who currently or previously used other tobacco products. The findings of the applicant's Consumer Perceptions and Likelihood of Use study alone do not suggest that marketing the product with the proposed modified risk claim is likely to result in tobacco use patterns that substantially differ from those currently observed in the U.S. population.

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

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

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

Before an MRTP can be introduced into interstate commerce, an order from FDA under section 911(g) must be issued and in effect with respect to the tobacco product, and if the proposed MRTP is also a new tobacco product, it must comply with the premarket review requirements under section 910(a)(2).

To request a section 911(g) order from FDA, a person must submit a modified risk tobacco product application (MRTPA) under section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, titled "Modified Risk Tobacco Product Applications," which when finalized will contain FDA's current thinking on MRTPAs. This draft guidance discusses the submission of applications for an MRTP under section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (https://www.fda.gov/media/83300/download).

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

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

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

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

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

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

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

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

- Issuance of the exposure modification order is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

Per section 911(g)(4), when evaluating the benefit to health of individuals and of the population as a whole under sections 911(g)(1) and (g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the tobacco product that is subject of the application;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to the tobacco product that is subject of the application;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is subject of the application;
- The risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation and approved under chapter V to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and if accepted, whether to file it. In general, after filing an application, FDA begins substantive scientific review. This scientific review process involves soliciting and considering public comments on the application as well as recommendations from TPSAC. FDA intends to review and act on a complete MRTPA within 360 days of its filing. It's important to note that an order authorizing an MRTP pertains to a specific product, not an entire category of tobacco products (e.g., all smokeless tobacco products).

An FDA order authorizing an MRTP is not permanent; it is valid for a predetermined period specified in the order. To continue marketing an MRTP beyond this period, the applicant must request renewal of the order and FDA would need to determine that the findings continue to be satisfied. Additionally, section 911(j) specifies when FDA would withdraw an MRTP order after an opportunity for an informal hearing as mandated by law.

Appendix B: Tables for the Consumer Perceptions and Likelihood of Use Study

Table 1: Demographic Characteristics by Test/Control Group and Tobacco Use Category (Consumer Perceptions and Likelihood of Use Study)

Demographic Variables	**Current Combusted Cigarette (CC) Use**	**Current CC Use**	**Former CC Use/Current Other Tobacco Product Use**	**Former CC Use/Current Other Tobacco Product Use**	**Current Smokeless Use**	**Current Smokeless Use**	**Never Use (ages 21+)**	**Never Use (ages 21+)**	**Never Use (ages 21-24)**	**Never Use (ages 21-24)**
	Test (N=505) n(%)	**Control (N=505)** n(%)	**Test (N=305)** n(%)	**Control (N=305)** n(%)	**Test (N=305)** n(%)	**Control (N=305)** n(%)	**Test (N=305)** n(%)	**Control (N=305)** n(%)	**Test (N=305)** n(%)	**Control (N=305)** n(%)
Age										
21-24	30 (5.9%)	44 (8.7%)	14 (4.6%)	13 (4.3%)	63 (20.7%)	72 (23.6%)	11 (3.6%)	8 (2.6%)	305 (100%)	305 (100%)
25-44	265 (52.5%)	224 (44.4%)	92 (30.2%)	81 (26.6%)	151 (49.5%)	153 (50.2%)	92 (30.2%)	97 (31.8%)	0	0
45-64	165 (32.7%)	189 (37.4%)	105 (34.4%)	120 (39.3%)	66 (21.6%)	62 (20.3%)	147 (48.2%)	138 (45.3%)	0	0

65+	45 (8.9%)	48 (9.5%)	94 (30.8%)	91 (29.8%)	25 (8.2%)	18 (5.9%)	55 (18.0%)	62 (20.3%)	0	0
Gender										
Male	365 (72.3%)	302 (59.8%)	145 (47.5%)	145 (47.5%)	198 (64.9%)	190 (62.3%)	178 (58.4%)	184 (60.3%)	153 (50.2%)	146 (47.9%)
Female	140 (27.7%)	203 (40.2%)	160 (52.5%)	160 (52.5%)	107 (35.1%)	115 (37.7%)	127 (41.6%)	121 (39.7%)	152 (49.8%)	159 (52.1%)
Ethnicity										
Hispanic	73 (14.5%)	76 (15.1%)	25 (8.2%)	32 (10.5%)	45 (14.8%)	44 (14.4%)	25 (8.2%)	28 (9.2%)	57 (18.7%)	43 (14.1%)
White/Non-Hispanic	346 (68.5%)	313 (62.0%)	234 (76.7%)	230 (75.4%)	204 (66.9%)	202 (66.2%)	222 (72.8%)	219 (71.8%)	171 (56.1%)	180 (59.0%)
Black/Non-Hispanic	59 (11.7%)	87 (17.2%)	27 (8.9%)	29 (9.5%)	35 (11.5%)	37 (12.1%)	41 (13.4%)	43 (14.1%)	34 (11.2%)	47 (15.4%)
Asian/Non-Hispanic	11 (2.2%)	11 (2.2%)	7 (2.3%)	7 (2.3%)	8 (2.6%)	11 (3.6%)	11 (3.6%)	11 (3.6%)	22 (7.2%)	21 (6.9%)
Native American/Alaskan Native/Non-Hispanic	2 (0.4%)	4 (0.8%)	6 (2.0%)	3 (1.0%)	4 (1.3%)	2 (0.7%)	2 (0.7%)	1 (0.3%)	4 (1.3%)	4 (1.3%)

Multiple/Other/ Prefer not to answer	14 (2.8%)	14 (2.8%)	6 (2.0%)	4 (1.3%)	9 (3.0%)	9 (3.0%)	4 (1.3%)	3 (1.0%)	17 (5.6%)	10 (3.3%)
Education										
Some high school or less	11 (2.2%)	13 (2.6%)	7 (2.3%)	13 (4.3%)	4 (1.3%)	7 (2.3%)	4 (1.3%)	4 (1.3%)	19 (6.2%)	15 (4.9%)
High school graduate	144 (28.5%)	153 (30.3%)	81 (26.6%)	69 (22.6%)	79 (25.9%)	64 (21.0%)	56 (18.4%)	62 (20.3%)	107 (35.1%)	114 (37.4%)
Some college/technical trade school	153 (30.3%)	159 (31.5%)	94 (30.8%)	100 (32.8%)	84 (27.5%)	90 (29.5%)	84 (27.5%)	64 (21.0%)	87 (28.5%)	96 (31.5%)
College graduate	150 (29.7%)	138 (27.3%)	81 (26.6%)	96 (31.5%)	106 (34.8%)	110 (36.1%)	116 (38.0%)	127 (41.6%)	74 (24.3%)	71 (23.3%)
Post-graduate school	47 (9.3%)	42 (8.3%)	42 (13.8%)	27 (8.9%)	32 (10.5%)	34 (11.2%)	44 (14.4%)	48 (15.7%)	12 (3.9%)	7 (2.3%)
Prefer not to answer	0	0	0	0	0	0	1 (0.3%)	0	6 (2.0%)	2 (0.7%)
Income										
Less than $25,000	90 (17.8%)	98 (19.4%)	69 (22.6%)	66 (21.6%)	55 (18.0%)	44 (14.4%)	68 (22.3%)	61 (20.0%)	84 (27.5%)	80 (26.2%)

$25,000 but less than $35,000	66 (13.1%)	79 (15.6%)	30 (9.8%)	49 (16.1%)	45 (14.8%)	38 (12.5%)	32 (10.5%)	38 (12.5%)	45 (14.8%)	60 (19.7%)
$35,000 but less than $50,000	79 (15.6%)	67 (13.3%)	38 (12.5%)	37 (12.1%)	33 (10.8%)	45 (14.8%)	45 (14.8%)	37 (12.1%)	39 (12.8%)	34 (11.2%)
$50,000 but less than $75,000	107 (21.2%)	119 (23.6%)	76 (24.9%)	61 (20.0%)	58 (19.0%)	57 (18.7%)	49 (16.1%)	62 (20.3%)	57 (18.7%)	43 (14.1%)
$75,000 but less than $100,000	70 (13.9%)	66 (13.1%)	36 (11.8%)	41 (13.4%)	43 (14.1%)	53 (17.4%)	45 (14.8%)	33 (10.8%)	29 (9.5%)	33 (10.8%)
$100,000 but less than $150,000	71 (14.1%)	51 (10.1%)	33 (10.8%)	27 (8.9%)	46 (15.1%)	52 (17.1%)	32 (10.5%)	39 (12.8%)	20 (6.6%)	19 (6.2%)
$150,000 or more	21 (4.2%)	23 (4.6%)	19 (6.2%)	23 (7.5%)	24 (7.9%)	16 (5.3%)	24 (7.9%)	32 (10.5%)	11 (3.6%)	18 (5.9%)
Prefer not to answer	1 (0.2%)	2 (0.4%)	4 (1.3%)	1 (0.3%)	1 (0.3%)	0	10 (3.3%)	3 (1.0%)	20 (6.6%)	18 (5.9%)
Health Literacy										
Marginal	73 (14.5%)	52 (10.3%)	36 (11.8%)	33 (10.8%)	75 (24.6%)	59 (19.3%)	36 (11.8%)	34 (11.2%)	72 (23.6%)	89 (29.2%)
Adequate	432 (85.5%)	453 (89.7%)	269 (88.2%)	272 (89.2%)	230 (75.4%)	246 (80.7%)	269 (88.2%)	271 (88.9%)	233 (76.4%)	216 (70.8%)

Table 2: Current use of Tobacco Products among Adults Currently Using Cigarettes and Adults Currently Using Smokeless Tobacco (Consumer Perceptions and Likelihood of Use Study)

	Adults Using Cigarettes	**Adults Using Cigarettes**	**Adults Using Cigarettes**	**Adults Using Smokeless Tobacco**	**Adults Using Smokeless Tobacco**	**Adults Using Smokeless Tobacco**
	Total (N=1010) n(%)	**Test (N=505)** n(%)	**Control (N=505)** n(%)	**Total (N=610)** n(%)	**Test (N=305)** n(%)	**Control (N=305)** n(%)
Sample Size	1010	505	505	610	305	305
Use of Traditional tobacco Cigarettes						
Every day	800 (79.2%)	401 (79.4%)	399 (79.0%)	121 (19.8%)	66 (21.6%)	55 (18.0%)
Some days	210 (20.8%)	104 (20.6%)	106 (21.0%)	102 (16.7%)	50 (16.4%)	52 (17.1%)
Not at all	0	0	0	387 (63.4%)	189 (62.0%)	198 (64.9%)
Use of Loose Tobacco for Roll-Your-Own Cigarettes						
Every day	91 (9.0%)	48 (9.5%)	43 (8.5%)	43 (7.1%)	22 (7.2%)	21 (6.9%)
Some days	253	114	139	101	53	48

	(25.1%)	(22.6%)	(27.5%)	(16.6%)	(17.4%)	(15.7%)
Not at all	666 (65.9%)	343 (67.9%)	323 (64.0%)	466 (76.4%)	230 (75.4%)	236 (77.4%)
Use of Closed ENDS Cystems						
Every day	109 (10.8%)	49 (9.7%)	60 (11.9%)	92 (15.1%)	45 (14.8%)	47 (15.4%)
Some days	302 (29.9%)	161 (31.9%)	141 (27.9%)	158 (25.9%)	86 (28.2%)	72 (23.6%)
Not at all	599 (59.3%)	295 (58.4%)	304 (60.2%)	360 (59.0%)	174 (57.1%)	186 (61.0%)
Use of Disposable ENDS						
Every day	182 (18.0%)	86 (17.0%)	96 (19.0%)	149 (24.4%)	86 (28.2%)	63 (20.7%)
Some days	351 (34.8%)	178 (35.3%)	173 (34.3%)	189 (31.0%)	92 (30.2%)	97 (31.8%)
Not at all	477 (47.2%)	241 (47.7%)	236 (46.7%)	272 (44.6%)	127 (41.6%)	145 (47.5%)
Use of Open ENDS						
Every day	72	32	40	72	42	30

	(7.1%)	(6.3%)	(7.9%)	(11.8%)	(13.8%)	(9.8%)
Some days	203 (20.1%)	108 (21.4%)	95 (18.8%)	128 (21.0%)	64 (21.0%)	64 (21.0%)
Not at all	735 (72.8%)	365 (72.3%)	370 (73.3%)	410 (67.2%)	199 (65.3%)	211 (69.2%)
Use of Other ENDS						
Every day	22 (2.2%)	7 (1.4%)	15 (3.0%)	36 (5.9%)	21 (6.9%)	15 (4.9%)
Some days	149 (14.8%)	78 (15.5%)	71 (14.1%)	111 (18.2%)	61 (20.0%)	50 (16.4%)
Not at all	839 (83.1%)	420 (83.2%)	419 (83.0%)	463 (75.9%)	223 (73.1%)	240 (78.7%)
Use of Loose-Leaf Chewing Tobacco						
Every day	12 (1.2%)	3 (0.6%)	9 (1.8%)	36 (5.9%)	17 (5.6%)	19 (6.2%)
Some days	87 (8.6%)	46 (9.1%)	41 (8.1%)	114 (18.7%)	65 (21.3%)	49 (16.1%)
Not at all	911 (90.2%)	456 (90.3%)	455 (90.1%)	460 (75.4%)	223 (73.1%)	237 (77.7%)

Use of Moist Snuff or Dip in a Can						
Every day	30 (3.0%)	16 (3.2%)	14 (2.8%)	101 (16.6%)	51 (16.7%)	50 (16.4%)
Some days	101 (10.0%)	59 (11.7%)	42 (8.3%)	142 (23.3%)	79 (25.9%)	63 (20.7%)
Not at all	879 (87.0%)	430 (85.2%)	449 (88.9%)	367 (60.2%)	175 (57.4%)	192 (63.0%)
Use of Snus						
Every day	21 (2.1%)	13 (2.6%)	8 (1.6%)	42 (6.9%)	24 (7.9%)	18 (5.9%)
Some days	105 (10.4%)	56 (11.1%)	49 (9.7%)	128 (21.0%)	63 (20.7%)	65 (21.3%)
Not at all	884 (87.5%)	436 (86.3%)	448 (88.7%)	440 (72.1%)	218 (71.5%)	222 (72.8%)
Use of Nicotine Pouches						
Every day	51 (5.1%)	27 (5.4%)	24 (4.8%)	106 (17.4%)	50 (16.4%)	56 (18.4%)
Some days	145 (14.4%)	67 (13.3%)	78 (15.5%)	215 (35.3%)	120 (39.3%)	95 (31.2%)

Not at all	814 (80.6%)	411 (81.4%)	403 (79.8%)	289 (47.4%)	135 (44.3%)	154 (50.5%)
Use of Large Cigars, Cigarillos, or Little Filtered Cigars						
Every day	84 (8.3%)	38 (7.5%)	46 (9.1%)	48 (7.9%)	21 (6.9%)	27 (8.9%)
Some days	323 (32.0%)	156 (30.9%)	167 (33.1%)	139 (22.8%)	79 (25.9%)	60 (19.7%)
Not at all	603 (59.7%)	311 (61.6%)	292 (57.8%)	423 (69.3%)	205 (67.2%)	218 (71.5%)
Use of Nicotine Replacement Therapy						
Every day	16 (1.6%)	10 (2.0%)	6 (1.2%)	44 (7.2%)	23 (7.5%)	21 (6.9%)
Some days	152 (15.1%)	67 (13.3%)	85 (16.8%)	111 (18.2%)	53 (17.4%)	58 (19.0%)
Not at all	842 (83.4%)	428 (84.8%)	414 (82.0%)	455 (74.6%)	229 (75.1%)	226 (74.1%)
Use of Dissolvable Tobacco Products						

Every day	23 (2.3%)	9 (1.8%)	14 (2.8%)	48 (7.9%)	22 (7.2%)	26 (8.5%)
Some days	115 (11.4%)	53 (10.5%)	62 (12.3%)	152 (24.9%)	81 (26.6%)	71 (23.3%)
Not at all	872 (86.3%)	443 (87.7%)	429 (84.9%)	410 (67.2%)	202 (66.2%)	208 (68.2%)
Use of Other Tobacco Product(s)						
Every day	9 (0.9%)	5 (1.0%)	4 (0.8%)	17 (2.8%)	9 (3.0%)	8 (2.6%)
Some days	64 (6.3%)	29 (5.7%)	35 (6.9%)	49 (8.0%)	24 (7.9%)	25 (8.2%)
Not at all	937 (92.8%)	471 (93.3%)	466 (92.3%)	544 (89.2%)	272 (89.2%)	272 (89.2%)

References

Araghi M, Galanti MR, Lundberg M, et al. No association between moist oral snuff (snus) use and oral cancer: pooled analysis of nine prospective observational studies. *Scand J Public Health*. 2021;49(8):833-840. doi:10.1177/1403494820919572

Azzopardi D, Haswell LE, Frosina J, et al. Assessment of biomarkers of exposure and potential harm, and physiological and subjective health measures in exclusive users of nicotine pouches and current, former and never smokers. *Biomarkers*. 2023;28(1):118-129. doi:10.1080/1354750X.2022.2148747

Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health*. 1994;84(3):399-404. doi:10.2105/ajph.84.3.399

Brose LS, Brown J, Hitchman SC, McNeill A. Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug Alcohol Depend*. 2015;157:106-111.

Buta E, Gueorguieva R, Simon P, Garrison KA. Behavioral precursors of nicotine product use trajectories among youth. *Am J Prev Med*. 2024;67(3):360-369. doi:10.1016/j.amepre.2024.05.009

Byhamre ML, Araghi M, Alfredsson L, et al. Swedish snus use is associated with mortality: a pooled analysis of eight prospective studies. *Int J Epidemiol*. 2021;49(6):2041-2050. doi:10.1093/ije/dyaa197

Chaffee BW, Couch ET, Popova L, Halpern-Felsher B. Effects of a reduced risk claim on adolescents' smokeless tobacco perceptions and willingness to use. *J Adolesc Health*. 2023;73(3):445-451.

Chen-Sankey JC, Kechter A, Barrington-Trimis J, McConnell R, Krueger EA, Cruz TB, Unger JB, Chaffee BW, Leventhal A. Effect of a hypothetical modified risk tobacco product claim on heated tobacco product use intention and perceptions in young adults. *To Control*. 2023;32(1):42-50. doi:10.1136/tobaccocontrol-2021-056479

Dai HD, Young B. Biomarkers of exposure to tobacco-related toxicants among adult nicotine pouch users. *Nicotine Tob Res*, 2025. https://doi.org/10.1093/ntr/ntaf185

Dai HD, Leventhal AM. Prevalence of nicotine pouch use among US adults. *JAMA*. 2024;332(9):755-757. doi:10.1001/jama.2024.10686

Delnevo CD, Tomaino M, Hrywna M, Bover Manderski MT. Patterns of nicotine pouch use among adults in the US, 2022-2023. *JAMA Netw Open*. 2025;8(9):e2531155. Published 2025 Sep 2. doi:10.1001/jamanetworkopen.2025.31155

Dennison Himmelfarb CR, Benowitz NL, Blank MD, et al. Impact of smokeless oral nicotine products on cardiovascular disease: Implications for policy, prevention, and treatment: A policy statement from the American Heart Association. *Circulation*. 2025;151(1):e1-e21. doi:10.1161/cir.0000000000001293.

El-Toukhy S, Baig SA, Jeong M, Byron MJ, Ribisl KM, Brewer NT. Impact of modified risk tobacco product claims on beliefs of US adults and adolescents. *Tob Control*. 2018;27(Suppl 1):s62-s69.

Elton-Marshall T, Driezen P, Fong GT, Cummings KM, Persoskie A, Wackowski O, Choi K, Kaufman A, Strong D, Gravely S. Adult perceptions of the relative harm of tobacco products and subsequent tobacco product use: Longitudinal findings from waves 1 and 2 of the Population Assessment of Tobacco and Health (PATH) study. *Addict Behavi*. 2020;106:106337.

Fix BV, Adkison SE, O'Connor RJ, Bansal-Travers M, Cummings KM, Rees VW, Hatsukami DK. Evaluation of modified risk claim advertising formats for camel snus. *Health Ed J*. 2017;76(8):971-985. doi:10.1177/0017896917729723

Forster M, Fiebelkorn S, Yurteri C, et al. Assessment of novel tobacco heating product thp1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. *Regul Toxicol Pharmacol*. 2018;93:14-33. doi:10.1016/j.yrtph.2017.10.006.

Han D, Harlow AF, Miech RA, et al. Nicotine pouch and e-cigarette use and co-use among US youths in 2023 and 2024. *JAMA Netw Open.* 2025;8(4):e256739. doi:10.1001/jamanetworkopen.2025.6739

He Y, Zhang Z, Keller-Hamilton B, et al. Trends of oral nicotine pouch prices and sales by product characteristics in the USA, 2021-2024. *Tob Control*. Published online June 12, 2025. doi:10.1136/tc-2024-059222

Jaccard G, Djoko DT, Korneliou A, Stabbert R, Belushkin M, Esposito M. Mainstream smoke constituents and *in vitro* toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. *Toxicol Rep*. 2019;6:222-231. Published 2019 Feb 25. doi:10.1016/j.toxrep.2019.02.009

Jamal A, Park-Lee E, Birdsey J, et al. Tobacco product use among middle and high school students - National Youth Tobacco Survey, United States, 2024. Article. *MMWR Morb Mortal Wkly Rep.* 2024;73(41):917-924. doi:10.15585/mmwr.mm7341a2.

Juster FT. Consumer buying intentions and purchase probability: An experiment in survey design. *J Am Stat Assn*. 1966;61(315):658-696.

Kotz D, Brown J, West R. Predictive validity of the Motivation To Stop Scale (MTSS): a single-item measure of motivation to stop smoking. *Drug Alcohol Depend*. 2013;128(1-2):15-19. doi:10.1016/j.drugalcdep.2012.07.012

Lee PN, Coombs KJ, Hamling JS. Review with meta-analysis relating North American, European and Japanese snus or smokeless tobacco use to major smoking-related diseases. *World J Meta-Anal*. 2022; 10(3): 130-142 [DOI: 10.13105/wjma.v10.i3.130]

Li W, Osibogun O, Gautam P, Li T, Cano MÁ, Maziak W. Effect of harm perception on ends initiation among us adolescents and young adults: Longitudinal findings from the Population Assessment of Tobacco and Health (PATH) study, 2013–2018. *Drug Alcohol Depend*. 2023/03/01/ 2023;244:109784. doi:https://doi.org/10.1016/j.drugalcdep.2023.109784

Luo J, Ye W, Zendehdel K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*. 2007;369(9578):2015-2020. doi:10.1016/S0140-6736(07)60678-3

Majmundar A, Okitondo C, Xue A, Asare S, Bandi P, Nargis N. Nicotine pouch sales trends in the US by volume and nicotine concentration levels From 2019 to 2022. *JAMA Netw Open*. 2022;5(11):e2242235. Published 2022 Nov 1. doi:10.1001/jamanetworkopen.2022.42235

Mays D, Moran MB, Levy DT, Niaura RS. The impact of health warning labels for Swedish snus advertisements on young adults' snus perceptions and behavioral intentions. *Nicotine Tob Res*. 2015;18(5):1371-1375. doi:10.1093/ntr/ntv140

McKelvey K, Baiocchi M, Halpern-Felsher B. PMI's heated tobacco products marketing claims of reduced risk and reduced exposure may entice youth to try and continue using these products. *Tob Control*. 2020;29(e1):e18-e24.

O'Brien EK, Ruybal AL, Koblitz AR, Johnson SE. The effect of cigarette modified risk claims and brand on perceived risk, product appeal, and use intentions. *PLOS One*. 2022;17(10):e0274097.

Olivas M, Hays HL, Kistamgari S, et al. Nicotine ingestions among young children: 2010–2023. *Pediatrics*. 2025;doi:10.1542/peds.2024-070522.

Palmer AM, Smith TT, Chen AA, Rojewski AM, Carpenter MJ, Toll BA. Nicotine pouch use in youths and adults who use cigarettes, e-cigarettes, and smokeless tobacco. *JAMA Netw Open*. 2025;8(5):e2511630-e2511630. doi:10.1001/jamanetworkopen.2025.11630

Park-Lee E, Jamal A, Cowan H, et al. Notes from the field: e-cigarette and nicotine pouch use among middle and high school students - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(35):774-778. Published 2024 Sep 5. doi:10.15585/mmwr.mm7335a3

Reyes-Guzman CM, Baker L, Goss-Holmes H, Bloch MH. Patterns of emerging tobacco product use among U.S. adults, 2019-2022. *Am J Prev Med*. 2025;68(3):616-621. doi:10.1016/j.amepre.2024.11.001

Rezk-Hanna M, Warda US, Stokes AC, et al. Associations of smokeless tobacco use with cardiovascular disease risk: insights from the Population Assessment of Tobacco and Health Study. *Nicotine Tob Res*. 2022;24(7):1063-1070. doi:10.1093/ntr/ntab258

Rostron BL, Chang JT, Anic GM, Tanwar M, Chang CM, Corey CG. Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis. *Open Heart*. 2018 Oct 8;5(2):e000846. doi: 10.1136/openhrt-2018-000846. eCollection 2018.

Schivo M, Avdalovic MV, Murin S. Non-cigarette tobacco and the lung. *Clin Rev Allergy Immunol*. 2014;46(1):34-53. doi:10.1007/s12016-013-8372-0

Stevenson CS, Koch LG, Britton SL. Aerobic capacity, oxidant stress, and chronic obstructive pulmonary disease—A new take on an old hypothesis. *Pharmacol Ther*. 2006 Apr 1;110(1):71-82

Strong DR, Leas E, Elton-Marshall T, Wackowski OA, Travers M, Bansal-Travers M, Hyland A, White M, Noble M, Cummings KM. Harm perceptions and tobacco use initiation among youth in wave 1 and 2 of the population assessment of tobacco and health (path) study. *Prev Med*. 2019;123:185-191. https://escholarship.org/content/qt5p8613hd/qt5p8613hd.pdf

Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368(4):351-364. doi:10.1056/NEJMsa1211127

Vogel EA, Tackett AP, Unger JB, Gonzalez MJ, Peraza N, Jafarzadeh NS, Page MK, Goniewicz ML, Wong M, Leventhal AM. 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. *Tob Control*. 2025;34(3):315-322.

Wackowski OA, Rashid M, Greene KL, Lewis MJ, O'Connor RJ. Smokers' and young adult non-smokers' perceptions and perceived impact of snus and e-cigarette modified risk messages. *Int J Environ Res Public Health*. 2020;17(18):6807.

Wagoner KG, Reboussin BA, Ross JC, Denlinger-Apte R, Spangler J, Sutfin EL. Exposure to e-cigarette health claims and association with e-cigarette use and risk perceptions: A cohort study of young adults. *Addict Beh*. 2022;132:107359.

Whaley RC, Vogel EA, Clementel AC, et al. Effects of exposure to snus marketing with versus without modified risk tobacco product claims on snus use intention and perceived harm among young adults. *Tob Control*. Published online July 31, 2024. doi:10.1136/tc-2024-058651

Yang B, Massey ZB, Popova L. Effects of modified risk tobacco product claims on consumer comprehension and risk perceptions of IQOS. *Tob Control*. 2022;31(e1):e41-e49.

Yuan S, Titova OE, Damrauer SM, Åkesson A, Larsson SC. Swedish snuff (snus) dipping, cigarette smoking, and risk of peripheral artery disease: a prospective cohort study. *Sci Rep*. 2022;12(1):12139. Published 2022 Jul 15. doi:10.1038/s41598-022-16467-x