U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead Review of MRTPA(s)

Modified Risk Tobacco Product(s) Subject of this Review[1]	
Submission tracking numbers (STNs)	MR0000256.PD1-MR0000256.PD5, MR0000256.PD7-MR0000256.PD9, see Appendix A
Common Attributes	
Submission date	July 17, 2023
Receipt date	July 17, 2023
Applicant	Swedish Match U.S.A. Inc.
Product manufacturer	Swedish Match U.S.A. Inc.
Application type	Renewal
Order Under 911(g)	☒ Risk Modification 911(g)(1) order ☐ Exposure Modification 911(g)(2) order
Product category	Smokeless Tobacco Products
Product subcategory	Loose Snus (MR0000256.PD1), Portioned Snus (MR0000256.PD2-MR0000256.PD5, MR0000256.PD7-MR0000256.PD9)
Modified Risk Claims	Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.
Cross-Referenced Submissions	
All STNs	PM0000010-PM0000017, MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	Factors CTP may consider when determining order length for authorizations under Section 911 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)
Recommendation	
Issue modified risk granted orders for the products subject of this review.	

Technical Project Lead (TPL):

Digitally signed by Jennifer K. Bernat -S
Date: 2024.11.07 09:15:38 -05'00'

Jennifer K. Bernat, Ph.D.
Chief, Social Science Branch 2
Division of Population Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Benjamin Apelberg -S
Date: 2024.11.07 09:52:38 -05'00'

Benjamin Apelberg, Ph.D.
Deputy Director
Office of Science

[1] Product details, amendments, and dates provided in the Appendix.

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1. EXECUTIVE SUMMARY

FDA issued a Modified Risk Granted Order (MRGO) on October 22, 2019, authorizing the applicant to market the General Snus products described in Appendix A with the following risk modification claim:

> "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

FDA issued this decision after examining the totality of evidence across scientific reviews and determining that the applicant has demonstrated that, as actually used by consumers, the products sold or distributed with the proposed modified risk information met the standard under Section 911(g)(1) of the FD&C Act by significantly reducing harm and the risk of tobacco-related disease to individual tobacco users, and benefitting 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 MRGO specified an order expiration date of October 22, 2024. On July 17, 2023, Swedish Match U.S.A., Inc. submitted a modified risk tobacco product (MRTP) renewal application for the General Snus products, requesting renewal authorization under Section 911(g)(1) of the FD&C Act to continue marketing the products specified in Appendix A with the risk modification claim listed above beyond the order expiration date.

Under Section 911(i)(1) of the FD&C Act, FDA must require postmarket surveillance and studies (PMSS) for any product for which an applicant received an order under 911(g)(1) to determine the impact of the order on consumer perception, behavior, and health.

Swedish Match's PMSS requirements included the following:

1. Monitoring use of the eight General Snus products that were authorized to be marketed with the MRTP claim in terms of uptake, dual use, and complete switching.
2. An assessment of consumers' perceptions of the products and understanding of the claim, particularly that, to reduce their risk of disease relative to smoking, they must use General Snus exclusively.
3. Surveillance of MRTP sales and distribution, adverse experiences (AE), and new research findings.

Swedish Match conducted the longitudinal "General Snus Patterns of Use Study" hereinafter referred to as the "Patterns of Use Study" and conducted surveillance of MRTP sales and distribution, AEs, and new research findings to fulfill PMSS requirements.

Under Section 910 of the FD&C Act, FDA authorized the marketing of PM0000010-PM0000017 without modified risk claims on November 10, 2015. The technical project lead (TPL) review for the accompanying premarket tobacco product applications (PMTAs) provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites.[2] No changes have been made to the products that would change the original review conclusions.

The focus of this review of the MRTP renewal application is on the assessment of the (1) scientific accuracy of the modified risk claim, (2) relative health risks of the MRTPs to people who use tobacco, (3) consumer understanding and perception of the MRTPs marketed with the claims, and (4) impact to the

[2] The TPL review and related materials are available at: https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/premarket-tobacco-product-applications.

population as a whole, including both users of tobacco products and persons who do not currently use tobacco products, from continuing to market the products with the modified risk claims.

The applicant's request was assessed, per Section 911(g)(1), to determine whether the applicant demonstrated that, as actually used by consumers, the products sold or distributed with the proposed modified risk information will continue to:

- 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.

As TPL, I conducted a thorough scientific review of the information contained in the renewal MRTPAs and amendments received in Appendix B, including cross-referenced content in the MRTPA that received the order (PM0000010-PM0000017, MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029) and the postmarket reports submitted under the order (PS0000064; PS0000146 – PS0000149; PS0000246 – PS0000249; PS0000263; PS0000306; PS0000307). I also considered the recommendations from the Tobacco Products Scientific Advisory Committee (TPSAC); comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, including evidence of any changing market conditions or tobacco product use behavior since the authorization of the MRTPs.

After examining the totality of evidence across scientific reviews, I found that the applicant **has demonstrated** that, as actually used by consumers, the products sold or distributed with the modified risk information continue to meet the standard under Section 911(g)(1) of the FD&C Act, including that the products sold or distributed with the modified risk information significantly reduce harm and the risk of tobacco-related disease to people who use tobacco and benefit the health of the population as a whole, taking into account both people who use tobacco and people who do not currently use tobacco products.

Therefore, as TPL, I recommend renewing the MRGO issued to Swedish Match U.S.A., Inc. for General Loose, General Dry Mint Portion Original Mini, General Portion Original Large, General Classic Blend Portion White Large - 12ct, General Mint Portion White Large, General Nordic Mint Portion White Large - 12ct, General Portion White Large, and General Wintergreen Portion White Large (MR0000256.PD1-MR0000256.PD5, MR0000256.PD7-MR0000256.PD9, respectively) subject to the postmarket requirements listed in Appendices C - D.

The claim "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis" continues to be scientifically accurate. The scientific evidence, particularly the long-term epidemiological evidence, reviewed under the original submission and the new evidence in the published literature continues to substantiate that relative to cigarette smoking, exclusive use of the eight General Snus products poses lower risk of the above-named health outcomes. Accordingly, as TPL, I find that the available scientific evidence demonstrates that exclusive use of the eight General Snus products will significantly reduce harm and the risk of tobacco-related disease to people who use tobacco.

The available scientific evidence, including the postmarket surveillance and studies conducted by the applicant, supports that, as actually used by consumers, the eight General Snus MRTPs will continue to benefit the health of the population as a whole. First, there is no evidence that the MRGO has led to

increased risk for youth initiation of the MRTPs or snus in general. National studies (i.e., National Youth Tobacco Survey (NYTS), Population Assessment of Tobacco and Health (PATH) study) show a low prevalence of use of snus among youth overall, with General Snus accounting for a small fraction of those estimates. Although there is limited uptake of General Snus among adults, conservative estimates of switching observed in the applicant's Patterns of Use Study suggest that some adults who smoke combusted cigarettes (CCs) and use General Snus at baseline, did stop smoking CCs. As TPL, I considered these findings regarding potential benefit alongside potential risks, particularly the likelihood that people who do not use tobacco products, including youth, could start using General Snus products. Given the limited impact to youth, any transition to the MRTPs and away from CCs by adults can provide a benefit to population health.

Additionally, evidence from the Patterns of Use Study shows that purchasers of General Snus MRTPs understand that General Snus poses lower risks of the health conditions specified in the modified risk claim than smoking CCs, while also understanding that the product still poses health risks. Importantly, the evidence also shows that these individuals understand that one must use General Snus exclusively to reduce one's risk of the health conditions specified in the modified risk claim.

Overall, the current scientific evidence continues to support the original conclusions that, as actually used by consumers, the eight General Snus MRTPs will benefit the health of the population as a whole. Section 911(h)(4) of the FD&C Act requires an MRTP order issued under section 911(g)(1) to be for a specified time period. FDA determines an appropriate order length based on the case-specific scientific evidence pertaining to the proposed MRTP(s) presented during the review process. The applicant fulfilled the PMSS requirements of their original order, and based on that evidence, we have a greater understanding of the adults who use the MRTPs. In addition, that evidence continued to support the finding that consumers have an appropriate understanding of the relative health risks of these products compared to CCs, including that they should use them exclusively to gain a benefit relative to continuing to smoke. Compared to the original authorization, we have lower uncertainty associated with the marketing of these products due to the very well-established health risk literature and continued low risk for youth initiation, including no new indicators that the appeal of the products among youth is rising. Therefore, I recommend authorization for a period of 8 years. As described below, postmarket surveillance and studies must include an assessment of use behaviors including uptake, dual use, and complete switching, as well as understanding of the modified risk claim among those who use the MRTPs.

2. BACKGROUND

2.1. MODIFIED RISK TOBACCO PRODUCTS

The applicant submitted information for the modified risk tobacco products listed on the cover page and with more detail in Appendix A, sold under the brand names General Loose, General Dry Mint Portion Original Mini, General Portion Original Large, General Classic Blend Portion White Large - 12 ct., General Mint Portion White Large, General Nordic Mint Portion White Large - 12 ct., General Portion White Large, and General Wintergreen Portion White Large. These products, which include loose snus and portioned snus, are oral smokeless tobacco products that are moistened to facilitate use in the oral cavity. These products are produced in Sweden and manufactured using a heat treatment process. Swedish snus is made mainly from air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. The applicant describes the snus products as "moist (50-60% moisture) to semi-moist (30-45% moisture) oral smokeless products which are typically placed between the upper lip and the gum and do not require expectoration during use."

2.2. MODIFIED RISK CLAIM

The applicant has requested renewal of a risk modification order under section 911(g)(1) of the FD&C Act to market the products specified in Appendix A with the following modified risk claim:

"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

2.3. REGULATORY ACTIVITY

Original MRTPA

On June 10, 2014, FDA received the following eight MRTPAs from Swedish Match North America Inc.: MR0000020, General Loose; MR0000021, General Dry Mint Portion Original Mini; MR0000022, General Portion Original Large; MR0000024, General Classic Blend Portion White Large – 12 ct.; MR0000025, General Mint Portion White Large; MR0000027, General Nordic Mint Portion White Large – 12 ct.; MR0000028, General Portion White Large; MR0000029, General Wintergreen Portion White Large.

FDA issued an Acceptance Letter to the applicant on June 23, 2014, and a Filing Letter to the applicant on August 25, 2014. On December 14, 2016, FDA completed review of the original MRTPAs and issued a partial decision on the applications. In the original MRTPAs, the applicant requested changes to the currently required smokeless tobacco warnings on its labels, labeling, and advertising (LLA) materials. The applicant requested to remove the gum disease, tooth loss, and mouth cancer warnings. The applicant requested to revise the "not a safe alternative" warning. The request to remove the gum disease and tooth loss warning was denied, while FDA deferred final action on the other requests. In deferring final action, FDA determined that the applications in their current form did not provide sufficient evidence to meet the standard of 911(g)(1), but could potentially be amended in a way that would support the issuance of a modified risk order. Accordingly, FDA issued a Response Letter, which included three deficiencies. On September 17, 2018, the applicant submitted an amendment to address the deficiencies in the FDA Response Letter. FDA issued a Modified Risk Granted Order (MRGO) on October 22, 2019, with the orders expiring on October 22, 2024.

Postmarket annual report submissions

Under Section 911(i)(1) of the FD&C Act, FDA must require postmarket surveillance and studies (PMSS) for any product for which an applicant received an order under 911(g)(1) in order to: "…determine the impact of the order issuance on consumer perception, behavior, and health, to enable the Secretary to review the accuracy of the determinations upon which the order was based, and to provide information that the Secretary determines is otherwise necessary regarding the use or health risks involving the tobacco product." FDA communicated the PMSS requirements to the applicant in the MRGO letter. Under Section 911(i)(2), the applicant is required to submit PMSS protocols for approval. The applicant did so, and FDA reviewed and approved the PMSS protocols before the studies began. The applicant submitted reports, as required under 911(i)(1), outlining its progress on PMSS activities each year as part of its annual reports.

The applicant's PMSS requirements included the following:

1. Monitoring use of the eight General Snus products that were authorized to be marketed with the MRTP claim in terms of uptake, dual use, and complete switching.

2. An assessment of consumers' perceptions of the products and understanding of the claim, particularly that, to reduce their risk of disease relative to smoking, they must use General Snus exclusively.
3. Surveillance of MRTP sales and distribution, AEs, and new research findings.

Swedish Match conducted the longitudinal "General Snus Patterns of Use Study" to fulfill PMSS requirements. FDA received the following annual reports that included information about PMSS activities:

- Swedish Match PMTA MRTP Combined Postmarket Annual Report October 19, 2020 (PS0000064)
- Swedish Match PMTA MRTP Combined Postmarket Annual Report November 10, 2021 (PS0000146 – PS0000149)
- Swedish Match PMTA MRTP Combined Postmarket Annual Report October 28, 2022 (PS0000246 – PS0000249)
- Swedish Match PMTA MRTP Combined Annual Report Amendment December 5, 2022 (PS0000263)
- Swedish Match PMTA MRTP Combined Postmarket Annual Report October 19, 2023 (PS0000306, PS0000307)

Under section 911(h)(5) of the FD&C Act, the applicant was required to submit periodic reports relating to the advertising and promotion of the products every 6 months to FDA, once during the month of June of each year and once during the month of December of each year, beginning June 2020. In the reports, the applicant was required to include all final printed labeling and all final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communication with consumers. FDA received the following periodic reports:

- Swedish Match USA, Inc General Snus Periodic Report (June 5, 2020) (PS0000026)
- Swedish Match USA, Inc General Snus Periodic Report (December 15, 2020) (PS0000090, PS0000089, PS0000099)
- Swedish Match USA, Inc General Snus Periodic Report (June 15, 2021) (PS0000124, PS0000125)
- Swedish Match USA, Inc General Snus Periodic Report (December 9, 2021) (PS0000151, PS0000152)
- Swedish Match USA, Inc General Snus Periodic Report (June 1, 2022) (PS0000186, PS0000187)
- Swedish Match USA, Inc General Snus Periodic Report (December 6, 2022) (PS0000264, PS0000265, PS0000266)
- Swedish Match USA, Inc General Snus Periodic Report (June 7, 2023) (PS0000286, PS0000287)
- Swedish Match USA, Inc General Snus Periodic Report (December 14, 2023) (PS0000314, PS0000315)
- Swedish Match USA, Inc General Snus Periodic Report (June 6, 2024) (PS0000338, PS0000339)

Current Renewal MRTPA

On July 17, 2023, FDA received eight renewal MRTPAs for the first renewal from the applicant for the following products:

- General Loose (MR0000256.PD1)
- General Dry Mint Portion Original Mini (MR0000256.PD2)
- General Portion Original Large (MR0000256.PD3)
- General Classic Blend Portion White Large – 12ct (MR0000256.PD4)
- General Mint Portion White Large (MR0000256.PD5)
- General Nordic Mint Portion White Large – 12ct (MR0000256.PD7)
- General Portion White Large (MR0000256.PD8)
- General Wintergreen Portion White Large (MR0000256.PD9)

FDA issued an Acceptance Letter to the applicant on August 31, 2023. FDA issued a Filing Letter to the applicant on November 30, 2023. FDA issued a Deficiency Letter to the applicant on January 17, 2024.

During the MRTPA review process, FDA contacted the applicant to request additional information and clarification on the application. These requests resulted in the applicant submitting four amendments.

Refer to Appendix B for a complete list of amendments received by FDA related to these renewal MRTPAs.

2.4. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the modified risk tobacco products subject to this review. Specifically, this review considered all available evidence, including peer-reviewed scientific literature and new information that the applicant submitted to FDA since the issuance of their modified risk granted order, including PMSS status updates, interim reports, and other information submitted as part of their annual reports.

Table 1. Disciplines included in review

Discipline	Reviewer(s)	Review Date
Engineering	Mary Searing	11/6/2024
Chemistry	Trevor Harris	11/5/2024
Microbiology	La'Chia Harrison	11/6/2024
Toxicology	Thomas Hill	11/6/2024
Behavioral Clinical Pharmacology	Colin Cunningham, Emma Sutherland	11/6/2024
Medical	Vy Nguyen	11/1/2024
Epidemiology	Nicole Tashakkori, Mo'Nique Gaines Harris	11/6/2024
Social Science	Samantha Venrick, Mark Rinella	11/5/2024
OCE – BIMO	Rachel Dailey	5/14/2024
OCE – Manufacturing/ Lab	Mykeshia McNorton	1/3/2024
Environmental Science	Dilip Venugopal	11/6/2024

Table 2. Consultations

Discipline or Office	Reviewer(s)	Review Date
Statistics	Jia Wang & Li Deng	11/6/2024
OCE – DPAL	Mahua Deb	11/5/2024
OHCE	Emily Talbert	11/4/2024
Evaluation	Taylor Lee	11/6/2024

2.5. TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC)

Pursuant to section 911(f) of the FD&C Act, FDA referred the renewal MRTPAs to TPSAC, and TPSAC reported its recommendations on the renewal applications during an open public committee meeting held on June 26, 2024. At the meeting, the committee discussed the renewal MRTPAs, including the adequacy of the scientific evidence to support the marketing of these modified risk products. Information about the meeting, including the complete transcript, is available on FDA's website.[3]

FDA shared its preliminary assessment of the renewal applications with the committee, focusing on product use behavior since authorization, as well as consumer understanding and perceptions of the modified risk claims. TPSAC was asked to discuss the use behaviors of consumers using these MRTPs and any implications, as well as the evidence related to consumer understanding and perceptions of the modified risk claim and any implications.

A summary of TPSAC's discussions on these topics is presented here. FDA's assessment of these discussions is included in the relevant portions of section 3 of this review, as well as in individual discipline reviews.

Regarding the use behaviors of General Snus, TPSAC members discussed the limitations of the applicant's Patterns of Use Study regarding sampling strategy, measurement, and analysis. For example, TPSAC members discussed concerns with the use of a convenience sample and concerns regarding the level of attrition in the applicant's study. These concerns are addressed elsewhere in this review and in the epidemiology review.

Regarding the evidence related to consumer understanding and perceptions of the modified risk claim, TPSAC members discussed issues with study design, namely the study did not assess past exposure or familiarity with the modified risk claim. Additionally, TPSAC members discussed the wording of the claim and if alternate wording (i.e., switching completely) would increase understanding of the claim. These concerns are addressed elsewhere in this review and in the social science review. Other concerns raised by committee members included halo effects, such as whether consumers would believe the modified risk claim is applicable to other smokeless tobacco products, especially if the products were co-marketed on the same website. The TPSAC chair clarified that the products were co-promoted on a third-party website, which is separate from the applicant's advertising. FDA assesses the applicant's marketing plan and the applicant's adherence to it, along with evidence from broader tobacco marketplace surveillance efforts in

[3] https://www.fda.gov/advisory-committees/tobacco-products-scientific-advisory-committee/2024-tpsac-meeting-materials-and-information.

its assessment of potential risks of the MRTPs to youth and overall benefit to the population as a whole.

TPSAC members discussed a variety of potential health effects of using snus products including oral lesions, diabetes, and cardiovascular disease mortality. In addition, TPSAC members discussed monitoring health outcomes not included in the MRTP claim. FDA previously assessed the evidence related to oral lesions. The literature indicates Swedish snus use does have a negative effect on dental health (i.e., gingival recession, oral lesions), but malignant transformation of oral lesions is uncommon. Overall, the evidence supports that use of General Snus has a lower risk of oral cancer than use of other smokeless tobacco products. FDA also indicated that they continue to review the applicant's annual reports, and any submitted serious and unexpected AEs associated with the tobacco product.

TPSAC members also discussed the applicant's proposed marketing strategy. The applicant indicated that they currently limit marketing of the products with the modified risk claim to the company's age-gated website. All other General Snus marketing does not include the modified risk claim. However, the applicant's MRGO does not require the applicant to limit marketing of the products with the modified risk claim to its own age-gated website. The applicant proposed to begin using the modified risk claim in email and direct mail to consumers 21 years or older, point of sale materials, print advertisements in publications where 85% of the audience is 21 years or older, and other age-verified platforms, like social media. TPSAC members voiced differing opinions about the implications of additional marketing with the claim. See Section 3.5 for details about the applicant's marketing and labels, labeling, and advertising.

Lastly, TPSAC members gave several suggestions about how to improve future PMSS requirements, including thoughts about study design, measurement, and sample replenishment. FDA considered these suggestions when making future PMSS requirements discussed in section 5.4 and Appendix C.

2.6. PUBLIC AVAILABILITY OF MRTPAS

Pursuant to Section 911(e) of the Food, Drug, and Cosmetic (FD&C) Act, FDA made the applicant's MRTPA renewal available to the public. FDA redacted trade secrets, and confidential and commercial information. The docket for public comment on this MRTPA renewal was open from December 1, 2023, to August 14, 2024. During this period, FDA received 11 submissions from individuals, academia, and other organizations. All 11 submissions were unique relative to comments received for the applicant's original MRTPA. One submission was not relevant to this MRTPA renewal. The other 10 submissions included comments on legal and advocacy issues, consumer understanding and perceptions, critiques of the applicant's study methods, measures, and findings, and product marketing concerns similar to issues discussed during the TPSAC meeting (see Section 2.5). One comment expressed concerns that the modified risk claim was only visible to people who smoke and are registered on the Swedish Match website; therefore, it limits exposure to the applicant's intended audience. Some comments included broader topics that were not specific to this MRTPA renewal, such as comments related to the general MRTPA process, accessibility and awareness of MRTPs, misperceptions of nicotine, and the application of a harm reduction approach to address youth use. The issues and concerns raised in the public comments were also identified during FDA's scientific review of the applications and are discussed throughout this review. FDA considered all significant comments when making the final determination. Specific comments are addressed in the epidemiology and social science reviews.

3. SCIENTIFIC REVIEW

3.1. PRODUCT CHARACTERIZATION

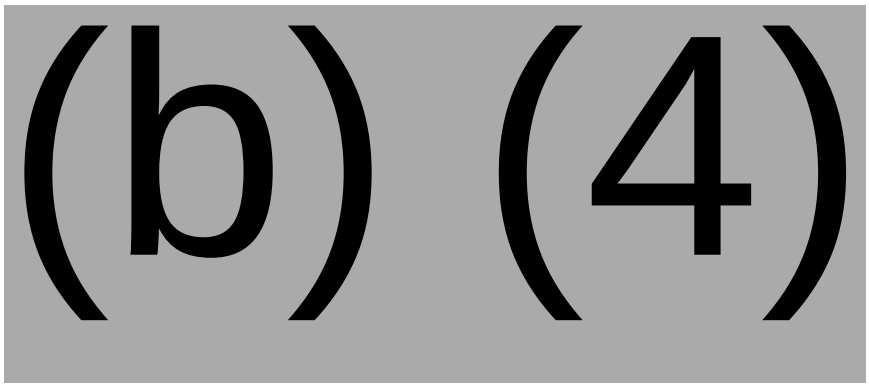
This section describes the product design and composition and examines whether the application sufficiently describes the products, how they are made, and the consistency of the manufacturing of the products. This information is necessary to fully understand the product science, which, in turn, influences the potential health risks of the product.

Key findings from Original MRTPA TPL review

In the 2016 TPL review, the engineering, microbiology, and chemistry reviews concluded that the eight General Snus products were adequately characterized. The engineering review concluded that the applicant proposed a well-controlled manufacturing process of the products.

The microbiology review concluded sufficient information was provided to ensure that manufacturing processes and controls that can affect the product composition, chemical stability, HPHC levels meet the manufacturer's specifications and ensure that the products do not contain microbial counts at levels that would pose risks to users of the products. The specifications set by the manufacturer meet or exceed those observed in products traditionally marketed in Sweden and Norway over the past several decades.

The chemistry review concluded that the applicant follows procedures to control the quality of tobacco and appropriate procedures for controlling HPHC levels, including storing the raw tobaccos in climate-controlled warehouses. The chemistry review also concluded that the applicant demonstrates that the products adhere to the GOTHIATEK standard, a voluntary product quality standard established by Swedish Match that applies to the manufacture of the company's Swedish snus products and includes tolerance limits for the following nine (9) constituents in the finished products:



In addition to GOTHIATEK, the chemistry review states the products also meet limits on constituents established by the Swedish National Food Agency and the Swedish Medical Product Agency. The limits for lead, propylene glycol, aflatoxins, and ethanol, listed below, are set by the Swedish national regulatory agencies intended to limit harmful constituents in Swedish consumer goods. While these limits are required under Swedish laws, FDA has not adopted these limits for tobacco products; thus, they are voluntary. The limits for lead, propylene glycol, aflatoxins, and ethanol are:

- Lead: (b) mg/kg (as is)
- Propylene glycol: (b) (4) g/kg (as is)

- Aflatoxins (b) (4) mg/kg (as is)
- Ethanol: (b) (4) % v/v (as is)

(b) (4)
:

(b) (4)

Adherence to the GOTHIATEK standard and the Swedish National regulatory limits supported bridging and allowed the 2016 TPL review to conclude that it is reasonable that people who use General Snus products and people who use other snus products in Sweden and Norway would likely experience exposures to harmful constituents at similar levels.

Evaluation of new MRTPA Data

The renewal MRTPA cross-references product characterization information in PM0000010–PM0000017 and MR0000020–MR0000022, MR0000024, MR0000025, MR0000027–MR0000029. The applicant reports no changes in product design and composition. The applicant also reports no manufacturing deviations and no changes in the manufacturing facility or manufacturing controls. The chemistry review also notes that the applicant states their routine product testing shows compliance with the GOTHIATEK standard through the observation of low HPHC levels. Therefore, the Office of Compliance and Enforcement (OCE) Division of Product Compliance (DPC) and OCE Bioresearch Monitoring (BIMO) did not inspect any facilities.

The literature in the PMTA annual reports for 2020 (PS0000066–PS0000074), and combined PMTA/MRTPA annual reports for 2021 (PS0000146), 2022 (PS0000246, PS0000263), and 2023 (PS0000306, PS0000307) do not contain product design or product characterization studies that are relevant to engineering, microbiology, or chemistry review. Each discipline conducted an independent literature review (2019 – 2023), and engineering and microbiology did not find any relevant literature. Chemistry reviewed the literature and retrieved three articles specific to the General Snus products under review. Chemistry reviewed the HPHC quantity data and pH data from the retrieved articles and compared this literature data with the original MRTPA chemistry review data. Chemistry concludes that from 2019 to 2023 there are no findings published that alter the chemistry review's conclusion from the original MRTPA review.

Section Summary Statement

In the original MRTPA review, the engineering, microbiology, and chemistry reviews concluded that the eight General Snus products were adequately characterized and product composition, chemical stability, and HPHC levels met the manufacturer's specifications.

In this present renewal application, the engineering, microbiology, and chemistry reviews conclude that no new scientific information alters their original conclusions.

As TPL, I agree with the engineering, microbiology, and chemistry review conclusions that there is no new information that changes the assessment of manufacturing, product design, or other product characterization information that would result in a change to FDA's original conclusions on product characterization.

3.2. RELATIVE HEALTH RISKS TO PEOPLE WHO USE TOBACCO

Key findings from Original MRTPA TPL review

The 2019 TPL review summarized the 2016 TPL review which provided a comprehensive evaluation of the evidence related to the health risks to individuals who use General Snus products. The behavioral and clinical pharmacology review concluded the General Snus products had an abuse potential because they were expected to produce reinforcing effects. The toxicology review "generally support[ed] the FDA's conclusion regarding the lower risks to health presented by the General Snus products" relative to CCs.

The strongest evidence regarding long-term health risks of Swedish snus use compared to CC smoking was from the epidemiology review which summarized long-term epidemiological studies from Sweden and Norway. While epidemiological literature is not product-specific, the applicant justified use of the studies by asserting that snus products that dominated the market during the time periods of the studies and their General Snus products both conform to the GOTHIATEK standard. The 2016 TPL review concluded, "it is reasonable to expect that General Snus products, when used in a manner similar to that observed in the submitted studies, would result in similar exposures and potential health effects as those reported in those studies" (p. 33). The applicant stated that their General Snus products have lower levels of HPHCs than the snus products that were the basis of the long-term epidemiological studies. Additionally, they provided data in the 2019 TPSAC meeting showing substantial reductions in total tobacco-specific nitrosamines, NNN, NNK, and benzo(a)pyrene from the mid-1980s until 2019.

The 2019 TPL review focused on reporting health risk findings regarding the risk of Swedish snus use compared to cigarette smoking for each of the health outcomes in the modified risk claim (i.e., mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis). The 2016 TPL review provided findings on additional health outcomes, including tooth loss and gum disease, esophageal cancer, stomach cancer, pancreatic cancer, diabetes, adverse pregnancy outcomes, and all-cause mortality.

The 2019 TPL review also explains how the risk of each health outcome was assessed in the 2016 review and after the 2018 amendment. Table 3 (from 2019 TPL review, p. 22) presents relative risks of Swedish snus use and oral cancer, heart disease, stroke, lung cancer, and emphysema and chronic bronchitis compared to no tobacco use. For comparison, the table also presents the relative risks of smoking CC based on the American Cancer Society's Cancer Prevention (CPS) II study. Overall, the risks of all disease endpoints are lower in people who exclusively use Swedish snus compared to people who smoke CCs. For more details, see the 2016 and 2019 TPL reviews.

Table 3. Cross-referenced table from 2019 TPL Review: Results from published studies[1] of health effects for oral cancers, heart disease, stroke, lung cancer, and emphysema and chronic bronchitis associated with Swedish snus use or smoking compared to non-users of tobacco.

Reference	Tobacco Product Used	Mouth Cancer	Heart Disease	Stroke	Lung Cancer	Emphysema and Chronic Bronchitis
		RR (95% CI), n	RR (95% CI), n	RR (95% CI), n	RR (95% CI), n	RR (95% CI)
Boffetta et al. 2008	Swedish snus	1.0 (0.7-1.3), n=4	n/a	n/a	0.8 (0.6-1.0), n=2	n/a
Lee & Hamling 2009; Lee 2011	Swedish snus	1.01 (0.71-1.45)†, n=4	n/a	n/a	0.82 (0.52-1.28)†, n=2	n/a
Rostron et al. 2018	Swedish snus	n/a	1.04 (0.93-1.16)†§, n=3	1.04 (0.92-1.17)†‖, n=1	n/a	n/a
Boffetta & Straif 2009	Swedish snus	n/a	Any MI: 0.87 (0.75-1.02), n=6 Fatal MI: 1.27 (1.07-1.52), n=5	Any stroke: 1.02 (0.93-1.13), n=3 Fatal stroke: 1.25 (0.91-1.70), n=2	n/a	n/a
Lee 2011	Swedish snus	n/a	0.99 (0.85-1.14)†, n=9	1.06 (0.96-1.17)†, n=6	n/a	n/a
Roosaar et al. 2008	Swedish snus	n/a	n/a	n/a	n/a	0.8 (0.2-3.0)†‡ (<80 years old) 2.0 (1.2-3.4)†‡ (80+ years old)
CPS II Population 1982-1988*	Smoking	10.89	2.80 (35-64 years old) 1.51 (64+ years old)	3.27 (35-64 years old) 1.63 (64+ years old)	23.26	Bronchitis, Emphysema: 17.1 Chronic Airway Obstruction: 10.58

Abbreviations: RR=relative risk; CI=confidence interval; n=number of risk estimates for meta-analysis; n/a=not applicable; MI=myocardial infarction
[1]All but one study (Roosaar et al. 2008) are meta-analyses
*Male current smokers
†RR estimate is for never smokers
‡Nonmalignant respiratory disease death (which includes chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, pneumonia, and influenza)
§RR estimate includes a pooled study of 8 cohorts from Hansson et al. 2012
‖RR estimate includes a pooled study of 8 cohorts from Hansson et al. 2014

Evaluation of new MRTPA Data

Toxicant Exposure, Including HPHCs

The toxicology review confirmed that the applicant did not provide any new information regarding toxicant exposure. Toxicology conducted two literature searches and found 24 relevant articles that are summarized in their review. All the identified studies evaluated Swedish snus tobacco products and six specifically included General Snus products. While the retrieved articles were related, they did not provide any new information regarding toxicant exposures that differed from previously reviewed information. The toxicology review concluded that the literature published since the original authorization continues to support their original conclusions.

Clinical Assessment

Likelihood and effects of product misuse

The behavioral and clinical pharmacology (BCP) and medical reviews state that no new information about the likelihood and effects of product misuse was submitted by the applicant or identified in their own independent literature searches. The applicant-submitted AE/consumer complaint reports did not include any AEs pertaining to the health effects related to misuse of the products subject to this review. Additionally, a search of the Safety Reporting Portal for Tobacco Products did not reveal any AEs involving misuse of the products subject to this review.

Biomarkers of Exposure

No new information about biomarkers of exposure was submitted, and BCP did not find any new information in the published literature that differed from previously reviewed information.

Biomarkers of Potential Harm

The medical review summarized literature published since the original authorization assessing arterial stiffness and endothelial vasodilatory function and lipid status as biomarkers of potential harm. Antoniewicz et al. (2022) found increased increased arterial stiffness and an underlying endothelial dysfunction in Swedish men who use snus daily as compared to Swedish men who do not use tobacco. Conclusions from the Antoniewicz et al. study, however, are based on comparing biomarkers of potential harm between people who use snus and people who do not use tobacco and does not explore biomarkers of potential harm between people who use snus and people who smoke CCs. Byhamre et al. (2023) found that Swedish men who use snus had higher HDL cholesterol and lower triglyceride concentrations compared to Swedish men who smoke cigarettes. These higher HDL cholesterol and lower triglyceride concentrations are indicators of lower risk for cardiovascular disease (CVD), which indicates a benefit for people who use snus compared to people who smoke CCs.

Relative Individual Health Risks to People Who Use Tobacco

The applicant submitted literature relevant to individual health risks. In addition to reviewing the applicant-submitted literature, the medical and epidemiology reviewers conducted individual literature searches and retrieved five articles published after issuance of the original MRTP order relevant to their disciplines and disease endpoints in the risk modification claim. (Table 4)

Table 4. Summary results from published studies after the issuance of the original MRTP order of health effects for mouth cancer, heart disease, and stroke[1] associated with current Swedish snus use or smoking compared to people who have never used tobacco

Reference	Tobacco Product Used	Mouth Cancer	Heart Disease	Stroke
		aHR (95% CI), n	**aHR (95% CI), n**	**aHR (95% CI), n**
Araghi* et al, 2021	Swedish Snus	0.79 (0.63, 1.00), n=92	n/a	n/a
Titova† et al., 2021	Swedish Snus	n/a	n/a	Total stroke: **1.53 (1.02-2.32), n=24** Ischemic stroke: **1.65 (1.06-2.57), n=21**
Lee§ et al., 2022	Snus[b]	n/a	Ischemic heart disease/acute myocardial infarction: 1.00 (0.91-1.11), n=5	Stroke: 1.05 (0.95-1.17), n=2
Yuan† et al., 2022	Swedish Snus	n/a	Peripheral artery disease: 0.88 (0.66-1.17) n=56	n/a
Byhamre* et al., 2021	Swedish Snus	n/a	CVD mortality: **1.27 (1.15-1.41) n=443**	n/a
Thun et al., 2013 Contemporary Cohort*[c]	CCs	n/a	Ischemic heart disease mortality: **2.50[a] (2.34-2.66), n=1286** (men, 55-85 years old)	Stroke mortality: **1.92[a] (1.66-2.21), n=236** (men 55-85 years old)

Abbreviations: aHR=adjusted hazard ratio; CI=confidence interval; n/a=not applicable; CC=combusted cigarettes
Bolded entries are significant
[1] The other health effects listed in the modified risk claim include lung cancer, emphysema, and chronic bronchitis. No newly published studies since the original authorization assessed risks of lung cancer, emphysema, and chronic bronchitis.
*pooled analysis
§Meta-analysis
†Individual study
[a]Risk Ratio
[b]Lee et al., 2022 meta-analysis includes epidemiological studies in North America, Europe, and Japan. The tobacco product used is not limited to Swedish snus.
[c]The Thun et al., study was published before the issuance of the MRTP order; however, it is a large, pooled study used for comparison.

Mouth cancer: The applicant submitted a 2020 pooled analysis of men in nine Swedish cohort studies, which found that ever vs. never snus use was not associated with oral cancer (aHR 0.90; 95% CI: 0.74, 1.09), including among people who have never smoked CCs (HR 0.87; 95% CI: 0.57, 1.32) (Araghi et al., 2021).

Stroke and Ischemic Stroke: A prospective cohort study of Swedish adults investigated the association between snus use and various cardiovascular disease events, including ischemic stroke and cardiovascular disease mortality. The study controlled for factors such as age, sex, education, alcohol consumption, walking/bicycling, and exercise. The findings revealed no significant association between snus use and the risk of total stroke (including ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and undefined type of stroke) among the entire sample. However, among individuals who had never smoked CC, current snus use was associated with a higher risk of total stroke and ischemic stroke compared to those who had never used tobacco (adjusted Hazard Ratio [aHR] 1.53, 95% CI: 1.02-2.32 and aHR 1.65, 95% CI: 1.06-2.57, respectively) (Titova et al., 2021).

Cardiovascular Disease Mortality: A pooled analysis of eight prospective studies investigated the relationship between snus use and all-cause and cause-specific mortality among Swedish men with no history of smoking, controlling for age and BMI. Exclusive current snus use, compared to never tobacco use, was associated with increased cardiovascular disease mortality ([aHR] 1.27, 95% CI: 1.15-1.41) (Byhamre et al., 2021).

Additionally, a meta-analysis by Lee et al. (2022) found no significant increase in the risk of ischemic heart disease (IHD) or acute myocardial infarction (AMI) among people who have never smoked CCs and currently use snus compared to people who have never smoked CCs and never used snus or do not currently use snus. Moreover, a prospective cohort study conducted by Yuan et al. (2022) that controlled for age, BMI, education level, history of hypertension, hypercholesterolemia, diabetes mellitus, CC smoking in the analysis of snus use, snus use in the analysis of CC smoking, physical activity, and diet score (continuous), revealed that while CC smoking was associated with peripheral artery disease (PAD) (HR = 4.01, 95% CI = 3.17-5.08), snus use was not (HR = 0.88, 95% CI=0.66-1.17). Specifically, the risk of PAD was higher among people who currently smoke CC and people who had quit smoking for both more than and less than 10 years compared to those who never smoked.

Lung cancer, emphysema, and chronic bronchitis: No newly published studies since the original authorization assessed risks of lung cancer, emphysema, and chronic bronchitis.

Assessment of Claim Substantiation

The toxicology, behavioral and clinical pharmacology, medical, and epidemiology reviews conclude that no new information, including the published literature, changes the original FDA assessment regarding claim substantiation. As TPL, I agree that the claim continues to be supported by the available long-term epidemiological evidence.

Synthesis and Assessment of Relevant Statutory Standards

All four reviews agree that no new information submitted by the applicant or found in FDA's independent review of the published literature changes FDA's original conclusions that the risk modification claim was substantiated. The toxicology review confirms that the literature published since the original authorization continues to support their original conclusions.

The behavioral and clinical pharmacology review confirmed that no new information was submitted regarding the clinical assessment of the products and no new relevant studies were identified in the literature, therefore, they support FDA's original conclusions.

The medical review concludes that "the current body of literature since the modified risk granted order is consistent with FDA's original MRTPA assessment." Additionally, the medical reviewer confirmed that no consumer health risks were identified by the Safety Reporting Portal AE search, and similarly, the applicant did not report any serious or unexpected AEs.

The epidemiology review states: "The literature published since the MRGO is generally consistent with the body of literature reviewed during the original MRTPA and provides additional evidence that the risks of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis due to Swedish snus use are lower than the risk from CC smoking. Several studies have not observed an association between Swedish snus use and stroke risk. The results in Titova et al. (2021) based on a single cohort are consistent with prior findings that the level of risk is below the well-established stroke risk of CC smoking. Similarly, the risk of cardiovascular mortality associated with snus use reported by Byhamre et al. (2021) is still lower than that for CC smoking. For example, data from the Contemporary Cohort (data from a pooled analysis of five large cohort studies, 2000–2010) among men aged 55 to 74, indicate that people who smoke CCs have elevated risks of stroke (Risk Ratio (RR) 1.92, 95% CI: 1.66-2.21) and cardiovascular mortality (RR 2.50, 95% CI: 2.34-2.66) (Thun et al., 2013). Therefore, the risks of stroke and cardiovascular disease mortality in people who exclusively use snus are lower relative to people who smoke CCs, as FDA's prior evaluation concluded, and the scientific evidence published since the original MRGO continues to support the modified risk claim as scientifically accurate."

As TPL, I find that the claim "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis" continues to be scientifically accurate. The scientific evidence, particularly the long-term epidemiological evidence, reviewed under the original submission and the new evidence in the published literature continues to substantiate that relative to cigarette smoking, exclusive use of the eight General Snus products poses lower risk of the above-named health outcomes. Accordingly, as TPL, I find that the available scientific evidence demonstrates that exclusive use of the eight General Snus products will significantly reduce harm and the risk of tobacco-related disease to people who use tobacco.

3.3. CONSUMER UNDERSTANDING AND PERCEPTIONS

Key findings from Original MRTPA TPL review

The social science reviewer concluded that consumers generally understood the proposed modified risk claim and the health risks of using the proposed modified risk General Snus products in the context of total health. Exposure to the claim led to consumers understanding that the relative risk of snus is lower compared to smoking with respect to the health outcomes described in the claim. In terms of whether consumers understood how the product must be used to attain the purported risk reduction (i.e., exclusively), the data provided evidence that the proposed claim did *not* lead smokers to believe that partial substitution would reduce their disease risk. Based on perceptions of the relative risk of exclusive snus use compared to dual use with CCs, and an item about the number of CCs one could smoke while using snus to reduce their risk, the findings provide support that most consumers *do not* infer that partial substitution is associated with a reduction in risk. The 2019 TPL review concluded that overall, the pattern of results shows an improvement in the participants' understanding of the risks of the product after being exposed to the modified risk claim. Taken together, the evidence supported the conclusion that the claim will be understood by consumers in the context of total health and in a manner that could reduce individual risk and benefit population health.

Evaluation of new MRTPA Data

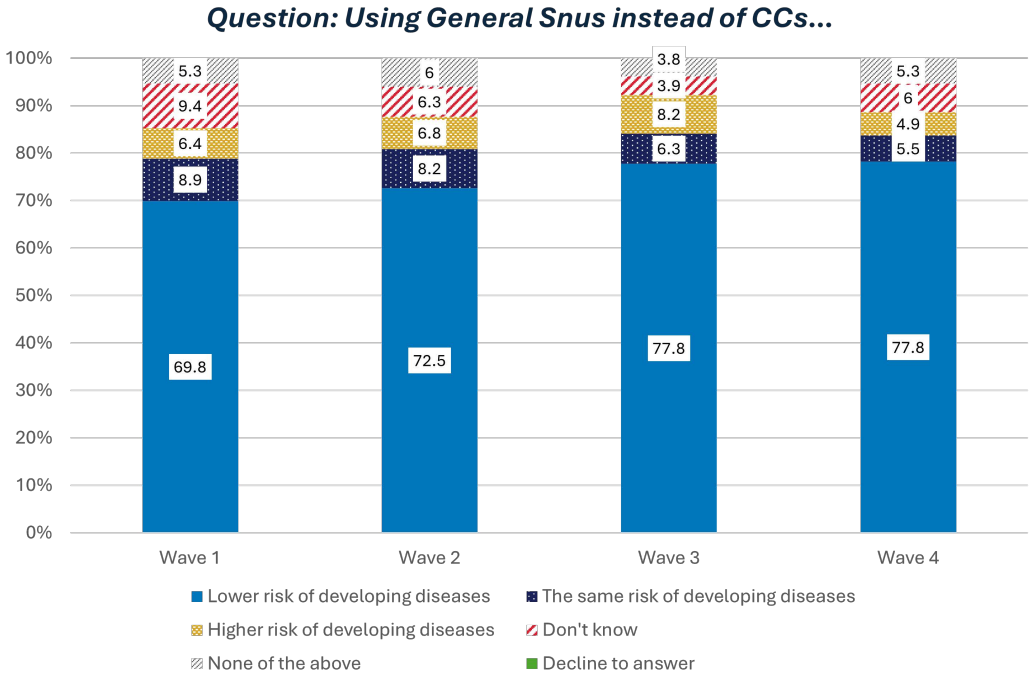
The applicant's PMSS requirements included an assessment of consumers' perceptions of the products and understanding of the claim, particularly that, to reduce their risk of disease relative to smoking, they must use General Snus exclusively. To fulfill the PMSS requirement, the applicant conducted the Patterns of Use Study, a longitudinal survey conducted online over 4 waves every 6 months from July 2020 to September 2022. Study methods are summarized below in the "Tobacco Use Behavior and Impacts to the Population as a Whole" section. Of note, all participants reported using General Snus at baseline, which was one of the study's eligibility criteria.

Participants answered items assessing perceptions of absolute risk for various tobacco products and understanding of the modified risk claim. Participants did not view the claim at any time during the Patterns of Use Study and the study did not assess prior exposure to the claim. This study was designed to be an observational study of actual use behavior in the real world among people who currently use General Snus. FDA advised the applicant not to show the claim to avoid biasing participants in the study sample by providing them with information that they would not have if they had not participated in the study. There was concern that showing participants the claim during the study could reduce the study sample's representativeness of people who use General Snus in the general population.

Understanding of the Risk Reduction Described in Claim

Most baseline participants (69.8%) responded correctly that using General Snus instead of CC "puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." The percentage of participants who understood that using General Snus instead of CCs "puts you at lower risk" remained high over all waves, ranging from 72.5% to 77.8% across waves 2-4 (Figure 1).

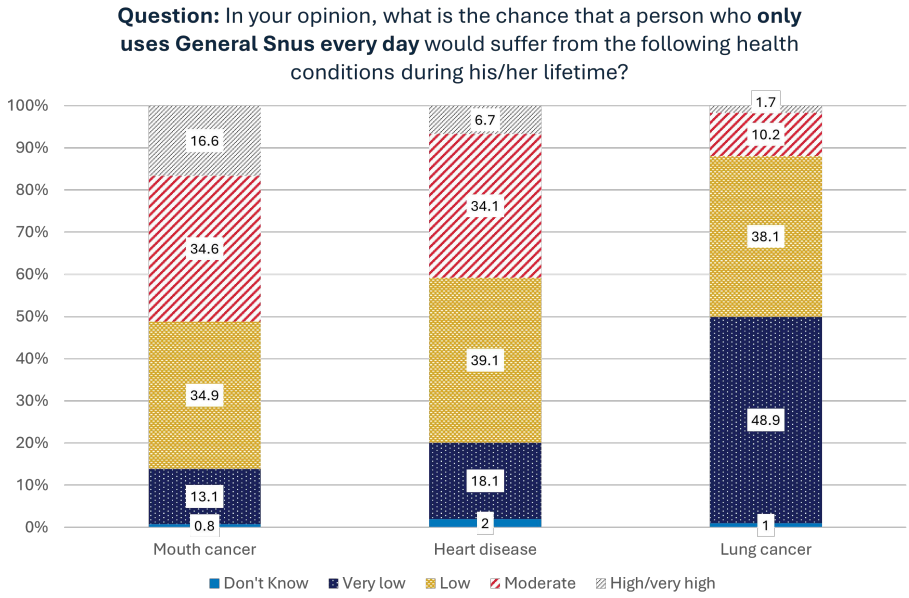
Figure 1. Understanding that using General Snus presents less risk of various diseases than smoking CCs by participants who completed each wave



Understanding the MRTPs Confer Health Risks

Participants generally viewed using General Snus every day as having some, but generally low, health risk, particularly for mouth cancer and heart disease. Figure 2 shows at baseline, 34.9% of participants perceived a low risk and 34.6% perceived a moderate risk that a person who only uses General Snus every day would suffer from mouth cancer; 39.1% perceived a low risk and 34.1% perceived a moderate risk that a person who only uses General Snus every day would suffer from heart disease. In comparison, 13.1% and 18.1% perceived a very low risk of suffering mouth cancer and heart disease, respectively. These perceptions did not change over the 4 study waves.

Figure 2. Baseline understanding that using General Snus still presents some risk



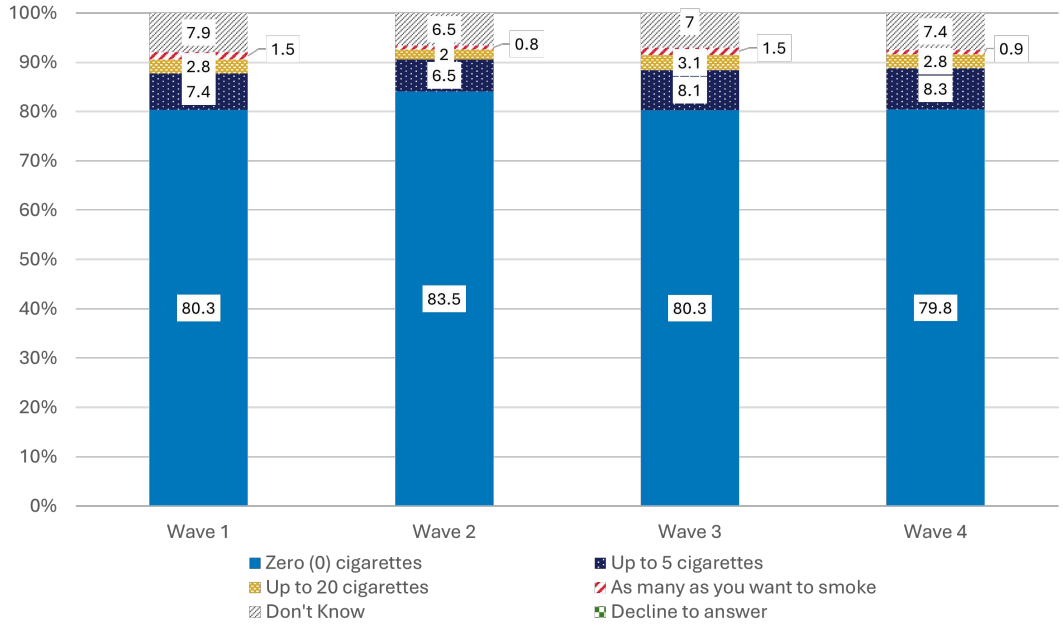
Understanding How to Use the MRTPs to Reduce One's Risk

The Patterns of Use Study used one item to assess participants' understanding that the modified risk claim does not apply to partial switching. The item asked, "If you are going to use General Snus instead of cigarettes to lower your risk of diseases, how many cigarettes, if any, can you smoke per day?" Response options were: zero (0) cigarettes; up to 5 cigarettes; up to 20 cigarettes; as many as you want to smoke; don't know; decline to answer. This item was asked only of the subset of participants who correctly responded (69.8%, n = 1155) that using General Snus instead of CCs "puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

Among the subset of participants, 80.3% correctly responded "zero cigarettes," indicating they understood that a person must exclusively use General Snus instead of CCs to reduce risk. The percentage of participants who responded correctly remained relatively stable across waves. Among participants who completed both baseline and Wave 2 and selected "lower risks" at both Waves (n = 418), 73.0% believed that the modified risk claim only applies to complete switching at both baseline and Wave 2. From baseline to Wave 2, 7.2% changed from the correct response of "zero cigarettes" to a different response at Wave 2; 13.4% changed from other responses at baseline to the correct response of "zero cigarettes" at Wave 2. Together, these results are consistent with findings submitted in the original MRTPA and suggest that people understand that they must exclusively use General Snus instead of CCs to reduce their disease risk (see Figure 3).

Figure 3. Understanding how to use General Snus to reduce risk

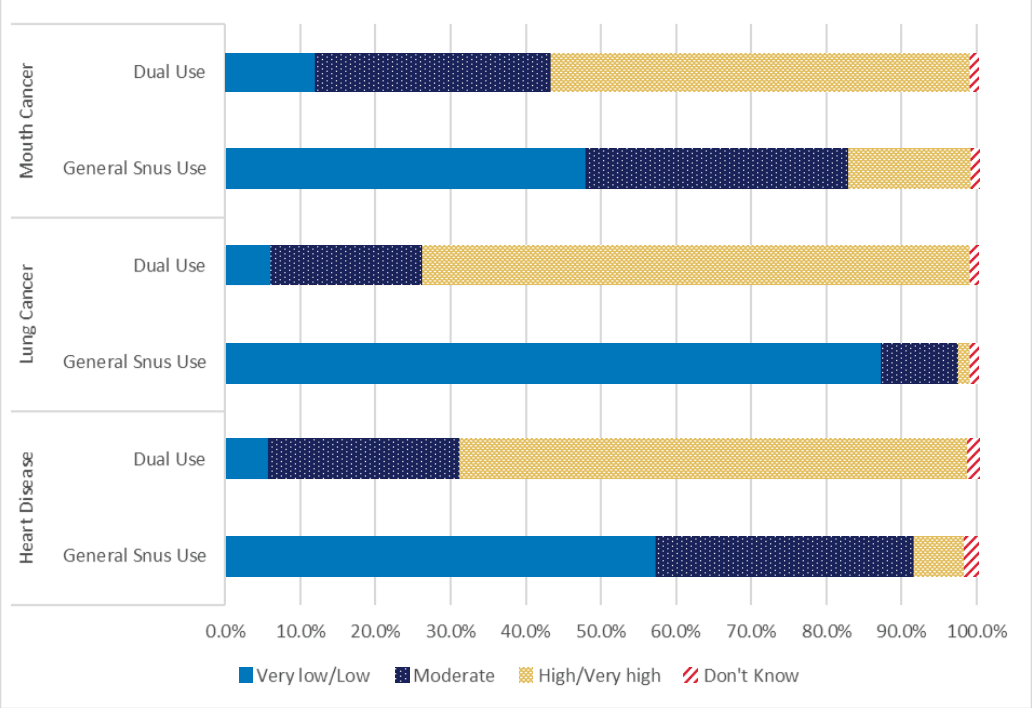
Question: If you are going to use General Snus instead of CCs to lower your risk of diseases, how man CCs, if any, can you smoke per day?



FDA also evaluated perceived risk of exclusive General Snus use relative to dual use indirectly by comparing the absolute risk of exclusively using General Snus every day with the absolute risk of daily dual use of General Snus and CCs to inform our assessment of participant understanding of how to use the MRTP to reduce risk.

At baseline and at each subsequent study wave, participants perceived dual use of CCs and General Snus as more harmful than exclusive use of General Snus across all three health outcomes (Figure 4) (Combined Postmarket Annual Report Oct. 19, 2023, PS0000306 pp. 247-248). This indicates that participants understood the reduced risk described in the claim does not apply to dual use of CCs and snus. These results are consistent with the findings submitted in the original MRTPA.

Figure 4. Perceived absolute risk of exclusive daily General Snus use and perceived absolute risk of daily dual use of General Snus with CCs at baseline, by disease outcome



Synthesis and Assessment of Relevant Statutory Standards

The 2019 TPL review concluded that exposure to the modified risk claim led to consumers understanding that the relative risk of General Snus is lower compared to CC smoking with respect to the health outcomes described in the claim. Additionally, the data provided evidence that the proposed claim did *not* lead smokers to believe that partial substitution would reduce their disease risk.

In this renewal application, the social science review concluded that the applicant demonstrates that most study participants, all of whom were General Snus users at baseline, understood that using General Snus instead of CC smoking "puts you at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

These findings, which are based on a sample of people who use General Snus, are consistent with the literature showing that people who use snus have more accurate relative risk perceptions of snus (i.e., they perceive snus as less harmful than CC smoking) compared to the general public, who tend to overestimate the relative and absolute risk of snus (Lund & Vedoy, 2019; Kaufman, et al., 2014; Wackowski & Delnevo, 2016). The findings are also consistent with Tan et al.'s (2024) study that examined participants' harm perceptions after they viewed a de-identified (i.e., product brand and product type were not disclosed) version of General Snus' modified risk claim. This study found that across groups of people who use CCs and do not use CCs, 64.6-69.2% of participants perceived that the modified risk product would be much less or slightly less harmful to their health than CCs. Overall, people who use CCs were significantly more likely to perceive modified risk products as much less harmful than CCs compared to people who never or formerly used CCs.

Most study participants also understood that using General Snus still presents health risks and they perceived that using General Snus every day carries some risk of developing mouth cancer and heart disease. Lastly, among the study participants who accurately responded that using General Snus instead of CCs "puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis," 80% understood that they could not use General Snus with CCs and experience the potential health benefits described in the modified risk claim. These proportions did not change over the course of the study. They align with similar research finding that most people who use CCs understand that to receive health benefits of using snus, they need to stop smoking completely and exclusively use snus (Pillitteri, 2020). Providing further support of consumer understanding of how to use the MRTP to reduce their risk, study participants accurately perceived dual use of General Snus with CCs as higher risk than exclusive use of General Snus (Figure 4). This suggests that participants understand that the reduced risk described in the claim does not apply to dual use of CCs and General Snus.

Overall, the new evidence provided by the applicant is consistent with evidence from the original MRTPA and shows that the risk perceptions of most people who use General Snus align with current scientific evidence regarding the health risks of using General Snus and most adult consumers understand how to use General Snus to reduce their health risk.

Evidence from the Patterns of Use Study shows that purchasers of General Snus understand that General Snus poses lower risks than smoking, while also understanding that the product still poses health risks. Importantly, the evidence also shows that these individuals understand that one must use General Snus exclusively to reduce one's risk. Overall, the evidence supports the conclusion that the claim will be understood by consumers in the context of total health and in a manner that could reduce individuals' risk and benefit population health.

3.4. TOBACCO USE BEHAVIOR AND IMPACTS TO THE POPULATION AS A WHOLE

Key findings from Original MRTPA TPL review

The 2019 TPL review noted that FDA could draw conclusions from the Perception and Behavioral Intentions (PBI) study about potential behavioral effects of the proposed modified risk products. The PBI study provided evidence that the modified risk claim would positively impact intentions to use General Snus among older (25+) people who smoke and people who use smokeless tobacco products. The PBI study also included adults who do not use tobacco, and results show mean levels of intentions to buy General Snus were low among all three groups of people who do not use tobacco (i.e., people who formerly used tobacco, older adults who never used tobacco, and young adults who never used tobacco). The 2019 TPL review concludes, "these results are supportive of the conclusion that the claim will not increase interest in the product among unintended groups, namely non-users of tobacco."

Lastly, the 2019 TPL review noted some concern with potential youth initiation rates if a modified risk claim were introduced even though surveillance data on U.S. youth tobacco use suggest snus is not a product category of interest among youth. Thus, the review concluded, "it is critical that an MRTP marketing plan target adult smokers and minimize exposure to youth…"

Evaluation of new MRTPA Data

Impacts to People Who Use Tobacco

Abuse Liability

The BCP reviewer did not identify any new information regarding abuse liability of these products.

Patterns of Use

The epidemiology review summarized U.S. nationally representative studies, as well as the applicant's Patterns of Use Study to describe current patterns of use of General Snus and its impact on the population. This section also includes summaries of published literature, analyses conducted by the applicant, and summaries of FDA's own analyses.

U.S. Prevalence of Snus Use

Among adults in the United States, the prevalence of snus use is low. The applicant cites results from the Population Assessment of Tobacco and Health (PATH) Wave 1 study (fielded September 2013 – December 2014), where Cheng et al. (2017) reports that 0.4% of U.S. adults reported currently using pouched snus. Based on population estimates from an internal analysis of PATH Study Wave 7 (fielded January 2022 – April 2023), 0.7% of adults (unweighted n = 29,780) reported currently using snus every day, some days, or on at least one of the past 30 days. The epidemiology review notes that these PATH data include all brands of snus, and General Snus would represent only a fraction of these estimates.

General Snus Patterns of Use Study

The applicant's PMSS requirements included monitoring use of the eight General Snus products in terms of uptake, dual use, and complete switching. In response to the PMSS requirement, the applicant conducted the General Snus Patterns of Use Study, a prospective study spanning two years (and four data collection time points). The study examined self-reported past 30-day tobacco and nicotine product (TNP[4]) use among people who currently use General Snus. Participants were recruited via invitation stickers placed on General Snus canisters from July 25, 2020 – August 7, 2020. Participants were also recruited directly via email to known General Snus consumers who opted in/registered to receive communications from General Snus.

To be eligible for the study, individuals must have reported current use of a General Snus product at baseline, defined as using at least once within the past 30 days prior to study initiation and using it every day or on some days prior to study initiation. They also had to be U.S. residents, aged 21 years or older, who reported being able to read and speak English. Lastly, they had to agree to participate in four surveys over a 24-month period and provide consent and personal contact information.

The applicant excluded individuals who selected "don't know" or "decline to answer" to survey questions about their gender or geographic region, who participated in consumer research on TNP in the two weeks prior to accessing the baseline survey, or who were employed in market research, marketing, advertising, TNP manufacturing, or as a physician.

[4] In the General Snus Patterns of Use Study, the applicant defines TNP use as using the following products: CC, e-cigarette, moist snuff, chewing tobacco, snus, General Snus pouches, nicotine pouches, nicotine replacement therapy, all cigars (cigar, cigarillo, filtered cigar filled with tobacco), pipe tobacco, hookah or waterpipe.

The study experienced significant attrition. Results are presented below in the "FDA's Attrition Analysis" section.

Sample characteristics

At baseline, participants had a mean age of 36.1, were predominantly White and male, and were more likely to have some college, an Associate's or Bachelor's degree, have a household income of $50,000-99,999 per year, and reside in the South and Midwest. Regarding tobacco use behaviors, at baseline most participants had used more than 200 General Snus pouches in their lifetime. Among those participants who currently smoked CCs at baseline, most had smoked more than 100 CCs in their lifetime and started smoking over 36 months prior. Among people who used CCs at baseline (n=299), more than 60% reported a readiness to quit by a quit attempt in the past 29 days (16.4%), currently trying to quit (36.8%), or having high intention to quit in the future (8.4%). Participant characteristics were mostly similar between baseline and those who participated in Wave 4; however, compared to all baseline participants, those who completed Wave 4 were more likely to have reported an income >$100,000 (33.7% vs. 28.0%) and an educational attainment of post-graduate degree (13.1% vs. 11.8%). In terms of tobacco use characteristics, those who completed Wave 4 were more likely to have had used >200 lifetime number of General Snus pouches (82.3% vs. 75.0%). Among those who smoked CCs at baseline, participants who completed Wave 4 were more likely to have reported trying to quit smoking CCs (39.7% vs 36.8%) or have a higher intention to quit smoking CCs (9.5% vs. 8.4%) than those who did not complete Wave 4. FDA notes that participant demographics in the current study differ somewhat from the general population of people who smoke CCs in terms of sex, race, and education level (Cornelius et al., 2023).

Tobacco Product Use Patterns

Table 5 presents cross-sectional patterns of tobacco use data at Waves 1 and 4 using values provided by the applicant and values derived by FDA.

Table 5. Patterns of Tobacco Use Among People Who Use General Snus, Waves 1 and 4 (cross-sectional)

	W1 (Baseline) *n*=1,655		W4 *n*=451	
	n	**% (95% CI)**	***n***	**% (95% CI)**
Any General Snus Use				
Every day	1,358	82.1 (80.1, 83.9)	273	60.5 (55.9, 65.1)
Some days	297	17.9 (16.1, 19.9)	121	26.8 (22.8, 31.2)
Exclusive General Snus Use	428	25.9 (23.8, 28.0)	100	22.2 (18.4, 26.3)
Dual use with CCs overall[a]				
Every day	120	7.3 (6.0, 8.6)	16	3.5 (2.0, 5.7)
Some days	179	10.8 (9.4, 12.4)	37	8.2 (5.8, 11.1)
Dual use with CCs only	70	4.2 (3.3, 5.3)	11	2.4 (1.2, 4.3)
Polyuse with CCs and any other TNP	229	13.8 (12.2, 15.6)	42	9.3 (6.8, 12.4)
Dual use with any non-cigarette tobacco product	928	56.1 (53.6, 58.5)	241	53.4 (48.7, 58.1)
Dual use with nicotine pouches overall[b]				
Every day	97	5.9 (4.8, 7.1)	59	13.1 (10.1, 16.5)
Some days	451	27.3 (25.1, 29.5)	107	23.7 (19.9, 27.9)

Dual use with moist snuff[c] overall

Every day	185	11.2 (9.7, 12.8)	53	11.8 (8.9, 15.1)
Some days	364	22.0 (20.0, 24.1)	75	16.6 (13.3, 20.4)

CC = combusted cigarette.

a. The applicant defined people who "dual use" as participants who reported General Snus use and CCs, regardless of other TNPs; therefore, this value is for dual use of CCs and snus regardless of other tobacco product use.

b. The applicant defined people who "dual use" as participants who reported General Snus use and nicotine pouches, regardless of other TNPs; therefore, this value is for dual use of nicotine pouches and snus regardless of other tobacco product use.

c. The applicant defined people who "dual use" as participants who reported General Snus use and moist snuff, regardless of other TNPs; therefore, this value is for dual use of moist snuff and snus regardless of other tobacco product use.

As described above, due to study eligibility criteria, all participants currently used General Snus at baseline, and the majority of participants at baseline used General Snus every day (82.1%).

Dual/Poly Use of General Snus, CCs, and Other Tobacco Products: At baseline, 25.9% of participants reported exclusive use of General Snus. The applicant defined dual use as participants who reported using General Snus and CCs regardless of other tobacco product use. FDA examined these data to further characterize dual/poly use in the sample. At baseline, 18.1% of participants reported current use of General Snus and CCs, with 4.2% reporting use of General Snus and CCs only and 13.8% reporting use of General Snus, CCs, and any other tobacco product (see Table 5). The majority of baseline participants reported either former CCs use (37.0%) or never CCs use (44.8%). More than half of the baseline sample reported using General Snus with another non-cigarette tobacco product (56.1%). Approximately 33.2% of the baseline respondents reported use of nicotine pouches and 33.2% reported use of moist snuff (groups are not mutually exclusive).

Among Wave 4 participants, approximately 3.5% (n=16) reported smoking CCs every day and 8.2% (n=37) reported smoking CCs on some days in the past 30 days. Between baseline and Wave 4, the applicant reported no significant change in the number of days smoked per month or the number of CCs smoked per day (p=0.22) among people who smoked CCs at baseline who returned for Wave 4. FDA notes that the applicant did not account for missing data when assessing percent change in frequency of smoking over time. The applicant reports that the prevalence of past 30-day CC smoking at Wave 4 did not significantly differ from baseline prevalence (p=0.62). The applicant also reports a significantly increased proportion of people who used nicotine pouches between baseline and Wave 4 (p<0.0001); however, the applicant observed no difference in moist snuff use (p=0.79).

Complete Substitution and CC Cessation: The applicant defined complete substitution as people who used General Snus and CCs at baseline but quit CCs and only used General Snus at Waves 2, 3, or 4. The applicant defined CC cessation as study participants who completely substituted General Snus for CCs plus those who quit both products. Participants in both the "complete substitution" or "CC cessation" groups may also have used other tobacco products.

The applicant provided estimates of complete substitution using the total participants who remained in the study for each follow-up wave (including people who did not smoke CCs at baseline) as the denominator. Using this approach, among all participants who completed Waves 2 (n=695), 3 (n=586), and 4 (n=451), 4.2%, 4.9%, and 5.5% of people who used General Snus reported completely substituting General Snus in place of CCs, respectively. Similarly, among participants who completed all waves of the Patterns of Use Study (n=281), 4.6% reported completely substituting General Snus for CCs at Wave 4.

FDA does not agree with the applicant's approach of including people who did not smoke CCs at baseline in the denominator when calculating proportions of CCs quitting. When calculating proportions, the numerator must be a subsample of the denominator, so it was not appropriate to include people who were not using CCs at baseline in the denominator when calculating the proportion of people who quit. Therefore, we independently analyzed the applicant's data to calculate complete substitution and CC cessation using only people who report smoking CCs at baseline (n=299) as the denominator (note: 299 includes 49 individuals who reported making a quit attempt sometime in the past 29 days at baseline, as they have not demonstrated sustained cessation behavior). As displayed in Table 6, the proportion of participants who reported completely substituting CCs with General Snus was 9.7% in Wave 2, 9.7% in Wave 3, and 8.3% in Wave 4. Notably, 9% (n=27) reported CC cessation at Wave 4. In addition, among participants who quit CCs, five used General Snus exclusively, 20 used General Snus plus another non-cigarette tobacco product, and two quit both General Snus and CCs. This reflects a conservative estimate of complete switching and CC cessation because it assumes that all the people who use CCs at baseline and who were lost to follow-up, i.e., did not complete the follow-up wave of the study, remained as people who use CCs. An alternative approach would be to assume that the people who use CCs were missing at random and calculate these estimates among people who use CCs and returned for waves 2, 3, or 4. However, as described below, participants were not missing at random. Instead, those lost to follow-up were more likely to have a low intention to quit CCs (see "FDA Attrition Analysis" section for more detail), meaning this alternative approach would not be appropriate.

Table 6. Waves 2-4 Complete Substitution and CC Cessation Among People Who Dual-Used General Snus and CCs at Baseline (n=299)

	Participants who Completed Wave 2		Participants who Completed Wave 3		Participants who Completed Wave 4	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Complete Substitution[a] of General Snus for CCs	29	9.7 (6.6, 13.6)	29	9.7 (6.6, 13.6)	25	8.4 (5.5, 12.1)
CC Cessation[b]	32	10.7 (7.4, 14.8)	31	10.4 (7.2, 14.4)	27	9.0 (6.0, 12.9)

CC = combusted cigarette.

a. The applicant defined complete substitution as participants who used General Snus and CCs at baseline but quit CC smoking and only used General Snus at Waves 2, 3, or 4. Participants who completely substituted General Snus for CCs may also use other tobacco products.

b. The applicant defined CC cessation as participants who completely substituted General Snus for CCs plus those who quit both products.

FDA's Attrition Analysis

The Patterns of Use Study experienced the highest dropout percentage between Wave 1 and Wave 2, resulting in a reduced sample size of 695 (42%) participants in Wave 2. As noted previously, by Wave 4, only 451 (27%) of the original study population (n=1,655) remained in the cohort. FDA found that attrition at Wave 2 was higher among participants who were younger, female, possessed lower levels of education, and had a lower household income (all $p < 0.05$). Similarly, at Wave 4, FDA found that attrition was higher among participants who were younger and had a lower household income (all $p<0.05$). Overall, participants who were older, male, possessed higher levels of education, and had a higher household income were more likely to be retained in the study.

Regarding tobacco use behaviors, FDA found that attrition at Wave 2 was higher among participants who used General Snus non-daily; had used less than 200 General Snus pouches in their lifetime; and smoked CCs (either daily or some-day), regardless of whether they used other tobacco/nicotine products. Likewise, FDA found that retention at Wave 2 was higher among participants who used General Snus daily; had used 200 or more General Snus pouches in their lifetime; and did not smoke CCs regardless of whether they used other tobacco/nicotine products. Quit intentions understandably appear to have played a role in study attrition. People who smoked CCs who reported greater intention to quit smoking were more likely to return at Wave 2 compared to participants who did not return (all $p < 0.05$). At Wave 4, attrition was higher among participants who used General Snus non-daily and had used less than 200 General Snus pouches in their lifetime (all $p < 0.05$). Among those who smoked CCs, there were differences in readiness to quit between baseline and those who returned at Wave 4. FDA notes that a greater proportion of those who reported trying to quit CCs returned for Wave 4 (39.7% at Wave 4 versus 36.8% at baseline), and among those not currently trying to quit, those who reported high intention to quit CCs at baseline were more likely to return two years later (9.5% at Wave 4 versus 8.4% at baseline). These findings suggest that observed tobacco use transitions may not accurately represent the actual likelihood of transition when the data appears to not be missing at random (i.e., associated with tobacco use).

Impacts to People Who do not Use Tobacco Including Youth

The applicant cites results from the 2022 NYTS finding that 1% of students reported ever use of snus and 0.5% indicated use of snus at least once in the past 30 days. An additional study provided by the applicant examining NYTS data from 2011–2020 found the prevalence of ever snus use among youth declined from 5.2% in 2011 to 2.4% in 2020, with an average annual percent reduction of 4.8% (Dai & Leventhal, 2023). Results from an internal analysis of the 2023 NYTS indicate that 0.8% of middle and high school students reported current snus use. Further, population estimates from an internal FDA analysis of wave 7 of the PATH Study (fielded January 2022 – April 2023) found that among youth (unweighted n=10,632), 0.08% reported using snus in the past 30 days. FDA notes that these estimates include all brands of snus, and General Snus would represent only a fraction of these estimates. Therefore, the percentage using General Snus, in particular, would be even lower. Overall, evidence shows low risk of initiation of General Snus products among people who do not use tobacco, including youth.

Sales Data

Overall, sales of General Snus have declined since the issuance of the MRGO. The applicant's data show that during 2019-2023, both wholesale unit and dollar sales decreased. Wholesale units (by cans) decreased from 4.94M cans to 3.47M cans between Q4 2019 – Q3 2020 and Q4 2022 – Q3 2023, and wholesale dollar sales decreased from 17.52M to 14.96M during the same period. The NielsenIQ Retail Measurement Service (RMS) Total US xAOC+Convenience data between 2019 and 2023 show that sales of General Snus products have fallen from $6.6M in the quarter the General Snus MRGO was issued (Q4 2019) to $4.9M in Q4 2023.[5]

[5] Disclaimer: The author's own analyses, calculations and conclusions informed in part by the NielsenIQ Retail Measurement Service (RMS) data through NielsenIQ's RMS for the tobacco product category smokeless tobacco for the time period 2019 through 2023 for Total US Expanded All Outlets Combined (xAOC) and convenience stores are those of the FDA and do not reflect the views of NielsenIQ. NielsenIQ is not responsible for, had no role in, and was not involved in analyzing and preparing the results reported herein, or in developing, reviewing, or confirming the research approaches used in connection with this report. NielsenIQ RMS data consist of weekly purchase and pricing data generated from participating retail store point-of-sale systems in all U.S. markets. See https://NielsenIQ.com/global/en/ for more information.

We compared retail sales trends in both units and dollars of the General Snus products in NielsenIQ RMS data to applicant reported wholesale distribution trends. For each of the four General Snus STNs, the retail and wholesale trends appear to qualitatively match across two datasets; however, it is not possible to quantitatively compare wholesale and retail sales data because of the differences in the data sources.

Overall, based on internal FDA analyses, and information submitted by the applicant, General Snus sales by units and dollars have decreased substantially since the MRGO.

Synthesis and Assessment of Relevant Statutory Standards

The 2019 TPL review concluded that the PBI study provided evidence that the modified risk claim would positively impact intentions to use General Snus among older (25+) people who smoke and people who use smokeless tobacco products and would not impact adults who do not use tobacco.

In the current application, both wholesale distribution data submitted by the applicant and retail sales data from internal FDA analyses show decreases in the dollar and unit sales of all the General Snus products. The applicant also described their attempt to limit General Snus marketing to adult tobacco consumers 21+ (see Section 3.5 below). The epidemiology review reports that NYTS and PATH data indicate generally low prevalence of snus use among U.S. youth and adults, with General Snus representing only a fraction of these small estimates because estimates are reported at the product category (not brand) level.

In the Patterns of Use Study, the majority of baseline participants who use General Snus report co-use with other tobacco products: 18% report also using CCs (4.2% General Snus and cigarette only use and 13.8% use General Snus, CCs, and other tobacco products), and 56.2% report also using a non-cigarette tobacco product.

The results of FDA's attrition analysis showed differential attrition (i.e., participants who use CCs every day and have a lower readiness to quit smoking were more likely to leave the study, and participants who used more General Snus products in their lifetime and had a higher readiness to quit, tended to remain in the study). Thus, FDA applied a conservative approach to estimating complete switching and cessation, whereby all participants who smoked at baseline and did not complete the final wave were assumed to have continued smoking. Among study participants who dual use General Snus and CCs at baseline (n=299), 9.0% reported quitting CCs by Wave 4.

The available scientific evidence supports that, as actually used by consumers, the eight General Snus MRTPs will continue to benefit the health of the population as a whole. First, there is no evidence that the MRGO has led to increased risk for youth initiation of the MRTPs or snus in general. National studies (i.e., NYTS, PATH Study) show a low prevalence of use of snus among youth overall, with General Snus accounting for a small fraction of those estimates. Although there is limited uptake of General Snus among adults, conservative estimates of switching observed in the applicant’s Patterns of Use Study suggest that some adults who smoke CCs and use General Snus at baseline, did stop smoking CCs. As TPL, I considered these findings regarding potential benefit alongside potential risks, particularly the likelihood that people who do not use tobacco products, including youth, would start using General Snus products. Given the evidence of limited impact on youth, any transition to the MRTP and away from CCs by adults can provide a benefit to population health.

3.5. MARKETING AND LABELS, LABELING, AND ADVERTISING (LLA)

Key findings from Original MRTPA TPL review

The 2019 TPL review reported that the applicant proposed to use the claim in advertisements but did not plan to add it to the products' labels. It also summarized the regulatory history regarding review of the applicant's marketing plan, sample advertisements or other marketing materials. Overall, the applicant proposed to include its claim in its advertising using the following platforms: its branded website, print and online advertising, earned media/public relations, direct mail, email, social media, and consumer activation selling events in adult only facilities. The applicant submitted a video advertisement with the proposed modified risk claim, which consumers would be able to view on the applicant's branded website.

Evaluation of new MRTPA Data

Marketing was a point of discussion at the 2024 TPSAC meeting. See the TPSAC section for more details.

We consulted the Office of Health Communication and Education (OHCE) to review the applicant's marketing materials and LLA. The OHCE review notes that the applicant's marketing was limited in scope, budget, and impressions (i.e., the number of times the intended audience(s) had an opportunity to view the advertisements). The applicant's marketing originally consisted of a branded website, trade print advertisements (i.e., advertising targeted to retailers and distributers), Facebook-only social media posts, paid digital advertising, earned media (i.e., unpaid media publicity that the applicant did not commission or pay for, such as news articles about the product), and point-of-sale advertisements using the modified risk claim. The applicant did not explicitly report media tracking and optimization or any corrective actions; however, they did report ongoing tactics to limit messaging to adult tobacco consumers 21+ (e.g., only using social media platforms with age-restriction controls; requiring age- and identity-verification at the first point of access to its branded website; avoiding use of influencers). On March 15, 2022, the applicant voluntarily removed all MRTP marketing materials from all platforms other than their age-gated website. OHCE concluded that the applicant's advertising and marketing plan implementation appears reasonably targeted to its intended audience, and that the applicant has taken appropriate actions to limit youth exposure to the products' advertising and marketing.

The social science review did not identify any implied potential modified risk claims or additional express modified risk claims that were outside the scope of the MRGO in the marketing materials and LLA submitted by the applicant since the last annual report.

The OCE Division of Promotion, Advertising, and Labeling (DPAL) reviewed the marketing materials and LLA, and concluded there is no evidence to suggest the labeling samples submitted in the renewal application are false or misleading or outside of the scope of the MRGO. If re-authorized, the applicant should be reminded that it is responsible for ensuring the MRTPs specified in the MRGO remain in compliance with the MRGO, and of its responsibility to ensure that the products comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations.

4. ENVIRONMENTAL IMPACT

4.1. DISCIPLINE FINDINGS

The following key findings were provided in the environmental science review.

The products currently under review have not been modified since the original MRGO. Therefore, their manufacture, use, and disposal are not expected to contribute to any significant new or additional environmental impacts. The applicant's environmental assessments (EA) summarize confidential business information in accordance with 21 CFR 25.51(a). The applicant's EAs include the names, qualifications, and position of the EA preparers and provide information about whether the applicant consulted any federal agencies.

Potential Environmental Impacts from Product Manufacturing and Alternatives
The continued marketing of the products with the modified risk claim is not expected to affect the environmental impacts associated with the manufacturing of the MRTPs. The applicant stated that their Gothenburg facility in Sweden is in compliance with all environmental laws in place at the time of application. The applicant stated that no additional resources for manufacturing waste disposal, such as onsite solid or hazardous waste accumulation capacity, new or expanded landfills, recycling centers, or other waste disposal or handling capacity would be needed upon renewal of the MRGO.

Potential Environmental Impacts from Product Use and Alternatives
The applicant stated that continued marketing of the products with the modified risk claim would not result in the direct introduction or changes in the ingredients due to the use of the products. The applicant-submitted EAs lack evaluation of environmental justice concerns from the use of the products or alternative actions. However, information relevant for evaluation of environmental justice impacts (e.g., demographic data) were available with other parts of the application including data submitted from the Patterns of Use Study and other peer-reviewed literature.

Potential Environmental Impacts from Product Disposal and Alternatives
The continued marketing of the products with the modified risk claim is not expected to affect the environmental impacts associated with the disposal of the MRTPs. The MRTPs and any associated waste will be disposed of in the same manner as the General Snus products without a modified risk claim. Thus, no new impacts on air, water, and land resources are anticipated from disposal of the products, per applicant provided information including the market volumes and packaging components.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Luis G. Valerio, Jr. on November 6, 2024. The FONSI was supported by an environmental assessment (EA) prepared by FDA on November 6, 2024.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1. STATUTORY REQUIREMENTS FOR AUTHORIZATION

The applicant has requested authorization under Section 911(g)(1) of the FD&C Act to continue to market the products specified in Appendix A with the following risk modification claim:

"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis."

In order for FDA to issue a risk modification order under Section 911(g)(1) of the FD&C Act, FDA must determine that the applicant has demonstrated that the proposed modified risk tobacco 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

In accordance with Section 911(g)(4) of the FD&C Act, in evaluating the benefit to health of individuals and of the population as a whole under Section 911(g)(1) of the FD&C Act, FDA must take into account:

- The relative health risks to individuals of the tobacco product that is the subject of the application;
- The increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to using the tobacco product that is the 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 the 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 approved under chapter V to treat nicotine dependence; and
  Comments, data, and information submitted by interested persons.

Under Section 911(h)(1) of the FD&C Act, FDA also must ensure that the advertising and labeling concerning the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products.

5.2. CONCLUSIONS: SCIENTIFIC EVIDENCE

My review of the scientific evidence integrated various lines of evidence regarding the MRTPs and their potential effects on health and tobacco use behavior. I undertook this assessment to determine whether the renewal of the MRGO for these MRTPAs met the statutory requirements listed above.

First, the claim “Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis" continues to be scientifically accurate. The scientific evidence, particularly the long-term epidemiological evidence reviewed under the original submission and the new evidence in the published literature, continues to substantiate that relative to CC smoking, exclusive use of the eight General Snus products poses lower risk of the above-named health outcomes. Accordingly, as TPL, I find that the available scientific evidence demonstrates that exclusive use of the eight

General Snus products will significantly reduce harm and the risk of tobacco-related disease to people who use tobacco.

Second, the available scientific evidence supports that, as actually used by consumers, the eight General Snus MRTPs will benefit the health of the population as a whole. There is no evidence that the MRGO has led to increased risk for youth initiation of the MRTPs or snus in general. National studies (i.e., NYTS, PATH Study) show a low prevalence of use of snus among youth overall, with General Snus accounting for a small fraction of those estimates. Although there is limited uptake of General Snus among adults, conservative estimates of switching observed in the applicant's Patterns of Use Study suggest that 9% of adults who smoked CCs and used General Snus at baseline (n=299), stopped smoking CCs two years later. As TPL, I considered these findings regarding potential benefit alongside potential risks, particularly the likelihood that people who do not use tobacco products, including youth, would start using General Snus products. Given the evidence of limited impact to youth, any transition to the MRTPs and away from CC by adults can provide a benefit to population health.

Third, the available scientific evidence demonstrates that General Snus consumers comprehend the information concerning modified risk and understand the relative significance of such information in the context of total health and in relation to all of the diseases and health conditions associated with the use of tobacco products. The Patterns of Use Study presents evidence that most consumers understood the information in the modified risk claim, and the findings are consistent with or exceed levels of understanding observed in studies published in peer-reviewed literature. Consumers also understand that the MRTPs confer health risks. Participants generally viewed using General Snus every day as having some, but generally low, health risk, particularly for mouth cancer and heart disease. Lastly, consumers understood how to use the MRTPs to reduce risk. Among study participants who comprehended the information in the modified risk claim, 80% understood that they could not use General Snus with CC and experience the potential health benefits described in the modified risk claim.

The available scientific evidence is consistent with the evidence reviewed in the original MRTPAs, and continues to support the original conclusions that, as actually used by consumers, the eight General Snus MRTPs will benefit the health of the population as a whole. Thus, the products sold or distributed with the modified risk information continue to meet the standards under Section 911 of the FD&C Act.

5.3. RECOMMENDATION FOR THE RENEWAL REQUEST

As TPL, I reviewed the scientific evidence regarding the MRTPs and their potential effects on health and tobacco use behavior. I undertook this assessment to determine whether the MRTPAs met the statutory requirements listed above. After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that with respect to the risk modification order renewal request, the applicant **has demonstrated** that the products sold or distributed with the modified risk information continue to meet the standard under Section 911(g)(1) of the FD&C Act, including that issuance of a renewal order is expected to benefit the health of the population as a whole, taking into account both people who use tobacco products and people who do not currently use tobacco products.

Section 911(h)(4) of the FD&C Act requires an MRTP order to be for a specified time period. FDA determines an appropriate order length on a case-by-case basis, evaluating factors specific to each MRTPA. The initial authorization for these MRTPs was for five years, and the rationale given in the 2019 TPL review was twofold. First, the General Snus products were the first MRTP authorizations issued by the Agency. Second, the TPL indicated that a five-year period would be a reasonable amount of time for trends in behavior to emerge so that FDA could assess whether the section 911(g)(1) standard of the FD&C Act continued to be met. After conducting a comprehensive review of the evidence for this renewal order, as TPL, I recommend authorization for a period of 8 years. The longer order length for this renewal reflects the lower level of uncertainty associated with the marketing of these products as MRTPs. In particular, the health risks of these Swedish snus products are very well-established in the scientific literature, and there is no new evidence that affects FDA's original conclusions on these risks. In addition, the experience to date suggests that youth initiation and use of these products remains low, and furthermore, the prevalence of youth use has remained stable over time, including after the products were authorized and marketed as MRTPs. Moreover, FDA did not identify any other indicators that the appeal of the MRTPs among youth rose during the authorization period. The applicant fulfilled the PMSS requirements of their original order, and based on that evidence, we have a greater understanding of the adults who use the MRTPs. In addition, that evidence continued to support the finding that consumers have an appropriate understanding of the relative health risks of these products compared to CCs, including that they should use them exclusively to gain a benefit relative to continuing to smoke CCs. Finally, given the relatively low prevalence of use of these products to date, an 8-year order length allows for additional time to conduct a comprehensive and robust assessment of the impact of the marketing of these products on tobacco use behaviors, including the likelihood of complete switching from CCs to these products.

5.4. POSTMARKET SURVEILLANCE AND STUDIES (PMSS)

Per 911(i)(1) of the FD&C Act, the applicant must conduct PMSS for such tobacco products to determine the impact of the order issuance on consumer perception, behavior, and health to enable FDA to review the accuracy of the determinations upon which the order was based. It is important for PMSS to continue to monitor use behaviors and consumer understanding among adults who smoke CCs to continue to assess population health.

A key to the population health benefit of these MRTPs is that adults who smoke CCs will not only adopt the products, but that they switch to exclusive use of them and cease smoking. The current behavioral evidence shows that some adults who smoke CCs and who use General Snus at baseline, stopped smoking over time. Therefore, monitoring the use of the MRTPs among adults who smoke CCs in terms of initiation, dual use, and complete switching continues to be required. The original MRTP order required the applicant to assess General Snus use behavior and consumer understanding at multiple time points. The applicant conducted a longitudinal cohort study, as this is the study design most likely to produce robust and reliable evidence to demonstrate the impact of the MRTPs in terms of uptake, dual use, and complete switching. For these renewal orders, given the specific circumstances of these MRTPs, including that they have already been marketed for the duration of the initial order and the applicant conducted a multi-year longitudinal study during this time, CTP has an increased understanding of the impact of the MRTPs on the population. As such, a repeated cross-sectional study that collects valid information on recalled history of tobacco use may also provide evidence across multiple time points to determine whether people who use the MRTPs used them to completely switch from

cigarette smoking. Such studies must also include an assessment of consumers' exposure to and understanding of the claim. In particular, PMSS must assess the extent to which users of these products understand that, to reduce their risk of disease relative to smoking CCs as described in the modified risk information, they must use General Snus exclusively. Additional requirements for PMSS are described in Appendix C below.

It is well documented that exposure to marketing impacts youth initiation of tobacco products. Even though the evidence shows low risk of youth initiation of General Snus, this could change over time. For this reason, it is critical that a marketing plan for any products that receive MRTP orders be designed to target adults who use tobacco and prioritize preventing youth exposure. Appendix D outlines controls in place, including digital marketing restrictions and tracking requirements, to ensure that marketing is appropriately targeted to adults who use tobacco. Assessment of the marketing plan and the applicant's adherence to it, along with metrics to ensure that youth exposure to tobacco marketing is being minimized, are important elements to assessing the degree to which the marketing of the MRTPs continues to benefit the population as a whole.

Modified risk granted orders should be issued for the products that are the subject of this review, as identified on the cover page of this review.

5.5. ENVIRONMENTAL CONSIDERATIONS

FDA has examined the environmental effects of continued marketing of the products with the modified risk claim and made a Finding of No Significant Impact (FONSI).

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7. APPENDICES

A. MODIFIED RISK TOBACCO PRODUCT(S)

Common Attributes of MRTPA[6,7,8,9]	
Submission date	July 17, 2023
Receipt date	July 17, 2023
Applicant	Swedish Match U.S.A. Inc.
Product manufacturer	Swedish Match U.S.A. Inc.
Product category	Smokeless Tobacco Products
Product order under 911(g)	911(g)(1) Risk Modification Order
Modified Risk Claim	Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.
Attributes	
STN	MR0000256.PD1[10]
Product subcategory	Loose Snus
Product Name	General Loose
Package Type	Cardboard Can with Plastic Lid
Product Quantity	45.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Tobacco
Additional Properties	Tobacco Cut Size: (b) (4)
STN	MR0000256.PD2[11]
Product subcategory	Portioned Snus
Product Name	General Dry Mint Portion Original Mini
Package Type	Plastic Can with Lid
Product Quantity	6.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Flavored
Flavored, as identified	Mint
Portion Count	20 pouches
Portion Mass	300 mg
Portion Length	28 mm
Portion Width	14 mm
Portion Thickness	5 mm
Additional Properties	Tobacco Cut Size: (b) (4)

[6] We interpret package type to mean container closure system and product quantity to mean quantity within the container closure system, unless otherwise identified.

[7] Product name is brand/sub-brand or other commercial name used in commercial distribution.

[8] Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. Therefore, nicotine source should be included in future submissions.

[9] Attributes in Appendix A may display converted values.

[10] Originally authorized under MR0000020.

[11] Originally authorized under MR0000021.

Attributes	Tobacco Product
STN	MR0000256.PD3[12]
Product subcategory	Portioned Snus
Product Name	General Portion Original Large
Package Type	Plastic Can with Lid
Product Quantity	24.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Tobacco
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	33 mm
Portion Width	18 mm
Portion Thickness	6 mm
Additional Properties	Tobacco Cut Size: (b) (4)
STN	MR0000256.PD4[13]
Product subcategory	Portioned Snus
Product Name	General Classic Blend Portion White Large - 12ct
Package Type	Plastic Can with Lid
Product Quantity	10.8 g
Nicotine Source	Tobacco
Characterizing Flavor	Tobacco
Portion Count	12 pouches
Portion Mass	900 mg
Portion Length	34 mm
Portion Width	14 mm
Portion Thickness	5 mm
Additional Properties	Tobacco Cut Size: (b) (4)
STN	MR0000256.PD5[14]
Product subcategory	Portioned Snus
Product Name	General Mint Portion White Large
Package Type	Plastic Can with Lid
Product Quantity	24.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Flavored
Flavored, as identified	Mint
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	34 mm
Portion Width	18 mm
Portion Thickness	5.5 mm
Additional Properties	Tobacco Cut Size: (b) (4)

[12] Originally authorized under MR0000022.

[13] Originally authorized under MR0000024.

[14] Originally authorized under MR0000025.

Attributes	Tobacco Product
STN	MR0000256.PD7[15]
Product subcategory	Portioned Snus
Product Name	General Nordic Mint Portion White Large - 12ct
Package Type	Plastic Can with Lid
Product Quantity	10.8 g
Nicotine Source	Tobacco
Characterizing Flavor	Flavored
Flavored, as identified	Mint
Portion Count	12 pouches
Portion Mass	900 mg
Portion Length	34 mm
Portion Width	14 mm
Portion Thickness	5 mm
Additional Properties	Tobacco Cut Size: (b) (4)
STN	MR0000256.PD8[16]
Product subcategory	Portioned Snus
Product Name	General Portion White Large
Package Type	Plastic Can with Lid
Product Quantity	24.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Tobacco
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	34 mm
Portion Width	18 mm
Portion Thickness	5.5 mm
Additional Properties	Tobacco Cut Size: (b) (4)
STN	MR0000256.PD9[17]
Product subcategory	Portioned Snus
Product Name	General Wintergreen Portion White Large
Package Type	Plastic Can with Lid
Product Quantity	24.0 g
Nicotine Source	Tobacco
Characterizing Flavor	Flavored
Flavored, as identified	Wintergreen
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	34 mm
Portion Width	18 mm
Portion Thickness	5.5 mm
Additional Properties	Tobacco Cut Size: (b) (4)

[15] Originally authorized under MR0000027.

[16] Originally authorized under MR0000028.

[17] Originally authorized under MR0000029.

B. AMENDMENTS AND ADDITIONAL SUBMISSIONS

Amendment(s) Received for These Applications

Submit Date	Receipt Date	Applications Being Amended	Reviewed	Brief Description
December 13, 2023	December 13, 2023	All	Yes	Response to December 13, 2023, FDA Information Request
January 17, 2024	January 17, 2024	All	Yes	Unsolicited amendment for EAs
January 30, 2024	January 30, 2024	All	Yes	Response to January 17, 2024, Deficiency Letter
February 13, 2024	February 13, 2024	All	Yes	Response to January 17, 2024, FDA Information Request

Additional Submission(s) Received for This Applicant

Submit Date	Receipt Date	Reviewed	Brief Description
Not applicable (N/A)	N/A	N/A	N/A

C. POSTMARKET SURVEILLANCE AND STUDIES (PMSS)

I recommend that the following language be included in the marketing authorization:
Under Section 911(i)(1) of the FD&C Act, FDA must require postmarket surveillance and studies for any product for which an applicant received an order under 911(g)(1) in order to: "…determine the impact of the order issuance on consumer perception, behavior, and health, to enable the Secretary to review the accuracy of the determinations upon which the order was based, and to provide information that the Secretary determines is otherwise necessary regarding the use or health risks involving the tobacco product."

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the MRTPs authorized under this order, as actually used by consumers, continue to satisfy the requirements of Section 911(g)(1)(A) and (B), is driven, in part, by use behavior. Therefore, monitoring use of the MRTPs authorized under this order in terms of initiation, dual use with other tobacco products, and complete switching is required. In particular, your PMSS must assess the tobacco use history of people who use the MRTPs (e.g., never, formerly, or currently smoke cigarettes; used other tobacco products before initiating the MRTPs). Also, your PMSS must assess the current tobacco use behaviors among people who use the MRTPs, including whether people exclusively use or dual use the MRTPs with cigarettes or other tobacco products. To adequately assess these impacts, you must conduct PMSS that includes assessing behavior and consumer understanding among people who use the MRTPs at multiple time points.

Your PMSS must also include an assessment of exposure to the modified risk claim, understanding of the modified risk claim, and perceptions of the MRTPs among people who use the MRTPs. Your PMSS must assess the extent to which people who use the MRTPs understand that to reduce their health risks relative to smoking as described in the modified risk information, they must switch from smoking cigarettes to using the MRTPs exclusively.

Your PMSS must have clear research objectives, including assessing whether the MRTPs are leading to changes in product use behaviors that are expected to benefit population health. Your PMSS protocols must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives and table shells reflecting how you plan to report your results. In addition, for each study involving human subjects, submit IRB-related information (e.g., consent forms) and recruitment strategy details (e.g., inclusion/exclusion criteria, recruitment materials, and statistical power calculations).

In addition, FDA has determined that assessing the impact of your MRTP orders on use of the MRTPs requires surveillance of sales and distribution of the MRTPs authorized under this order, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting sales and distribution of the MRTPs authorized under this order in the United States by product, major metropolitan areas, and channels where the products are sold (e.g., stores and kiosks, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the MRTPs by quarter since the granting of your modified risk granted order (for the initial reporting period) or the previous reporting period (for all reports that follow), including, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas and channels where the product was distributed and sold during the reporting period (e.g., convenience stores, food and drug stores, internet and digital

retailers, tobacco specialty shops).
- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly growth rate (percent change) in total U.S. sales and distribution of the MRTPs since this order was issued.

MRTP Use and Health Risks – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the MRTPs authorized under this order, as actually used by consumers, continue to benefit the health of the population as a whole, your PMSS must include ongoing surveillance of all adverse experiences associated with the use of the MRTPs authorized under these orders. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and unexpected adverse experiences for the MRTPs, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list, including all serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the MRTPs including nature, frequency, and potential aggravating factors.
- In addition, the PMTA orders for your tobacco products issued on November 10, 2015, require you to report to the FDA all adverse experiences that are serious, whether expected or unexpected, and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT FOR PM0000010-PM0000017, MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029, MR0000256.PD1-MR0000256.PD5, and MR0000256.PD7-MR0000256.PD9.** In addition, submit the information through our Safety Reporting Portal: https://www.safetyreporting.hhs.gov

For purposes of this reporting under this order, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening condition or illness;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting under this order, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the MRTPA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTPs and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the MRTPs authorized under this order, as actually used by the consumer, continue to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTPs and consumer perception, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTPs and consumer perception, behavior, or health. Your PMSS report must include:

- A summary of significant findings about the MRTPs from any internal and unpublished research studies conducted by you or on your behalf, and whether or not such studies were specifically required under this order.
- A bibliography of relevant publications about the MRTPs.

Submitting PMSS Protocols and Reports

Within 30 days of receiving this notice, you must submit complete protocols for your PMSS as required under section 911(i)(2) of the FD&C Act.

Label your submission clearly as a "PMSS Protocol," and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, submit each protocol as a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study.

Within 60 days of receipt of the protocol(s), FDA will determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of the data or other information that FDA designates as necessary to protect public health, pursuant to section 911(i)(2) of the FD&C Act.

FDA will notify you of and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(i) of the FD&C Act requires that the results of the PMSS be submitted on an annual basis based on the timeline outlined in the order letter. These reports must be identified as "PMSS Report" and reference the MRTPA STNs for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.

D. ADVERTISING AND PROMOTION REQUIREMENTS

I recommend the following language be included in the marketing authorization:

I. Recordkeeping and Retention

Under section 911(h)(5) of the FD&C Act, these risk modification orders require you to establish and maintain the following records:

- Records pertaining to the products' labeling, advertising, marketing, and/or promotion – whether conducted by you, on your behalf, or at your direction – including:
  - Specimens of all labeling, (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information;
  - Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers;
  - Copies of any formative research studies conducted among any audiences in the formation of the labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
  - Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing;
  - Copies of any contractual agreements regarding the creation and/or dissemination of the products' labeling, advertising, marketing, and/or promotional materials, including for example, in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction;
  - Copies of all advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including any:
    - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
    - Targeting of specific groups by age-range(s), including young adult audiences, ages 21-24, and other demographic or psychographic characteristics that reflect your intended audience(s);
    - With respect to individuals under the federal minimum age of sale of tobacco products, actions taken to restrict access to the product and limit exposure to the products' labeling, advertising, marketing, and/or promotion;
    - Use of owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the products;
    - Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
    - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; or
    - Use of public-relations or other communications outreach to create labeling for,

advertise, market, and/or promote the products.

- Copies of all records pertaining to media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), and all post-launch delivery-verification reports submitted to you from an accredited source, by channel, by product, and by audience demographics; and
- Policies and procedures for real-time digital media monitoring to identify, correct, and prevent any delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, including documentation of such monitoring activities and implementation of corrective and preventive measures.

II. Notifications

Under section 911(h)(5) of the FD&C Act, these risk modification orders require that as of the authorization date of your modified risk orders, and for a period of six months after the date of your modified risk orders, you submit the following notifications of your marketing plans and materials to FDA and all other labeling, advertising, marketing, and promotion. This notification must be received by FDA at least 30 days prior to dissemination, which includes but is not limited to the publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials. This 30-day notification requirement to submit the product's labeling, advertising, marketing, and/or promotional materials and plans in advance of their use is not for pre-approval – that is, FDA is not requiring that it review and approve such materials or plans before they may be used. Rather, such advance notification will provide FDA timely access to such materials and plans and, if needed, may allow FDA to provide you advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and on the finding that continued marketing of your products will benefit the health of the population as a whole. You may begin disseminating the materials 30 days after the notification is received by FDA.

Each 30-day notification must include:

- A single submission with a cover letter that includes the following subject line: **30-DAY NOTIFICATION for MR0000256.PD1-MR0000256.PD5, MR0000256.PD7-MR0000256.PD9**. The cover letter should include the STN(s), static product ID if applicable, corresponding tobacco product name, applicant name, date of notification, and planned dissemination date;
- Full-color copies of all such labeling, advertising, marketing, and/or promotional materials for the products. The materials must include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the material does not allow for text to be read easily, the text may be provided separately and referenced. Digital media, such as videos, must be submitted in a format that FDA is able to open and review.
- All advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, and the details, dollar amount(s) and flighting of such plans, by channel and by product, including any plans to:
  - Use competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans an media buys;
  - Target specific groups by age-range(s), including young adult audiences, ages 21-24, and other demographic or psychographic characteristics that reflect your intended audience(s), including the source of such data;

- With respect to individuals below the federal minimum age of sale of tobacco products, actions taken to restrict access to the product and limit exposure to the products' labeling, advertising, marketing, and/or promotion;
- Use owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the products;
- Use partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
- Conduct consumer engagements – whether by you, on your behalf, or at your direction – including events at which the products will be demonstrated and how access will be restricted to individuals at or above the federal minimum age of sale of tobacco products; and/or
- Use public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the products.

III. Annual Reporting

Under section 911(h)(5) of the FD&C Act, these risk modification orders require that you submit the following reports to FDA **on an annual basis**, beginning twelve months from the date of this order. For each twelve-month reporting period, these annual reports must include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029, MR0000256.PD1-MR0000256.PD5 and MR0000256.PD7-MR0000256.PD9**. The cover letter should include the STN(s), static product ID if applicable, corresponding tobacco product name(s), applicant name, date of report, and reporting period.
- A summary of the creation and dissemination of the product's' labeling, advertising, marketing, and/or promotional materials including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities.
- A description of the implementation of all advertising and marketing plans – whether conducted by you, on your behalf, or at your direction – not previously submitted, including strategic creative briefs and paid media plans by channel and by product, and the details, dollar amount(s) and flighting of such plans, by channel and by product, including a description of any:
  - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
  - Targeting of specific groups by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect the intended audience(s), including the source(s) of such data;
  - Use of owned, earned, shared, or paid media to create labeling for, advertise, market, and/or promote the products;
  - Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
  - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated and how access was restricted to individuals at or above the federal minimum age of sale of tobacco products; or
  - Use of public-relations or other communications outreach to create labeling for, advertise, market, and/or promote the products; including the original date such plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel and by product.

- An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), not previously submitted. This analysis should be verified against post-launch delivery-verification reports for paid media submitted to you or entities working on your behalf or at your direction from an accredited source.
- A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products, and including a summary of implementation of any corrective and preventive measures, not previously submitted.
- All final printed labeling (including all variations, such as those reflecting different required warnings) not previously submitted (e.g., if previously submitted under section 905(i) or previously submitted at the last reporting period and no changes were made, please list the date and manner of submission), including the date the labeling was first disseminated and the date when the labeling was discontinued, and a description of all changes to the labeling. The labeling must include all the panels and be presented in the actual size and color with legible text. The labeling must include labels, inserts/onserts, instructions, and any other accompanying information or materials for the products.
- All final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers not previously submitted (e.g., if previously submitted under 905(i) or previously submitted at the last reporting period and no changes were made, please list the date and manner of submission), along with the original date such materials were first disseminated and the date they were discontinued, and a description of all changes to the materials. The materials must be legible, include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5” x 11” piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the complete text may be provided separately and clearly referenced. Digital media, such as videos, must be submitted in a format that FDA is able to open and review.

IV. Additional Conditions for Marketing

Under section 911(h)(5) of the FD&C Act, these risk modification orders require you to:

- For any of the products’ labeling, advertising, marketing, and/or promotion appearing in your **owned digital properties** (e.g., your company-owned, consumer-directed, product-branded website(s) and/or mobile applications) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products.
- For any of the products’ labeling, advertising, marketing, and/or promotion appearing in any **shared digital properties** (e.g., your product-branded social media accounts, pages and associated content; content promoting your products on your behalf disseminated through another entity’s social media accounts) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of the available site-, platform- and content-(e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded

account and all associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the products on your behalf through the influencer's account), at the first point of access to such properties, to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product(s) running on another company's website; paid advertising for the product(s) running in social media; paid distribution of influencer content; paid advertising in streaming/Over-The-Top video programming; paid advertising in streaming/internet radio) – whether conducted by you, on your behalf, or at your direction:
    - Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of such labeling, advertising, marketing, and/or promotion to only individuals who are at or above the federal minimum age of sale of tobacco products. Such targeting must use only first- and/or second-party age-verified data, where:
        - "First-party" age-verified data is data owned by you (e.g., your customer registration data collected via site traffic to your company-owned website; data you use in direct marketing to your adult smoking customers) that you have age-verified through independent, competent, and reliable data sources; and
        - "Second-party" age-verified data is first-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data) to which you have access. Such data must be age-verified by the second party.
        - "First-party" and "second-party" data does not include data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles marketers may use to enhance audience targeting. Such data is not considered age-verified and can only be used in combination with first- and/or second-party age-verified data.
- Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) – whether conducted by you, on your behalf, or at your direction – to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to individuals under the federal minimum age of sale of tobacco products. Such monitoring also requires post-launch delivery verification reports for paid media be submitted to you or entities working on your behalf or at your direction from an accredited source.
- For any use of **partners, influencers, bloggers, and/or brand ambassadors** to create labeling for, advertise, market, and/or promote the products – whether conducted by you, on your behalf, or at your direction – disclose to consumers or viewers, via the use of statements such as "sponsored by [firm name]" in such labeling, advertising, marketing, and/or promotional materials, any relationships between you and entities that create labeling for, advertise, market, and/or promote the products, on your behalf, or at your direction.

The requirements above are intended to help ensure that your modified risk tobacco products, as actually used by consumers, will continue to benefit the health of the population as a whole. Limiting youth initiation of the products and, relatedly, youth exposure to advertising and marketing materials for the products are important factors in the population health benefit analysis. Accordingly, FDA also recommends limiting youth-exposure to any of the tobacco products' labeling, advertising, marketing,

and/or promotion appearing in print media publications.

After receiving authorization, the determination of whether the eight modified risk tobacco products, as actually used by consumers, continue to benefit the health of the population as a whole is likely to be driven by use behavior. An uptake in youth initiation and use of the products would have a significant negative impact on the population health benefit analysis. To help ensure that your products, as actually used by consumers, continue to benefit the health of the population as a whole, we strongly recommend that you take measures to limit youth initiation and use of the products, beyond limiting advertising and promotion as required in this order. For example, we strongly recommend you adopt the following measures related to all digital sales of your products:

- For any **digital sales** – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent the sale of the products to individuals who are under the federal minimum age of sale of tobacco products.

Relatedly, we request that you submit the following information to CTP on an annual basis:

- A summary of the implementation and effectiveness of any policies and procedures regarding verification of the age and identity of purchasers of the products.
- A summary of the implementation and effectiveness of any policies and procedures regarding restrictions on youth access to the products.

We remind you that if FDA can no longer make the determination that your products, as actually used by consumers, will benefit the health of the population as a whole, FDA must withdraw the modified risk orders, after an opportunity for an informal hearing. See under section 911(j)(1) of the FD&C Act. Although adopting the measures above is not in itself a guarantee that the products will continue to benefit the health of the population as a whole, it is an important step in helping to ensure that there are no grounds for withdrawal of your orders.

E. MANUFACTURING INFORMATION

I recommend the following language be included in the marketing authorization:

The PMTA orders for your tobacco products issued on November 10, 2015, require you to report to the FDA manufacturing information. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products. When cross-referencing, please provide the date of submission and location in the submission where the information is covered.

For each twelve-month reporting period, the annual reports should include:

- A cover letter that includes the following text in your subject line: **ANNUAL REPORT for PM0000010-PM0000017, MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029, MR0000256.PD1-MR0000256.PD5, and MR0000256.PD7-MR0000256.PD9**. The cover letter should include the STN(s), static product ID if applicable, and corresponding tobacco product name(s), firm name, date of report, and reporting period.
- A description of each change made to the manufacturing process, facilities, or controls during the reporting period including:
    - A comparison of each change to what was described in the PMTA(s)/MRTPA(s);
    - The rationale for making each change; and
    - A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the tobacco product(s) and the basis for concluding that each manufacturing change did not result in any modification to the product(s).[18]
- A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution and indicate any deviation(s) that may affect the characteristics of the products. For additional information on manufacturing deviations, see below.

Manufacturing Deviations

You should promptly investigate all manufacturing deviations including, but not limited to, those associated with processing, testing, packing, labeling, storage, holding, and distribution. The PMTA orders for your tobacco products issued on November 10, 2015, require that, for products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that these tobacco products contain a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death, you are required to report the deviation to FDA within 15 calendar days of identification. We request that when submitting such reports, you reference both your PMTA(s) and your MRTPA(s) for these products.

Discontinuation and Reintroduction

If you discontinue the manufacture, preparation, compounding, or processing for commercial

[18] We note that any modifications made to a tobacco product would render it a new tobacco product that would be subject to the premarket review requirements under section 910 of the FD&C Act.

distribution of these modified risk tobacco products and later decide to reintroduce the modified risk tobacco products into the market, please contact the Office of Compliance and Enforcement prior to reintroduction. Section 905(i)(3) of the FD&C Act requires you to update your product listing biannually to reflect any products that have been discontinued and/or reintroduced into interstate commerce.