

Module 2: Integrated Summary

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY	2
2. COMPARISON PRODUCTS	7
3. PRODUCT DESCRIPTION AND MANUFACTURING	7
4. NON-CLINICAL AND CLINICAL INDIVIDUAL HEALTH DATA	7
5. CONSUMER USE BEHAVIOR AND RISK PERCEPTIONS	8
6. POPULATION AND PUBLIC HEALTH	10
7. POST-MARKET SURVEILLANCE AND STUDIES (PMSS) PLAN FOR <i>PROPOSED MRTPA's</i>	11
8. ENVIRONMENTAL ASSESSMENT	11
9. CONCLUSIONS	12

Confidentiality Statement: Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Swedish Match USA, Inc.

1. EXECUTIVE SUMMARY

We request authorization to label and advertise our *proposed modified risk tobacco products (MRTPs)*¹, the ZYN 3 mg and ZYN 6 mg products, with the same reduced risk claim as FDA authorized for use in marketing the eight General Snus products² (hereafter referred to as the *authorized MRTPs*). We submitted PMTAs³ for the 20 *proposed MRTPs* on March 4, 2020, which remain under scientific review as of this submission. Data and information from the original PMTAs, as well as data from subsequent amendments to the PMTAs, were added to a tobacco product master file (TPMF) owned by Swedish Match USA Inc. ((b) (4))⁴, which is cross-referenced throughout these MRTPAs (see [Attachment 1-3-1](#) in Module 1 for the list of cross-referenced documents).

For all *proposed MRTPs*, we request authorization of the following reduced 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.”

This claim is identical to the claim FDA authorized for the *authorized MRTPs*, except in product name. The primary reasons FDA authorized this claim for the *authorized MRTPs* include:

- Very low levels of harmful or potentially harmful constituents (HPHCs).
- GOTHIA TEK® manufacturing and testing standard.
- Very low youth appeal.
- Three decades of Swedish epidemiological data demonstrating a decline in tobacco-related disease (e.g., lung cancer, cardiovascular disease [CVD]) with increased uptake of snus over time (‘the Swedish experience’).⁵

We believe the *proposed MRTPs* meet the same requirements and health standard for authorization of the reduced risk claim as the *authorized MRTPs*. Due to the similarities between the *proposed MRTPs* and *authorized MRTPs*, the scientific findings from the FDA authorization to market the *authorized MRTPs* with the reduced risk claim can be extrapolated to the *proposed MRTPs*. More specifically, the *proposed MRTPs* also contain and deliver low HPHC quantities, meet the applicable product testing thresholds of the GOTHIA TEK® standard, and demonstrate low youth use. Therefore, we expect to observe a similar reduction in tobacco-related disease for smokers who switch from cigarettes to the *proposed MRTPs*, as seen for smokers who switched to the *authorized MRTPs* in Sweden.

The *authorized MRTPs* and *proposed MRTPs* are oral tobacco products intended for use in the same manner (i.e., held between the lip and gum for a period of use and then discarded) by the same population (i.e., current 21+ adult tobacco product consumers). We provide extensive behavioral and consumer research showing the *proposed MRTPs* are predominantly used by the intended population, similar to the *authorized MRTPs*. Data from post-market surveillance and studies (PMSS) for the

¹ Twenty *proposed MRTPs* are subject of these applications. See [Module 1-1-cover-ltr](#) in these MRTPAs for further details.

² FDA sent Swedish Match Modified Risk Granted Orders (MRGOs) on October 22, 2019, to authorize use of the reduced risk claim with the eight General Snus products (MR0000020–MR0000022, MR0000024–MR0000025, and MR0000027–MR0000029).

³ PM0000593–PM0000612

⁴ The Letter of Authorization (LoA) for the Swedish Match TPMF ((b) (4)) is in Module 1 of these MRTPAs.

⁵ 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>.

authorized MRTPs and consumer research studies for the *proposed MRTPs* show adult consumers understand the continuum of risk and have demonstrated a willingness to switch completely to nicotine pouches from combusted cigarettes and even from the *authorized MRTPs* to nicotine pouches. The General Snus® Patterns of Use (POU) Study, a study conducted as a function of FDA authorization for the *authorized MRTPs*,⁶ showed (b) (4) of users who reported using the *authorized MRTPs* at wave 1 stopped using the *authorized MRTPs* and used nicotine pouches by wave 4 on some or all days. These data show similar populations use the *authorized MRTPs* and *proposed MRTPs*. In the Patterns of Use (POU) study (b) (4) (b) (4) submitted in the original PMTAs, when asked their primary reasons for using the *proposed MRTPs*, the highest percentage of respondents (b) (4) answered they were using the products “to help reduce cigarette smoking”, and (b) (4) answered they were using the products “to help quit smoking cigarettes”. Data from both the POU study and the ZYN User profile study (b) (4)⁸ in the cross-referenced (b) (4) demonstrate users in both studies continue to decrease usage of other tobacco and nicotine products (TNPs), including cigarettes, when using the *proposed MRTPs*, with some users completely quitting cigarettes or all TNPs.

While the *authorized MRTPs* and *proposed MRTPs* are similar in both manner of use and intended user populations, one critical product design difference between the products is the *authorized MRTPs* contain tobacco, while the *proposed MRTPs* contain tobacco-derived nicotine. While the GOTHIA TEK® standard is a manufacturing and testing standard specific to products containing tobacco, information provided in the original PMTAs demonstrates the *proposed MRTPs* are consistently manufactured and tested against internal standards derived for nicotine pouch products.⁹ The *proposed MRTPs* are tested against the HPHC thresholds set by the GOTHIA TEK® standard to ensure HPHC levels remain consistently low and generally, as low as levels in the *authorized MRTPs*. Only eight of the 45 HPHCs measured were detectable in the *proposed MRTPs*, the majority of which were lower in the *proposed MRTPs* than the *authorized MRTPs*. Levels of all eight HPHCs were lower than the thresholds set by GOTHIA TEK® and all were significantly lower compared to cigarettes.¹⁰ Potentially carcinogenic HPHCs like NNN, NNK, and B[a]P were not detectable in the *proposed MRTPs*, whereas the *authorized MRTPs* had very low, but quantifiable levels of these HPHCs. Additionally, there are no HPHCs identified in the *proposed MRTPs* that are not identified in the *authorized MRTPs*, and because the *proposed MRTPs* are designed for oral use only and do not produce smoke or vapor, secondary formation of harmful constituents during product use and respiratory tract-related health effects are not a concern with the *proposed MRTPs*. Quantitative risk assessments (QRAs) of ingredients and detected HPHCs indicate, under reasonably foreseeable conditions of product use, the levels of all assessed ingredients and constituents in the *proposed MRTPs* are below the established health-based threshold values. Accordingly, the scientific evidence and data demonstrate the *proposed MRTPs* have the same or most likely lower risk profile compared to the *authorized MRTPs*, and thus, a significantly lower risk profile compared to combusted cigarettes.

⁶ Complete study information for the General Snus® POU can be found in the PMSS reports for the *authorized MRTPs*, which are cross-referenced (b) (4) MRTPA renewal for the *authorized MRTPs* (MR0000256).

⁷ Study documents are in (b) (4)

⁸ The referenced study documents are in (b) (4)

(b) (4)

⁹ Manufacturing information is in (b) (4) (b) (4) All documents are relevant. All referenced appendices are in (b) (4)

¹⁰ (b) (4)

(b) (4)

The previously submitted non-clinical data¹⁰ is further supported by a new clinical study demonstrating biomarkers of exposure (BoEs) for potentially carcinogenic compounds like NNN and NNK are not detectable in nicotine pouch users.¹¹ These levels are significantly lower compared to levels of the same BoEs measured in users of snus and combusted cigarettes. Levels of BoEs related to nicotine were comparable between nicotine pouch and snus user groups. In addition, nicotine pouch and snus users showed significantly lower levels of biomarkers of potential harm (BoPHs) related to CVD (sICAM-I and GDF-15) and lung cancer (NNAL) compared to combusted cigarette users. Overall, the study confirmed nicotine pouch users have significantly lower levels of BoEs and BoPHs compared to both snus and combusted cigarette users.

Previously submitted clinical studies¹² (b) (4)(b) (4) demonstrate measures of PK, PD, and abuse liability potential are comparable or improved after use of the *proposed MRTPs* compared to the *authorized MRTPs*. In general, these studies show the nicotine uptake in users is comparable between the *proposed MRTPs* and *authorized MRTPs*, but there are no major observed differences in pulse rate observed. However, increases in subjective effects (e.g., "head buzz") were higher for the *authorized MRTPs* compared to the *proposed MRTPs*.

Overall, the non-clinical and clinical data show measures of individual health (HPHC levels, PK, PD, abuse liability potential, BoEs, BoPHs) are comparable between the *proposed MRTPs* and *authorized MRTPs* or are significantly improved in the *proposed MRTPs* compared to the *authorized MRTPs*, which are already substantially improved compared to cigarettes.

Data from the PMSS for *authorized MRTPs*⁶ and submitted PMTA data for the *proposed MRTPs*¹⁶ show both users and non-users of TNPs understand the risk profile of the *proposed MRTPs* compared to cigarettes. However, it is also important consumers understand the specifics of the proposed reduced risk claim language. As this claim has already been authorized by FDA for use in marketing the *authorized MRTPs*, there is both pre- and post-market data for the *authorized MRTPs* demonstrating a high level of comprehension of the claim language amongst both users and non-users of TNPs. To complement these data, we evaluated comprehension of the claim language when used with the *proposed MRTPs* in a new tobacco product perceptions and intentions to use (TPPI) study¹⁷. The study results confirm the claim is still well understood when used with the *proposed MRTPs*. Our study findings are further supported by an independent study¹⁸ investigating use of the proposed claim with

¹¹ See all attachments associated with [Module 5.2](#) of these MRTPAs.

¹² (b) (4)

¹³ Study information is in (b) (4)

¹⁴ Study information is i (b) (4)

¹⁵ Study information is (b) (4)

(b) (4)

(b) (4) study documents are in (b) (4)

¹⁷ See all attachments associated with [Module 6.2](#) of these MRTPAs.

¹⁸ 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>

the *proposed MRTPs* among young adults¹⁹ who use inhalable nicotine products (e.g., e-cigarettes, cigarettes). This study concluded the claim increased the perceptions the *proposed MRTPs* are less risky compared to cigarettes, and increased intentions to switch to the *proposed MRTPs* from inhalable nicotine products amongst those exposed to the claim language.

The *proposed MRTPs* attract minimal interest among non-users of TNPs, particularly youth and young adults under 21 years of age, after 10 years of U.S. marketing. To limit underage exposure to the *proposed MRTPs*, we have very robust marketing controls in place, including:

- 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.

Complete information related to our marketing controls can be found in (b) (4).²⁰

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 and the reporting shows consistently low current²¹ youth use of nicotine pouches across all three years (1.0–1.5%), especially in comparison to youth use of e-cigarettes (7.6–9.4% over the same time period)^{22,23,24}, which remain the most popular tobacco product among youth. Despite the popularity of these products among youth, FDA has granted marketing orders for several e-cigarette products.^{25,26,27,28} 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

¹⁹ Defined as ages 21–34 years old with an average age of 24.5 years old.

²⁰ (b) (4) information is in section 7.3.4 in (b) (4)

²¹ Defined as use on ≥ 1 days during past 30 days for each product.

²² 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.

²³ 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>.

²⁴ 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>.

²⁵ 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>.

²⁶ 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>.

²⁷ 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>.

²⁸ 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>.

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.²⁹ 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 underage young adults (ages 18–20). The most recent Monitoring the Future (MTF) data³⁰ shows nicotine pouch use is low at 0.4% among 8th graders, and 1.4% among 12th graders. Of the nine other similar substances tracked in MTF, eight had higher use prevalence among 8th through 12th 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 recent FDA-authorized MRTP, showing use prevalence of smokeless tobacco products was at 3.5% among 8th through 12th graders. Therefore, current youth use of the nicotine pouch category, including the *proposed MRTPs*, 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 very low youth usage of the *proposed MRTPs*. These data suggest our robust marketing controls are effective in restricting youth access to our products.

FDA noted the importance of the ‘Swedish experience’ data in their decision to authorize use of the reduced risk claim in marketing of the *authorized MRTPs*.⁵ 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 significantly improved compared to the *authorized MRTPs* and clinical data further supports the reduced risk potential of the *proposed MRTPs*. Therefore, increased uptake of the *proposed MRTPs* and an associated decreased cigarette usage in the U.S. is highly likely to lead to a similar observed decline in U.S. smoking-related disease rates as expected for the *authorized MRTPs* and as observed in Sweden. We submitted a population health impact model (PHIM) as part of our PMTAs for the *proposed MRTPs*.³¹ Even under the most conservative and pessimistic assumptions, the model shows uptake of the *proposed MRTPs* is expected to reduce tobacco-related deaths by 600,000 by the year 2050. Though the products have not been on the U.S. market long enough to generate three decades of health data as in the ‘Swedish experience’ data, the PHIM data shows what is possible in the next three decades should the *proposed MRTPs* be authorized to market with the proposed reduced risk claim, allowing smokers to accurately understand their reduced health risks if they switch completely away from cigarettes.

We believe the newly submitted and cross-referenced data and literature scientifically substantiates authorizing the reduced risk claim for the *proposed MRTPs*. Our data establish the intended population (current adult tobacco consumers) are likely to switch to the *proposed MRTPs* after exposure to the claim, while there is minimal risk of tobacco product initiation by non-users (including youth) after exposure to the *proposed MRTPs* with the reduced risk claim. Therefore, the claim demonstrates a benefit to the population as a whole, when considering both users and non-users.

²⁹ 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>.

³⁰ 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/>

³¹ Documents related to the (b) (4)

2. COMPARISON PRODUCTS

We propose to use the same reduced risk claim with the *proposed MRTPs* as was FDA-authorized for use with the *authorized MRTPs*. Given we manufacture both the *proposed* and *authorized MRTPs*, and they demonstrate comparable product characteristics, use patterns, and risk profiles, we compare the *proposed MRTPs* to the *authorized MRTPs* throughout this submission. Given the language of the claim, the *proposed MRTPs* and *authorized MRTPs* are also compared to cigarettes throughout these MRTPAs.

3. PRODUCT DESCRIPTION AND MANUFACTURING

We do not provide any new product description and manufacturing information for the *proposed MRTPs*; such information is found in the PMTAs³² for these products. The *proposed MRTPs* are 400 mg sealed pouches containing tobacco-derived nicotine, (b) (4) without any whole, cut, or ground tobacco. All 20 *proposed MRTPs*¹ use identical pouch material and use the same ingredients, with the exception of the flavor-specific components. Information on product description, ingredients, and manufacturing is in Module 3 of these MRTPAs.

4. NON-CLINICAL AND CLINICAL INDIVIDUAL HEALTH DATA

4.1. Chemistry and Toxicology Data

We are not providing any new non-clinical information or data in these MRTPAs. In the original PMTAs, we submitted chemical and HPHC test data, QRAs for ingredients and the eight HPHCs detected in the *proposed MRTPs*, and two *in vitro* studies.¹⁰ Of the eight HPHCs detected in the *proposed MRTPs*, the majority are in lower quantities compared to the *authorized MRTPs*, and all are in any event significantly lower compared to cigarette smoke. Potentially carcinogenic HPHCs like NNN, NNK, and B[a]P, which are significantly lower in the *authorized MRTPs* compared to cigarette smoke, are not detectable in the *proposed MRTPs*. Additionally, because the *proposed MRTPs* are designed for oral use only and do not produce smoke or vapor, secondary formation of harmful constituents during product use and respiratory tract-related health effects are not a concern with the *proposed MRTPs* (or *authorized MRTPs*). The *in vitro* assays demonstrate a lack of mutagenic or genotoxic response to the *proposed MRTPs*, regardless of flavor, while cigarette smoke demonstrates positive responses for mutagenicity and genotoxicity. Lack of mutagenic and genotoxic response indicates a very low likelihood the *proposed MRTPs* will produce carcinogenic effects, which agrees with the lack of potentially carcinogenic HPHCs found in the *proposed MRTPs*. Overall, these data show the toxicological profile of the *proposed MRTPs* is significantly improved compared to the *authorized MRTPs* and even more so compared to cigarette smoke.

4.2. Clinical Study Data

The significantly reduced HPHC levels in the *proposed MRTPs* are consistent with the results of our new cross-sectional biomarker study comparing BoEs and BoPHs in plasma and urine across populations of nicotine pouch users, snus users, cigarette users, and non-users of TNPs. In the study,¹¹ BoEs are

³² Product description information is in (b) (4)



consistently lower in nicotine pouch users compared to all other product user groups or are below the limit of quantification (LOQ). BoPH levels for CVD (sICAM-1, GDF-15) were found to be comparable between nicotine pouch user, snus user, and non-user groups, all of which had significantly lower BoPH levels compared to combusted cigarette smokers. Additionally, the oral safety study submitted in the original PMTAs³³ demonstrates a significant decrease in the number of people with, and the severity of, oral lesions upon switching from the *authorized MRTPs* to the *proposed MRTPs*. Other clinical studies^{12,13,14,15} demonstrate PK, PD, and abuse liability potential are comparable or improved after use of the *proposed MRTPs* compared to the *authorized MRTPs*. Overall, these data show nicotine uptake in users is comparable across the *proposed MRTPs* and *authorized MRTPs*, no major differences in pulse rate between products, and increases in subjective effects (e.g., “head buzz”) in users of the *authorized MRTPs* compared to users of the *proposed MRTPs*.

4.3. Summary

Overall, submitted non-clinical and clinical data demonstrate the *proposed MRTPs* show a marked improvement in the toxicological profile and associated biomarkers compared to the *authorized MRTPs*. It is unlikely there are any specific health outcomes to expect with the *proposed MRTPs* relative to the *authorized MRTPs*. Therefore, the *proposed MRTPs* would be expected to have the same or improved health outcomes compared to the *authorized MRTPs*. In addition to the new and cross-referenced data in this submission, comprehensive literature reviews of snus³⁴ and nicotine pouches³⁵ further support our scientific assertions. As such, the *proposed MRTPs* provide benefit to individual users when they switch completely from combusted cigarettes.

5. CONSUMER USE BEHAVIOR AND RISK PERCEPTIONS

Two consumer research studies, a likelihood of use (LOU) study (b) (4) and a patterns of use (POU) study (b) (4) were included in the original PMTAs for the *proposed MRTPs*.¹⁶ A third consumer research study, the (b) (4) and the post-hoc analysis) was discussed in the October 2023 amendment to the original PMTAs.³⁶ The LOU study demonstrates:

- Minimal risk of initiation by non-users³⁷ after being exposed to stimuli with images of the *proposed MRTPs*.
- Current TNP users are interested in purchasing the *proposed MRTPs*, particularly current cigarette smokers with intentions to quit smoking.

³³ Study (b) (4) documents are in (b) (4)

³⁴ (b) (4) documents are in (b) (4)

³⁵ (b) (4) documents are in the cross-reference (b) (4)

³⁶ The referenced study documents are in (b) (4)

³⁷ Never users of TNPs and former users of TNPs

In the POU study, intentions to quit smoking were highest among *proposed MRTPs* users and dual use (i.e., nicotine pouches and cigarettes) rates were low. TNP users in the POU study and the ZYN Flagship Varieties User Profile Study demonstrated a continued decrease in use of other TNPs when using the *proposed MRTPs*, with some users demonstrating complete quitting of cigarettes or all TNPs. These data demonstrate a clear benefit to users and the population as a whole, as using the *proposed MRTPs* allowed current adult TNP users to decrease their consumption of combusted cigarettes, with minimal, risk of non-users beginning to use the *proposed MRTPs*.

Perceptions of health risks were evaluated in the LOU and POU studies, and results show current TNP users have a high understanding of the continuum of risk, perceiving daily use of the *proposed MRTPs* only as lower risk compared to cigarettes. However, respondents in both studies understood the *proposed MRTPs* are not without risk entirely, perceiving daily use of the *proposed MRTPs* as still carrying a higher risk to health than quitting all or never using any TNP. Across all health conditions tested (adult tooth loss, mouth cancer, gum disease, serious health problems), respondents generally perceived:

- Low/minimal absolute risk for developing these conditions when never using TNPs.
- Low-to-moderate absolute risk for developing these conditions if only using the *proposed MRTPs*.
- Moderate-to-very high absolute risk for developing these conditions when continuing to smoke cigarettes.

Overall, these studies demonstrate both users and non-users generally understand the health risks associated with the *proposed MRTPs* and illustrate minimal risk of initiation among non-users. Importantly, current adult TNP users understand using the *proposed MRTPs* rather than cigarettes may lower their risks of developing serious health conditions. While these studies did not investigate the proposed reduced risk claim specifically, the studies demonstrate both users and non-users of TNPs comprehend cigarettes pose a higher risk to human health, and switching completely to the *proposed MRTPs* presents a much lower risk to human health compared to continued use of cigarettes.

PMSS data from the General Snus® Patterns of Use Study⁶ demonstrate the *authorized MRTPs* are effective in transitioning cigarette smokers away from combusted products and some users (b) (4) even transitioned away from the *authorized MRTPs* over the two-year study, towards nicotine pouches, like the *proposed MRTPs*. As shown in Modules 4 and 5 of these MRTPAs, 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 additional benefit to individuals by further lowering exposure to potentially carcinogenic compounds compared to combusted cigarettes, and thus reducing risk of developing serious health conditions (e.g., lung cancer, mouth cancer, CVD).

In order to determine whether the same modified risk claim on different products has the same consumer comprehension, we investigated use of the same modified risk claim with the *proposed MRTPs* as was authorized by FDA for use in marketing the *authorized MRTPs*. Results from our (b) (4) show TNP users as well as former and non-established users³⁹ (b) (4) (b) (4) comprehend the claim language and perceive the *proposed MRTPs* as being lower risk than

³⁸ All study subjects were 21 years of age and older.

³⁹ Non-established is defined as using < 100 tobacco product units in lifetime and not using any in last 30 days.

combusted cigarettes in causing serious health conditions like mouth cancer, lung cancer, and heart disease. All cohorts understand the products are not without risk entirely and understand never using or quitting use of all TNPs is lower risk to human health than continued use of the *proposed MRTPs*. Critically, the study found non-users (non-established TNP users, former TNP users) were at minimal risk of TNP initiation or reinitiation after exposure to stimuli with the *proposed MRTPs* and the reduced risk claim language. Therefore, as expected, the modified risk claim on the *proposed MRTPs* produced results similar to those for the *authorized MRTPs*.

Our study results are supported by an independent study¹⁸ published in 2023, which discussed results from a randomized controlled trial on the impact of using an MRTP claim with the *proposed MRTPs* on risk perceptions amongst young adults¹⁹ who currently use inhalable nicotine products (i.e., cigarettes and e-cigarettes). Results from the study show use of the claim increased the likelihood of perceiving the *proposed MRTPs* as less harmful than cigarettes and increased intentions to use the *proposed MRTPs*. Intentions to use the *proposed MRTPs* to cut down on or switch entirely away from inhalable nicotine products were found to be greater among those exposed to the claim. The authors noted the claim was well understood across those exposed to the claim, ultimately concluding these products could “facilitate transition to [oral nicotine products] among those unready to quit nicotine/tobacco use, potentially conferring a harm reduction benefit.”

6. POPULATION AND PUBLIC HEALTH

The intended user population for the *proposed MRTPs* is current adult (21 years and older) tobacco and nicotine product consumers. We do not promote products to underage consumers and take great measures to prevent underage access to our products. We fully comply with and voluntarily go beyond the regulations governing our industry. We do not use social media influencers and refuse all requests for influencer partnerships. The digital platforms we own are age-gated at the point of access and restricted to current nicotine users of legal age. Our advertising only features individuals aged, and appearing to be, 35 years or older. We also employ independent age verification systems, like (b) (4) to restrict access to digital advertising from those under 21 years old and require retailers to conduct age verification at point of sale, and contracts may be terminated for non-compliance with this policy. Additional information about underage prevention controls in our marketing is available (b) (4).²⁰ While we don’t have control or authority over user-generated content on social media platforms, we remain vigilant in monitoring content and reporting concerns where possible to address underage use, product misuse, and inappropriate content or claims involving our products.

The 2023 NYTS data show current nicotine pouch use remains exceptionally low (1.5%).²⁴ Estimates from the UTUS were similar to those from the NYTS data.²⁹ 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 years old) and 1.7% or less among underage young adults (ages 18–20 years old). The data illustrates a lack of substantial youth nicotine pouch uptake. These data, which provide actual evidence related to product use or uptake among youth, demonstrate youth use and uptake of nicotine pouches as a category remain low across multiple surveys, age groups, and years tracked. Therefore, our continuous efforts to restrict youth access to the products and marketing restrictions are robust and continue to be

⁴⁰ See (b) (4) (last accessed January 29, 2024) (b) (4)
(b) (4)

effective (b) (4)

Not only is youth use of the product category low, but the *proposed MRTPs* will also benefit the population as a whole. FDA noted the importance of over three decades of epidemiological data from Sweden demonstrating reduction in tobacco-related diseases (e.g., lung cancer, CVD) observed over time with the uptake of snus and simultaneous decreased combusted cigarette use ('Swedish experience') in their decision to authorize use of the reduced risk claim in marketing of the *authorized MRTPs*.⁵ 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 significantly improved compared to the *authorized MRTPs* (see Module 4 of these MRTPAs) and thus, compared to combusted cigarettes. Clinical data further support the significant improvements and reduced risk potential of the *proposed MRTPs* (see Module 5 of these MRTPAs). Therefore, increased uptake of the *proposed MRTPs* and associated decreased cigarette usage in the U.S. is reasonably expected to lead to a similar observed decline in U.S. smoking related-disease rates in the observed over time as those observed in Sweden. We submitted a population health impact model (PHIM) as part of our PMTAs for the *proposed MRTPs*.³¹ Briefly, even under the most conservative and pessimistic assumptions, the model shows uptake of the *proposed MRTPs* is expected to reduce tobacco product-related deaths by 600,000 by the year 2050. Though the *proposed MRTPs* have not been on the U.S. market long enough to generate three decades of health data as submitted for the *authorized MRTPs*, the PHIM data shows what is possible in the next three decades should the *proposed MRTPs* be authorized to market with the reduced risk claim, allowing current adult tobacco product consumers to comprehend their reduced health risks if they switch away from cigarettes.

7. POST-MARKET SURVEILLANCE AND STUDIES (PMSS) PLAN FOR PROPOSED MRTPs

As we are proposing to use the same claim with the *proposed MRTPs* as was authorized by FDA for use with the *authorized MRTPs*, we plan to conduct similar PMSS as was completed for the *authorized MRTPs*. Namely, we will track consumer perceptions, behavior, and health over time to monitor changes in perceptions, behavior, or health to consumers after the *proposed MRTPs* are authorized to be marketed with the reduced risk claim. 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 in product design, manner of use, user behavior, and user populations between the *proposed MRTPs* and *authorized MRTPs*, we believe it is sufficient to propose a similar PMSS plan. If any additional PMSS is required by FDA, we will design studies to comply with the requirements and submit the protocol to FDA for approval before beginning data collection.

8. ENVIRONMENTAL ASSESSMENT

Environmental assessments (EAs) were prepared in accordance with 21 CFR 25.20 and 25.40, FDA's regulations implementing the National Environmental Policy Act (NEPA) of 1969. Under NEPA, "all applications or petitions requesting Agency action require the submission of an environmental assessment or a claim of categorical exclusion" (21 CFR 25.15(a)). The EAs for the *proposed MRTPs* are in Module 7 of these MRTPAs.

9. CONCLUSIONS

Available data and analyses demonstrate the *proposed MRTPs* meet the standard under section 911(g)(1) of the FD&C Act, and therefore, can be sold or distributed with the same reduced risk claim as the *authorized MRTPs*. The *proposed MRTPs*, as 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.

The product characteristics, manner of use, and intended populations are similar between the *proposed MRTPs* and the *authorized MRTPs*. There is no reason to believe the impact on population health will be different between the *proposed MRTPs* and the *authorized MRTPs*, due to the substantial reduction in HPHCs from both when compared to cigarettes. In most cases, the reduction in HPHCs compared to cigarettes from the *proposed MRTPs* is even greater than for the *authorized MRTPs*. These HPHC reductions are further supported by the substantial reductions in BoEs and BoPHs from users of nicotine pouches and tobacco-based snus, compared to cigarette users. BoEs for potentially carcinogenic HPHCs (e.g., NNN, NNK, B[a]P) were even below detectable levels in nicotine pouch users, and levels of BoPHs for CVD are comparable between non-users, snus users, and nicotine pouch users, which are significantly lower than for cigarette users. Consumer use behavior data support the conclusion current adult smokers who use the *proposed MRTPs* instead of cigarettes should achieve reduced exposure to HPHCs similar to or even better than when switching completely from cigarettes to the *authorized MRTPs*. Thus, consumers of the *proposed MRTPs* are at lower risk of developing smoking-related diseases (e.g., mouth cancer, heart disease, lung cancer, stroke, emphysema, chronic bronchitis), as observed for consumers of the *authorized MRTPs*.

The products are intended and marketed for use by current adult (21 years and older) tobacco consumers. Data from several national cross-sectional surveys demonstrate youth use of nicotine pouches is low and comparable to or lower than levels observed for smokeless tobacco products including snus, and cigarettes, depending on the survey and year. Given the similarities between the *proposed MRTPs* and the *authorized MRTPs*, and their respective product categories, there is no evidence of increased risk for youth initiation and use for the *proposed MRTPs* as compared to the *authorized MRTPs*. Additionally, consumer research studies show minimal risk of current adult non-users of TNPs (never TNP users, former TNP users) initiating or re-initiating TNP use after exposure to the *proposed MRTPs* with the reduced risk claim, similar to the *authorized MRTPs*. Therefore, an increased risk of unintended consequences (i.e., high tobacco use initiation and re-initiation with the *proposed MRTPs*) compared to the *authorized MRTPs* is not expected in the U.S. if the *proposed MRTPs* are authorized with the same reduced risk claim.

Overall, the *proposed MRTPs* are successfully switching adult smokers away from cigarettes, which is combined with evidence demonstrating minimal use or risk of use among non-users of tobacco products (including youth). Based on the similarities between the *proposed MRTPs* and *authorized MRTPs* in product characteristics, manner of use, user behavior, and user populations, issuing a reduced risk modification order for the *proposed MRTPs* is equally appropriate to promote the public health and is expected to benefit the health of the population as a whole. Therefore, an order under 911(g)(1) of the FD&C Act for the *proposed MRTPs* is warranted.