



Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911 (d) of the FD&C Act – Technical Project Lead

SUBMISSION INFORMATION			
Applicant	Swedish Match USA, Inc.		
Product Manufacturer	Swedish Match USA, Inc.		
Submission Date	June 10, 2014	FDA Receipt Date	June 10, 2014
Purpose	<input checked="" type="checkbox"/> Risk Modification (911(g)(1) order) <input type="checkbox"/> Exposure Modification (911(g)(2) order)		
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.		
Primary STN(s)	MR0000020	General Loose	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description N/A
	MR0000021	General Dry Mint Portion Original Mini	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A
	MR0000022	General Portion Original Large	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A
	MR0000024	General Classic Blend Portion White Large – 12 ct	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A
	MR0000025	General Mint Portion White Large	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A
	MR0000027	General Nordic Mint Portion White Large – 12 ct	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A
	MR0000028	General Portion White Large	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description N/A
	MR0000029	General Wintergreen Portion White Large	<input checked="" type="checkbox"/> Single <input type="checkbox"/> Co-Packaged Description: N/A

Amendments			
Amendment STN	Primary STN	Description	FDA Receipt Date
MR0000030	All	Market Tracker raw data	July 31, 2014
MR0000031	All	HPHC raw data	August 1, 2014
MR0000032	All	Background information related to cognitive testing for the premarket consumer perception study	August 5, 2014
MR0000033	All	Raw data for the consumer perception study	August 15, 2014
MR0000035	All	Response to November 12, 2014, FDA Information Request	December 3, 2014

MR0000036	All	Response to November 25, 2014, FDA Information Request	December 9, 2014
MR0000038	All	Response to January 9, 2015, FDA Information Request	January 27, 2015
MR0000039	All	Response to February 6, 2015, FDA Information Request	February 20, 2015
MR0000041	All	Response to March 6, 2015, FDA Information Request	March 11, 2015
MR0000042	All	Response to April 28, 2015, Information Request	May 22, 2015
MR0000044	All	Response to June 5, 2015, Information Request	June 19, 2015
MR0000131	All	Response to December 14, 2016, FDA Information Request	September 17, 2018
MR0000138	All	Response to October 24, 2018, FDA Information Request	November 28, 2018
MR0000148	All	Amended response of November 28, 2018 Amendment	January 30, 2019
MR0000158	All	Response to April 18, 2019, FDA Information Request	April 24, 2019

PROPOSED MODIFIED RISK TOBACCO PRODUCT (SINGLE PRODUCTS)	
STN	MR0000020
Product Name	General Loose
Product Category	Smokeless Tobacco
Product Sub-Category	Loose Snus
Package Type	Cardboard Can with Plastic Lid
Package Quantity	45.0 g
Characterizing Flavor	None
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing
STN MR0000021	
Product Name	General Dry Mint Portion Original Mini
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	6.0 g
Characterizing Flavor	Mint
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing

STN	MR0000022
Product Name	General Portion Original Large
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Characterizing Flavor	None
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing
STN	MR0000024
Product Name	General Classic Blend Portion White Large – 12 ct
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Characterizing Flavor	None
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing
STN	MR0000025
Product Name	General Mint Portion White Large
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Characterizing Flavor	Mint
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing
STN	MR0000027
Product Name	General Nordic Mint Portion White Large – 12 ct
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Characterizing Flavor	Mint
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing
STN	MR0000028
Product Name	General Portion White Large
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Characterizing Flavor	None
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing

STN	MR0000029
Product Name	General Wintergreen Portion White Large
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Characterizing Flavor	Wintergreen
Product Use	<input checked="" type="checkbox"/> For Consumer Use <input type="checkbox"/> For Further Manufacturing

DISCIPLINES REVIEWED**DATE OF REVIEW**

Engineering	September 14, 2016
Chemistry	September 15, 2016
Microbiology	September 15, 2016
Toxicology	September 19, 2016
Social Science	October 27, 2016; October 11, 2019
Addiction Clinical Pharmacology	October 28, 2016
Behavioral Clinical Pharmacology	October 31, 2016
Medical	October 26, 2016
Epidemiology	November 2, 2016
Statistics	October 24, 2016; October 27, 2016
Environmental Science	October 3, 2019
OCE Review (DEM & DPAL)	November 12, 2014; September 16, 2016; September 20, 2016; October 17, 2019

Recommended Action(s)

- Issue a Modified Risk Granted letter
 Issue a Denial letter

Technical Project Lead (TPL):

/s/

Benjamin J. Apelberg, Ph.D.
 Director
 Division of Population Health Science

Signatory Decision:

- Concur with TPL recommendation and basis of recommendation
 Concur with TPL recommendation with additional comments (see separate memo)
 Do not concur with TPL recommendation (see separate memo)

/s/

Matthew R. Holman, Ph.D.
 Director
 Office of Science

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I. Executive Summary

On June 10, 2014, FDA received applications from Swedish Match North America, Inc. (SMNA)¹ requesting modified risk tobacco product (MRTP) orders under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for eight General Snus products.

SMNA initially proposed marketing these products as modified risk through the removal and revision of certain health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products. In particular, the applicant proposed to:

1. Remove “WARNING: This product can cause gum disease and tooth loss.”
2. Remove “WARNING: This product can cause mouth cancer.”
3. Revise “WARNING: This product is not a safe alternative to cigarettes” to “WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes.”

The applicant did not propose a change to the warning: “WARNING: Smokeless tobacco is addictive.”

The requests to remove warnings were evaluated as implied modified risk claims that the products cannot cause the health outcomes named (gum disease and tooth loss; mouth cancer).

On December 14, 2016, FDA completed its review of the modified risk tobacco product applications (MRTPAs) and issued a partial decision on the applications. 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 they could be amended in a way that would support the issuance of a modified risk order. Accordingly, FDA issued a Response Letter, which included the following three deficiencies:

1. You request to omit from the label and advertising “WARNING: This product can cause mouth cancer.” This warning is currently required for smokeless tobacco products generally. Omission of this warning from a subset of smokeless tobacco products indicates that unlike other smokeless tobacco products, the eight General snus products cannot cause mouth cancer. Thus, the request is to market the products with an implied modified risk claim that the products, as compared to other smokeless tobacco products, cannot cause mouth cancer.

Although the eight General snus products contain significantly lower levels of harmful carcinogens than other smokeless tobacco products currently in the U.S. market, the products contain nitrosamines, including NNN and NNK, which have been demonstrated to cause cancer, including cancers of the mouth. NNN in particular has been found to be a potent oral

¹ The applicant changed its name from Swedish Match North America (SMNA) to Swedish Match USA, Inc. during the period between submission of their initial applications and their September 2018 amendment described below. In this document we will refer to the applicant as SMNA when describing events that took place during the time that was their name. We will refer to the applicant as Swedish Match when describing events occurring subsequent to the name change.

carcinogen, and since, according to the available toxicological evidence, there is no established threshold level for NNN carcinogenicity, the products pose an increased risk of mouth cancer compared to non-use. In addition, the available epidemiological evidence on the products, as actually used by consumers in Sweden and Norway, is not sufficient to conclude that the use of the products themselves does not increase the risk of cancers of the mouth. In fact, the most recent published epidemiological study found an association between snus use and mouth cancer. Accordingly, the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular “can cause mouth cancer” and the proposed modified risk claim is not substantiated. We therefore conclude that the scientific evidence currently before the agency does not support the removal of the warning related to mouth cancer. Additionally, you did not provide evidence regarding how the modified risk information (i.e., the removal of the mouth cancer warning) would impact consumer behavior or whether consumers would understand the modified risk information in the context of total health. As a result, we are not issuing modified risk orders based on the proposed claim in its current form.

Although your applications do not support the specific request related to removing the warning related to mouth cancer, the evidence you provided may support applications that seek to market the products with other claims about relatively lower risk of mouth cancer for these products as compared to other tobacco products. Compared to the claim in your current applications, any new claim should be more precisely tailored to the supporting science. For example, you may consider pursuing explicit claims that appear outside of the health warning, elsewhere on the label or in advertising, providing information to consumers concerning the differences in mouth cancer risks between the eight General snus products and other tobacco products. These claims will need to be carefully constructed and adequately tested so as to ensure that the products meet the modified risk standards, including the requirement for consumer comprehension. We recommend that you meet with the Office of Science in FDA’s Center for Tobacco Products to discuss how your applications could be amended.

2. You request to revise the currently required “WARNING: This product is not a safe alternative to cigarettes” on the label and advertising, by replacing it with an express modified risk claim “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” Our review concluded that the claim that the eight General snus products present substantially lower risks to health may be substantiated, but only in part. That is, there is evidence to support that the eight General snus products, as actually used by consumers in Sweden and Norway, as compared to smoking cigarettes may substantially reduce the risks of some, but not all, tobacco-related diseases to individual tobacco users. The scientific evidence is insufficient to support that substantial reductions would be observed across the full range of risks posed by tobacco products, as implied by a generalized statement about health risks as compared to smoking (i.e., “substantially lower risks to health than cigarettes”). The evidence is also insufficient that U.S. consumers would use the products in the same manner as consumers in Sweden and Norway (e.g., frequency or intensity of usage; exclusive snus use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S. consumers, the products would substantially reduce the risks to smokers. In addition, FDA assessed the potential benefits and harms to the health of the population and concluded that the evidence is insufficient to determine that the products will benefit the population as a whole, taking into account, for example, smokers who switch completely to the General snus products, non-users who initiate use, and dual use by current tobacco users. Furthermore, the

scientific evidence is not sufficient to conclude that the modified risk information would be comprehended by the public in the context of total health and in relation to all tobacco-related disease, particularly in the context of a warning. As a result, we are not issuing modified risk orders based on the proposed claim in its current form.

Although your applications do not support the specific request to revise the warning, the evidence you provided may support applications that seek to market the products with other claims about relative health risks compared to cigarettes. Compared to the claim in your current applications, any new claim should be more precisely tailored to the supporting science. For example, you may consider pursuing explicit claims that appear outside of the health warning, elsewhere on the label or in advertising, providing information to consumers concerning the differences in specific health risks between the eight General snus products and cigarettes. These claims will need to be carefully constructed and adequately tested so as to ensure that the products meet the modified risk standards, including the requirement for consumer comprehension. We recommend that you meet with the Office of Science in FDA's Center for Tobacco Products to discuss how your applications could be amended.

3. The Consumer Perception Study you conducted was deficient for purposes of providing insight on potential behavioral impacts of the modified risk information or on consumer comprehension because it did not use appropriate stimuli and the methods used to assess comprehension, perceptions, and behavioral intentions were problematic. If you choose to conduct a new consumer perception and comprehension study (e.g., as part of addressing the deficiencies discussed in 1 and 2 above), you should address the deficiencies identified in our review of the Consumer Perception Study. To best inform an evaluation of the effects of the modified risk information, study stimuli should test the proposed modified risk information verbatim. As noted above, consider providing modified risk information by some means other than through the removal or revision of the warning statements. However, if modified risk information remains in the warning statement itself, your study should also examine the impact of the context of the modified risk information, i.e., how the context of the modified risk information (e.g., whether presented within a warning or as a standalone claim) affects consumer perception and comprehension.

Although a well-designed study on consumer perception and comprehension will provide indirect information on potential impacts on behavior, we recommend that you also consider assessing consumer perception, comprehension, and intentions in the context of an actual use study designed to address behavioral outcomes, particularly among current users of tobacco products. Such data would provide direct evidence of the impact of the proposed claims on consumer behavior, including evidence that U.S. consumers will use the proposed products as intended, e.g., the products will be used by current tobacco users, in lieu of, and not in addition to, smoking cigarettes.

On September 17, 2018, Swedish Match submitted an amendment to address the FDA Response Letter. The applicant addressed the deficiencies accordingly:

- Deficiencies 1 and 2: The applicant has tested and proposed a revised modified risk claim that is more precisely tailored to the scientific evidence. Specifically, the revised claim conveys specific health risks that are reduced relative to cigarette smoking, describes how the products should be used relative to cigarettes (i.e., "instead of") and *does not* include a subjective qualifier of the

risk reduction (e.g., “substantially”). The revised modified risk claim is explicit and appears outside of the health warning label. The applicant no longer requests to change or remove any warning labels.

- Deficiency 3: The applicant has conducted a new consumer perception study to evaluate the revised modified risk claim and redress the initial study’s deficiencies in terms of study stimuli and measures.

To communicate modified risk information to consumers, the applicant proposes to add the following claim to the advertising of the eight General Snus products that are the subject of these applications:

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

The applicant proposes to use the claim in advertisements but does not plan to add it to the products’ labels. The applicant submitted a new consumer study, the Perceptions and Behavioral Intentions (PBI) study, to evaluate consumer reactions to the product with the proposed claim, including consumer understanding, perceptions, and intentions to buy the products.

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:

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

The assessment of whether the products meet the MRTTP standard begins with an assessment of the scientific substantiation of the proposed modified risk information. Under Section 911(g)(1), the modified risk inquiry also involves an assessment of whether the proposed modified risk products, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users. This assessment includes an evaluation of the relative health risks to individual tobacco users, including a broad range of health risks beyond those specifically addressed in the proposed modified risk claim.

The modified risk inquiry further includes an assessment of the potential benefits and harms to 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. This assessment considers the impact of the products with the proposed modified risk information on tobacco use behaviors, such as the potential for adoption of the products on the part of current tobacco users, dual or poly use of tobacco products by current users, the likelihood of product uptake among current non-tobacco users, and the ensuing health outcomes resulting from those behaviors in the population. This evaluation includes assessments of:

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the MRTTPs;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the MRTTPs;

- The risks and benefits to persons from the use of the MRTPs compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence.

The modified risk standard also involves an assessment of consumer perception, understanding, and comprehension of the modified risk information, which may be an important precursor to consumer behavior and could affect how consumers actually use the products. Relatedly, Section 911(h)(1) of the FD&C Act requires that “any advertising or labeling concerning modified risk products 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.”

To the extent possible, the assessment integrates the various threads of evidence regarding the products and their potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the products on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population, e.g., harms to current non-users that result from significant increases in initiation of tobacco use.

In addition to the information contained in the MRTPAs, the assessment 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.

After conducting a thorough scientific review of all of these materials, I conclude that:

- The applicant **has demonstrated** that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

The 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” is scientifically accurate. The available scientific evidence, in particular the long-term epidemiological studies, reviewed under the original submission and summarized again in this review, substantiates that relative to cigarette smoking, exclusive use of the eight General Snus products poses lower risk of the above-named health outcomes. The applicant provided sufficient justification to determine that the epidemiological evidence from Sweden and Norway, although not specific to the products that are subjects of these applications, provides a reasonable characterization of the risks that would be expected to be observed among General Snus users in the U.S. if they used the products in a similar manner.

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 individual tobacco users. As described above, exclusive use of these products poses lower risks than cigarette smoking for many of the major causes of tobacco-related disease. In addition to these lower risks relative to cigarette smoking, FDA has previously determined that the levels of NNN and NNK, two potent carcinogens in smokeless tobacco products, in these General Snus products are lower than those in the vast majority of smokeless tobacco products on the U.S. market, and when used exclusively instead of other smokeless tobacco products, the General Snus products offer the potential for reductions in oral cancer risk.

Although exposure to harmful and potentially harmful constituents (HPHCs) is lower than many other smokeless tobacco products, exposure is still elevated compared with non-use and, therefore, long-term use of General Snus is not without health risks. FDA's 2016 Technical Project Lead (TPL) review concluded that Swedish snus use (compared with no use of tobacco) has been associated with increased risk of specific disease endpoints in individual epidemiological studies, including pancreatic cancer, fatal MI and stroke, diabetes, and adverse pregnancy outcomes. In addition, there are potential negative effects of nicotine exposure on the developing adolescent brain.

The additional evidence provided in the amendment also supports that, as actually used by consumers, the eight General Snus MRTPs will benefit the health of the population as a whole. The PBI study demonstrated that exposure to the claim positively impacted relative risk perceptions and intentions to buy the product among smokers aged 25 years and older, a group who stands to benefit the most from the marketing of the products. For instance, among adult smokers aged 25 years and older, participants who were exposed to a marketing video with the modified risk claim reported significantly higher intentions to buy the product compared to those who did not see the modified risk claim. Smokers under age 25 years showed a similar pattern, although the impact of the claim on intentions was not statistically significant for this group. Similarly, although not statistically significant, the pattern of results also suggested the claim may have a positive impact on smokeless tobacco users' intentions to buy the product. In addition, smokeless tobacco users across conditions showed the highest mean levels of intentions to buy the product, suggesting that the marketing of the products with the claim could increase the likelihood of current smokeless users transitioning to the eight General Snus products, which are likely to be a less toxic alternative. The applicant also provided evidence to show that consumers can understand the claim and its significance in the context of total health, including understanding that the risk reduction is not achieved via partial switching (i.e., dual use of General Snus with continued use of cigarettes). In fact, the proposed claim improved consumers' understanding of the risks of General Snus relative to cigarettes and their understanding that dual use presents greater health risks than exclusive General Snus use, thereby increasing the likelihood that consumers who use the products will do so exclusively. Together, the demonstrated impact of the claim on understanding, perceptions, and behavioral intentions, even in the context of a relatively brief exposure, supports that the proposed MRTPs will benefit the population as a whole.

The PBI study provided sufficient evidence to support product authorization. However, the results were not without limitations. In particular, although the evidence showed that exposure to the modified risk claim significantly impacted perceptions of the absolute and relative risk of the products—shifting perceptions in line with the claim, towards greater accuracy—this was true, on average, but not necessarily for all participants. In fact, a proportion of participants was not affected by the claim and continued to perceive the product as just as harmful as cigarettes, for instance. Likewise, just as some participants did not perceive General Snus as less harmful compared to cigarettes, a proportion also did not understand that exclusive use of General Snus would be less harmful than dual use of General Snus with cigarettes. Considered in the context of the totality of the evidence, these results do not undermine my conclusion that the product meets the standard in Section 911(g)(1) of the FD&C Act. However, given their relevance to the population health impact of these MRTPs, these are areas that need to be monitored through postmarket surveillance and studies (PMSS).

Finally, the new evidence supports that the population health benefits gained by cigarette smokers (and potentially other smokeless tobacco users) switching to these products will not be outweighed by the risks of initiating new tobacco use. The PBI study found low levels of intentions to buy the product among non-users of tobacco (including young adults) and, importantly, found that the inclusion of the

modified risk claim did *not* affect these intentions. Prevention of youth initiation of tobacco products is a key consideration in FDA's evaluation. Although the available evidence from epidemiological studies does not demonstrate significant youth initiation of snus products at this time, it is possible that marketing the product as a modified risk product could change this. In fact, some studies suggest that risks perceptions predict tobacco product use among youth (e.g., Song et al. 2009; Strong et al. 2019). Thus, it is essential that modified risk marketing be targeted to current tobacco users and disseminated in ways to minimize exposure among youth. Based on these conclusions, the postmarket requirements described below include measures to limit youth exposure to the products' labeling, advertising, and marketing. In addition, reporting requirements will enable FDA to monitor, among other things, the degree to which the implementation of the marketing plans is effectively targeting the intended audience and limiting exposure to youth.

Section 911(h)(4) of the FD&C Act requires an MRTP order to be for a specified time period. I recommend authorization for a period of five years, given that these would be the first MRTP authorizations issued by the Agency. Although this review has found that the products will benefit the health of the population as a whole, that determination may change over time as a function of how the product is actually used by consumers. Therefore, monitoring use of the eight General Snus products that are the subject of these applications in terms of uptake, dual use, and complete switching is required. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and understanding at multiple time points. A five-year period is a reasonable amount of time for trends in use behavior to emerge to evaluate in postmarket surveillance and studies and assess whether the standard continues to be met and whether the order should be renewed.

II. Background

A. FDA Evaluation of the Initial Submissions

On June 10, 2014, FDA received applications from SMNA seeking risk modification orders under Section 911(g)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) for 10 smokeless snus tobacco products² listed by the following FDA Submission Tracking Numbers:

- MR0000020: General Loose, smokeless tobacco, loose snus, 1.59 oz (45g), cardboard can (SKU 4852);
- MR0000021: General Dry Mint Portion Original Mini, smokeless tobacco, snus portions, 0.21 oz (6g), 20 – 0.3g portions, plastic can (SKU 4800);
- MR0000022: General Portion Original Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4880);
- MR0000023: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can (SKU 4877);

² Although ten applications were initially submitted, a request for withdrawal of two applications, MR0000023, General Classic Blend Portion White Large-15 count and MR0000026, General Nordic Mint Portion White Large-15 count, was submitted on October 7, 2015. On October 15, 2015, FDA issued withdrawal acknowledgement letters for these two products. Therefore, the remaining eight products were considered for an order under Section 911(g)(1). FDA also issued premarket tobacco product authorization (PMTA) marketing orders for these eight products but with no modified risk information in October 2015.

- MR0000024: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can (SKU 4878);
- MR0000025: General Mint Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4352);
- MR0000026: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can (SKU 4876);
- MR0000027: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can (SKU 4875);
- MR0000028: General Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4881); and
- MR0000029: General Wintergreen Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can (SKU 4882).

SMNA initially proposed marketing these products as modified risk through the removal and revision of certain health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products. In particular, the applicant proposed to:

1. Remove “WARNING: This product can cause gum disease and tooth loss.”
2. Remove “WARNING: This product can cause mouth cancer.”
3. Revise “WARNING: This product is not a safe alternative to cigarettes” to “WARNING: No tobacco product is safe but this product presents substantially lower risks to health than cigarettes.”

The requests to remove warnings were evaluated as implied modified risk claims that the products cannot cause the health outcomes named (gum disease and tooth loss; mouth cancer).

The MRTPAs were referred to TPSAC in April 2015. On December 14, 2016, FDA completed its review of the MRTPAs and issued a partial decision on the applications. Based on its evaluation of the evidence, the TPL Review (2016) reached several conclusions regarding the requested warning label changes.

In regard to the request to remove the gum disease and tooth loss warning, FDA issued a denial, concluding that the claim was not substantiated and that the applicant had not demonstrated that as actually used by consumers, the products sold or distributed with the proposed modified risk information 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.

In regard to the request to remove the mouth cancer warning and revise the “safe alternative” warning, FDA determined that the applications in their current form did not provide sufficient evidence to meet the standard of Section 911(g)(1), but they could be amended in a way that would support the authorization of a modified risk order. Accordingly, FDA issued a Response Letter, describing three deficiencies:

1. You request to omit from the label and advertising “WARNING: This product can cause mouth cancer.” This warning is currently required for smokeless tobacco products generally. Omission of this warning from a subset of smokeless tobacco products indicates that unlike other smokeless tobacco products, the eight General snus products cannot cause mouth cancer. Thus, the request is to market the products with an implied modified risk claim that the products, as compared to other smokeless tobacco products, cannot cause mouth cancer.

Although the eight General snus products contain significantly lower levels of harmful carcinogens than other smokeless tobacco products currently in the U.S. market, the products contain nitrosamines, including NNN and NNK, which have been demonstrated to cause cancer, including cancers of the mouth. NNN in particular has been found to be a potent oral carcinogen, and since, according to the available toxicological evidence, there is no established threshold level for NNN carcinogenicity, the products pose an increased risk of mouth cancer compared to non-use. In addition, the available epidemiological evidence on the products, as actually used by consumers in Sweden and Norway, is not sufficient to conclude that the use of the products themselves does not increase the risk of cancers of the mouth. In fact, the most recent published epidemiological study found an association between snus use and mouth cancer. Accordingly, the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular “can cause mouth cancer” and the proposed modified risk claim is not substantiated. We therefore conclude that the scientific evidence currently before the agency does not support the removal of the warning related to mouth cancer. Additionally, you did not provide evidence regarding how the modified risk information (i.e., the removal of the mouth cancer warning) would impact consumer behavior or whether consumers would understand the modified risk information in the context of total health. As a result, we are not issuing modified risk orders based on the proposed claim in its current form.

Although your applications do not support the specific request related to removing the warning related to mouth cancer, the evidence you provided may support applications that seek to market the products with other claims about relatively lower risk of mouth cancer for these products as compared to other tobacco products. Compared to the claim in your current applications, any new claim should be more precisely tailored to the supporting science. For example, you may consider pursuing explicit claims that appear outside of the health warning, elsewhere on the label or in advertising, providing information to consumers concerning the differences in mouth cancer risks between the eight General snus products and other tobacco products. These claims will need to be carefully constructed and adequately tested so as to ensure that the products meet the modified risk standards, including the requirement for consumer comprehension. We recommend that you meet with the Office of Science in FDA’s Center for Tobacco Products to discuss how your applications could be amended.

2. You request to revise the currently required “WARNING: This product is not a safe alternative to cigarettes” on the label and advertising, by replacing it with an express modified risk claim “WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.” Our review concluded that the claim that the eight General snus products present substantially lower risks to health may be substantiated, but only in part. That is, there is evidence to support that the eight General snus products, as actually used by consumers in Sweden and Norway, as compared to smoking cigarettes may substantially reduce the risks of some, but not all, tobacco-related diseases to individual tobacco users. The scientific evidence is insufficient to support that substantial reductions would be observed across the full range of risks posed by tobacco products, as implied by a generalized statement about health risks as compared to smoking (i.e., “substantially lower risks to health than cigarettes”). The evidence is also insufficient that U.S. consumers would use the products in the same manner as consumers in Sweden and Norway (e.g., frequency or intensity of usage; exclusive snus use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S.

consumers, the products would substantially reduce the risks to smokers. In addition, FDA assessed the potential benefits and harms to the health of the population and concluded that the evidence is insufficient to determine that the products will benefit the population as a whole, taking into account, for example, smokers who switch completely to the General snus products, non-users who initiate use, and dual use by current tobacco users. Furthermore, the scientific evidence is not sufficient to conclude that the modified risk information would be comprehended by the public in the context of total health and in relation to all tobacco-related disease, particularly in the context of a warning. As a result, we are not issuing modified risk orders based on the proposed claim in its current form.

Although your applications do not support the specific request to revise the warning, the evidence you provided may support applications that seek to market the products with other claims about relative health risks compared to cigarettes. Compared to the claim in your current applications, any new claim should be more precisely tailored to the supporting science. For example, you may consider pursuing explicit claims that appear outside of the health warning, elsewhere on the label or in advertising, providing information to consumers concerning the differences in specific health risks between the eight General snus products and cigarettes. These claims will need to be carefully constructed and adequately tested so as to ensure that the products meet the modified risk standards, including the requirement for consumer comprehension. We recommend that you meet with the Office of Science in FDA's Center for Tobacco Products to discuss how your applications could be amended.

3. The Consumer Perception Study you conducted was deficient for purposes of providing insight on potential behavioral impacts of the modified risk information or on consumer comprehension because it did not use appropriate stimuli and the methods used to assess comprehension, perceptions, and behavioral intentions were problematic. If you choose to conduct a new consumer perception and comprehension study (e.g., as part of addressing the deficiencies discussed in 1 and 2 above), you should address the deficiencies identified in our review of the Consumer Perception Study. To best inform an evaluation of the effects of the modified risk information, study stimuli should test the proposed modified risk information verbatim. As noted above, consider providing modified risk information by some means other than through the removal or revision of the warning statements. However, if modified risk information remains in the warning statement itself, your study should also examine the impact of the context of the modified risk information, i.e., how the context of the modified risk information (e.g., whether presented within a warning or as a standalone claim) affects consumer perception and comprehension.

Although a well-designed study on consumer perception and comprehension will provide indirect information on potential impacts on behavior, we recommend that you also consider assessing consumer perception, comprehension, and intentions in the context of an actual use study designed to address behavioral outcomes, particularly among current users of tobacco products. Such data would provide direct evidence of the impact of the proposed claims on consumer behavior, including evidence that U.S. consumers will use the proposed products as intended, e.g., the products will be used by current tobacco users, in lieu of, and not in addition to, smoking cigarettes.

Finally, in addition to the above deficiencies, the Response Letter included requests and recommendations for any potential future submission, summarized as: (1) if a population model is

provided, a request for detailed information pertaining to its construction and inputs; and (2) a recommendation to follow best practices for conducting systematic reviews and meta-analyses.

B. September 2018 Amendment

On September 17, 2018, Swedish Match submitted an amendment to address the FDA Response Letter. The applicant addressed the deficiencies accordingly:

- Deficiencies 1 and 2: The applicant has tested and proposed a revised modified risk claim that is more precisely tailored to the scientific evidence. Specifically, the revised claim conveys specific health risks that are reduced relative to cigarette smoking, describes how the product should be used relative to cigarettes (i.e., “instead of”) and *does not* include a subjective qualifier of the risk reduction (e.g., “substantially”). The revised modified risk claim is explicit and appears outside of the health warning label. The applicant no longer requests to change or remove any warning labels.
- Deficiency 3: The applicant has conducted a new consumer perception study to evaluate the revised modified risk claim and redress the initial study’s deficiencies in terms of study stimuli and measures.

In addition, the applicant acknowledged the request and recommendation provided by FDA.

With this amendment, the applicant requests marketing authorization under Section 911(g)(1) to market the above mentioned eight modified risk General Snus products with the following explicit risk modification claim in product advertising: “Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.” The applicant submitted a new consumer study, the Perceptions and Behavioral Intentions (PBI) study, to evaluate consumer reactions to the product with the revised proposed claim, including consumer understanding, perceptions, and intentions to buy the product.

C. Proposed Modified Risk Labels, Labeling, and Advertising (LLA)

The applicant seeks MRTP orders under Section 911(g)(1) of the FD&C Act for the eight General Snus tobacco products 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.”

The applicant proposes to use the claim in advertisements but does not plan to add it to the products’ labels. The applicant is no longer requesting any changes to the currently required smokeless tobacco warning labels on its LLA materials.

The September 2018 amendment did not include a description of the marketing plan, sample advertisements or other marketing materials, with the exception of the storyboard for the video used as the PBI study stimulus. FDA requested this information on October 24, 2018, to which the applicant responded on November 26, 2018. Upon review of this submission and the sample marketing materials included, FDA identified possible additional modified risk claims. FDA contacted the applicant to clarify

the applicant's intentions. The applicant later submitted an amendment on January 30, 2019, which replaced the information previously provided in the November 2018 amendment related to the general marketing strategy and sample advertisements. This amendment also included a revised video storyboard. In particular, after discussions with the Agency, the applicant revised the storyboard for the proposed video by removing the text related to reducing impurities and the word "approved".

As described in that amendment, the applicant proposes 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.

D. Tobacco Products Scientific Advisory Committee

Pursuant to Section 911(f) of the FD&C Act, FDA referred the original MRTPAs to the Tobacco Products Science Advisory Committee (TPSAC), and TPSAC reported its recommendations on the applications during an open public committee meeting held on April 9-10, 2015. At the meeting, TPSAC discussed the ten submitted MRTPAs, including the adequacy of the scientific evidence to support the originally proposed modified risk claims.³ The TPSAC discussion was summarized in the 2016 TPL Review.

The September 2018 amendment to the applications was also referred to TPSAC and TPSAC reported its recommendations on February 6, 2019, during an open public meeting. TPSAC discussed FDA's preliminary assessment of the amendment and had the opportunity to raise any additional issues or concerns raised by the revised claim. A brief summary is provided here. Meeting materials, including complete meeting transcript, are available at: <https://www.fda.gov/advisory-committees/tobacco-products-scientific-advisory-committee/2019-tpsac-meeting-materials-and-information>

FDA shared its preliminary assessment of the amendment with TPSAC, noting that the applicant has addressed previous concerns by proposing an explicit modified risk claim that is more specific and independent of the warning label, and by conducting a new consumer perception study that does not suffer from the methodological flaws of its original study. TPSAC was asked to discuss FDA's preliminary assessment, including whether the revised modified risk claim raises new or additional concerns regarding the potential impact on: (a) consumer understanding, and (b) population health. TPSAC did not identify specific concerns about FDA's preliminary assessment. The TPSAC discussion addressed a number of topics. One topic of discussion was the issue of youth, including the lack of youth data provided by the applicant and the potential risks to youth, suggesting that while snus use among youth may currently be low, this could change. Another topic of interest was the claim wording. The committee discussed the importance of communicating accurate information and acknowledged challenges to ensuring universal interpretation among all subgroups. Some members felt that the phrase "instead of" was vague and suggested alternative phrasing (e.g., "switching completely"). The committee also discussed the level of misunderstanding among the U.S. population regarding the relative harms of smokeless products in general, and some argued that the proposed modified risk products may help benefit the health of the population as a whole by providing "corrective" information

³ Information about the meeting, including the complete transcript, is archived and available at: <https://wayback.archive-it.org/7993/20170404143857/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm434209.htm>.

in the context of widespread misinformation. In general, TPSAC felt that the applicant's study was reasonable, and its proposed modified risk claim seems to convey an accurate message. TPSAC highlighted the importance of strategic post-market surveillance for any product that obtains marketing authorization as an MRTP. Concerns raised in TPSAC's discussion related to (a) youth and (b) claim interpretation are addressed elsewhere in this review and in the Social Science review.

E. Public Availability

Pursuant to Section 911(e) of the FD&C Act, FDA made SMNA's MRTPAs available to the public (except matters in the applications that are trade secrets or are otherwise confidential, commercial information). The public comments on the original applications (including their amendments) are discussed in the individual discipline and TPL reviews (2016). The September 2018 amendment (including its subsequent amendments) was also made available to the public. The docket for public comment on this amendment to the MRTPAs was open from October 29, 2018 to May 13, 2019. FDA received 24 public comments from individuals, academia, and other organizations. In addition to legal and advocacy issues, the comments included independent consumer perception information, critiques of the applicant's studies and interpretation of findings, and concerns about potential appeal to youth. The issues and concerns raised in the public comments were also identified during FDA's scientific review of the applications. FDA considered all significant comments when making the final determination. Specific comments are addressed in the Social Science review.

III. Summary of Scientific Evidence

The September 2018 amendment proposes a revised modified risk claim and includes a new consumer perception study conducted to assess that claim. The evidence provided in the original submissions, along with this amendment, is the basis for FDA's assessment. This review integrates the new evidence with our existing assessment and conclusions to evaluate (1) substantiation of the revised claim and assessment of the relative health risks of the products to individual tobacco users, (2) consumer understanding of the proposed revised modified risk claim, and (3) the potential impact of the products with the proposed revised claim on tobacco use behavior and the health of the population as a whole. Where appropriate, this review will quote or directly reference the 2016 TPL review.

A. Relative Health Risks of the Proposed MRTPs to Individual Tobacco Users

The 2016 TPL review provided a comprehensive review of the evidence related to the health risks to individuals from the use of General Snus products. This included an assessment of the manufacturing process, product ingredients, and levels of harmful and potentially harmful constituents (HPHCs) in the finished products, clinical studies, toxicological evidence, and long-term epidemiological evidence of the health effects of Swedish snus. No additional information regarding health risks was included in the September 2018 amendment.

The original evaluations from the perspective of engineering, chemistry, and microbiology led to the following conclusion in the 2016 TPL review (p.31):

We conclude that sufficient information has been provided to characterize the product composition in terms of ingredients and additives and ensure that manufacturing processes and controls that can affect the product composition, chemical stability, [and] 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 clinical pharmacology review concluded that the products were expected to produce reinforcing effects and have an abuse potential. The underlying scientific findings from the toxicological review "generally support[ed] the FDA's conclusion regarding the lower risks to health presented by the General Snus products."

In the scientific review of the original applications, epidemiological studies provided the strongest evidence for assessing the long-term health risks of Swedish snus use as compared to the risks from cigarette smoking. Although the epidemiological literature is not product-specific, the body of literature from Sweden and Norway is particularly relevant to the assessment of the long-term health risks of the General Snus products that are the subject of these MRTPAs, as noted in the 2016 TPL review (p.33):

Many, if not all, of the studies included in the modified risk applications for the General Snus products did not include the specific products that are the subject of the applications. Rather, the studies included products that were available in Sweden and Norway. SMNA justifies the use of the studies by asserting that during the period of study, SMNA products dominated the Scandinavian snus market; that the SMNA products in those studies conformed to the GOTHIA TEK® standard; and, any observed health effects are the result of use of products that meet the GOTHIA TEK® standard.

FDA's review of the eight General Snus products confirms that the eight General snus products also conform to the GOTHIA TEK® standard. 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.

The applicant also argues that the products it manufactures today have lower HPHCs than the products that were the basis of the long-term epidemiological studies of Swedish snus. During the February 6 TSPAC meeting, the applicant described the GOTHIA TEK® standard as one that has changed over time with the inclusion of new HPHCs and the reduction of maximum allowable levels of HPHCs. In its February 6 presentation, the applicant presented data showing substantial reductions in total tobacco-specific nitrosamines, NNN, NNK, and benzo(a)pyrene from the mid-1980s until today.

In the section that follows, we review the epidemiological evidence on the health risks of Swedish snus to assess whether the proposed revised modified risk claim is scientifically accurate and to describe the health risks to individual tobacco users of Swedish snus relative to other use behaviors.

1. Claim Substantiation and Health Risks of the Proposed MRTPs Compared to Cigarettes

This section provides a summary of and builds on FDA's findings, as reported in the 2016 TPL and Epidemiology reviews, regarding the risk of Swedish snus use compared to cigarette smoking, for each of the health outcomes included in the revised modified risk claim. We focus on these outcomes both because they are the subject of the revised modified risk claim and because they make up the vast majority of the tobacco-related disease burden. For detailed information on additional health

outcomes, including tooth loss and gum disease, esophageal cancer, stomach cancer, pancreatic cancer, diabetes, and adverse pregnancy outcomes as well as all-cause mortality, see FDA's previous findings in the 2016 TPL and Epidemiology reviews.

Note, the intended meaning of the claim may be subject to interpretation. In particular, the phrase "instead of" might be interpreted as complete replacement of one product for another (i.e., use of snus to the exclusion of cigarettes). Alternatively, it is possible that one might interpret the phrase to mean a discrete instance of substitution – i.e., substituting snus for one cigarette. The assessment of scientific accuracy in this section is based on a comparison of exclusive snus use to cigarette smoking (i.e., for the former interpretation). The issue of consumer understanding of the claim is addressed separately, in the context of the consumer perception study, including the degree to which consumers understand that exclusive use of the General Snus products is the means by which the described risk modification is achieved.

Table 1 presents summary relative risks from published meta-analyses or pooled analyses of the association between Swedish snus use and mouth cancer, heart disease, stroke and lung cancer compared with non-users of tobacco. The Roosaar et al. (2008) study, which is not a meta-analysis, was the only study FDA is aware of that assessed the relationship between Swedish snus use and emphysema or chronic bronchitis. For comparison, Table 1 provides the cigarette smoking relative risks based on the American Cancer Society's Cancer Prevention (CPS) II study, which was used for comparison in Appendix 6a of the original MRTPAs.

In characterizing the health risks of the products that are the subject of these MRTPAs, the applicant relied on published epidemiologic studies of the health effects of Swedish snus conducted in Sweden and Norway over the last several decades. The applicant presented this information on health risk in various sections of the applications: Sections 6.1.1 "Health Risks Associated with the Use of Snus as Compared to Using Cigarettes," 6.1.2. "Health Risks Associated with Switching to Snus from Cigarettes and Dual Use as Compared to Quitting Tobacco Entirely or Continued Smoking," 6.1.3. "Health Risks Associated with Switching from Cigarettes to Swedish Snus compared to Switching to FDA-approved Tobacco Cessation Products or Medication," and Chapter 5 and the accompanying Appendix V of the 2013 ENVIRON Snus Monograph.

In assessing the scientific accuracy of the revised modified risk claim, we focus on the epidemiologic evidence, drawing on the review conducted by the Epidemiology Branch in 2016. Epidemiology reviewers conducted a full substantive review of the epidemiological evidence provided in the body of the applications, along with supplemental material provided in the appendices. In addition, the review incorporated findings from the independent systematic search for published epidemiologic studies of Swedish snus use to identify any additional studies that pertain to the health risks of Swedish snus.

Table 1. Results from published studies¹ 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 (Data Source: MRTPAs, Appendix 6A 2013 Environ Snus Monograph; Rostron et al. 2018)

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

¹All 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

In its 2016 review, FDA considered the available evidence regarding the health risks of these snus products in its evaluation of the scientific accuracy of the requested claims and to inform its assessment of individual health risks of the product. The assessment of evidence pertaining to mouth cancer was in response to the request to remove the mouth cancer warning, i.e., an implied modified risk claim that the products, as compared to other smokeless tobacco products, cannot cause mouth cancer. In the revised claim, the question is not whether snus can cause mouth cancer, but whether the risk of mouth cancer among exclusive snus users is lower than among cigarette smokers. The remaining health outcomes were originally assessed in regard to the applicant's request to change the "not a safe alternative" warning to "substantially lower risks to health than cigarettes" claim. For this claim, FDA evaluated the evidence regarding how the risks among exclusive snus users compared to cigarette smokers across a host of tobacco-related diseases, to assess whether there was a reduction of risk among the former group, and if so, whether it could be characterized as "substantial". Because the revised claim does not use the modifier "substantially", the question here is limited to the first part: whether the risk of the specific diseases listed in the proposed modified risk claim is lower among exclusive snus users than among cigarette smokers.

Mouth Cancer

FDA previously assessed the evidence related to mouth cancer to evaluate the request to remove the mouth cancer warning and determined that the evidence did not support the implied claim that snus use cannot cause mouth cancer.

The conclusions related to mouth cancer were summarized in the 2016 TPL review (p. 37):

Given the presence of nitrosamines in the products that are the subject of these applications, the lack of a threshold dose for mouth cancer, the fact that the most recent published epidemiological study (Roosaar et al. (2008)) found a statistically significant association between snus use and mouth cancer, and the limitations related to the epidemiological evidence, the totality of the available toxicological and epidemiological evidence demonstrates that the eight General snus products can cause mouth cancer, and, correspondingly, does not support the removal of the warning that these products can cause mouth cancer.

However, as noted in its Response Letter, FDA also concluded that the evidence the applicant provided may support applications that seek to market the products with other claims about relatively lower risk of mouth cancer for these products as compared to other tobacco products. The revised modified risk claim from the applicant does not claim that the product cannot cause mouth cancer, but instead refers to the General Snus products having lower risk for mouth cancer than cigarettes. In support of the revised modified risk claim, the 2016 Epidemiology review concluded that the risk of oral cancer is lower in exclusive Swedish snus users than in cigarette smokers. In particular, the review concluded that "...based on the evidence presented by the applicant, the risk of oral cancer is lower in exclusive Swedish snus users than in cigarette smokers". This is clearly seen by comparing the relative risks for Swedish snus and cigarette smoking compared to non-users, shown in Table 1.

Heart Disease

FDA previously assessed the evidence pertaining to heart disease and concluded that although the risk of cardiovascular disease (CVD) in exclusive snus users may be lower than in cigarette smokers, there was insufficient evidence to conclude that use of these products instead of smoking would result in substantially lower risk of CVD. The revised modified risk claim no longer uses the phrase "substantially lower."

The evidence related to CVD (ischemic heart disease, coronary heart disease, myocardial infarction (MI), and overall CVD) was summarized in the 2016 TPL review (p. 51):

The applications contained studies evaluating the association between snus use and acute cardiovascular effects as well as chronic effects. Acute effects evaluated included increased heart rate and blood pressure. Longer term risk factors considered were hypertension, obesity, and evidence of vascular disease (e.g., myocardial infarction, sudden cardiac death, and stroke). Biochemical markers such as lipids or insulin resistance were also considered. The body of published literature examining the relationship between use of snus and the various measures of CVD risk and disease outcomes includes four experimental/clinical studies, two cohort studies, two case-control studies, and twelve cross-sectional studies.

The physiologic effects of nicotine would not be expected to be different for snus compared to other nicotine-containing products. Cigarette smoke, however, has other cardiovascular toxins not found in snus, e.g., carbon monoxide and fine particulate matter. Inhalation of these toxins has significant cardiovascular effects.

Six cohort studies (Bolinder et al., 1994; Haglund et al., 2007; Hansson et al., 2009; Janzon and Hedblad, 2009; Johansson et al., 2005; Roosaar et al., 2008), four case-control studies (Hergens et al., 2005; Huhtasaari et al., 1992; Huhtasaari et al., 1999; Wennberg et al., 2007), and one cross-sectional study (Bolinder et al., 1992) reported relative cardiovascular risk estimates for both snus users and smokers in the same population. The study by Janzon and Hedblad (2009) was excluded from the sponsor's analysis because this study did not provide a smoking relative risk estimate that was adjusted or controlled to exclude the potential effects of snus use. The cross-sectional study conducted by Bolinder et al. (1992) was not included in the sponsor's plot analysis because a later study by Bolinder et al. (1994), which was included, presented a prospective analysis of the same cohort. Additional studies evaluating short-term effects of snus on biochemical markers were included in the monograph.

A number of studies suggest an association between Swedish snus and fatal MI and post-MI mortality. In the Swedish Construction worker cohort among never-smoking men, there was a positive association between Swedish snus use and fatal MI (RR= 1.32, 95% CI=1.08-1.61) (Hergens et al. 2007). Two different case-control studies observed elevated but not statistically significant associations between Swedish snus use and fatal MI (Huhtasaari et al., 1999; Hergens et al., 2005). A recent pooled analysis of 8 prospective cohort studies observed a borderline elevated 28-day case-fatality after an acute myocardial infarction (AMI) among current Swedish snus users (RR=1.28, 95% CI=0.99-1.68) (Hansson 2012). In a meta-analysis, Boffetta and Straif (2009) pooled six studies from Sweden and did not find an elevated risk of any myocardial infarction (cardiovascular diseases, ischemic heart disease or myocardial infarction) (RR = 0.87, 95% CI = 0.75, 1.02). However, they did find a significant association between Swedish snus and fatal myocardial infarction based on five Swedish studies (RR=1.27, 95% CI=1.07-1.52). In another meta-analysis, Lee (2007) pooled five studies from Sweden and did not find an association between Swedish snus and ischemic heart disease or acute myocardial infarction (RR = 1.06, 95% CI = 0.83, 1.37).

In our independent systematic search of the literature, we identified an additional study that examined Swedish snus use and mortality risk after myocardial infarction (Arefalk et al., 2014). Among MI patients who were followed up for an average of 2 years, those quitting Swedish snus had nearly half the risk of dying post-MI compared with patients who continued to use Swedish

snus post-MI (age and sex-adjusted HR=0.51, 95% CI=0.29-0.91; multivariable-adjusted HR=0.57, 95% CI=0.32-1.02).

The data clearly show acute cardiovascular effects related to use of snuff or snus. These effects, which include increased heart rate and blood pressure, are likely due to nicotine. It is not clear whether these acute effects lead to long-term changes or chronic cardiovascular disease. Many of the epidemiological studies are limited by the fact that a large percentage of the snuff/snus users were current or former smokers. In the studies where 'snus only' users can be clearly identified, the number of snus users is small. Additionally, in most of the studies that had long-term follow-up, information about subjects' tobacco usage was obtained at baseline so any changes in behavior over the course of the study were not recorded.

In summary, while the negative effects of cigarette smoking on cardiovascular health are well established, the data for SLT, including Swedish snus, are less so. Nevertheless, several studies have found an association between snus use and CVD mortality, fatal MI, or post-MI mortality, including recent pooled and meta-analyses. These findings deserve further investigation. Although the risk of CVD in exclusive snus users may be lower than in cigarette smokers, there is insufficient evidence to conclude that use of these products instead of smoking would result in substantially lower risk of CVD.

Subsequent to the completion of FDA's review, Rostron and colleagues (2018) conducted a systematic review and meta-analysis of studies pertaining to smokeless tobacco use and circulatory disease risk, providing a more comprehensive examination of this relationship, including more recent data (e.g., Timberlake et al., 2017). Based on this review, risk of ischemic heart disease was not increased in Swedish studies of current smokeless tobacco users who were never smokers (vs. non-users) (RR=1.04, 0.93-1.16, n=3), but was significantly increased in U.S. studies of smokeless tobacco users who were never smokers (RR=1.17, 95% 1.08-1.27, n=3). As described above and in the 2016 TPL review, the evidence derived from studies of Swedish smokeless tobacco users is particularly relevant to this assessment because products manufactured by Swedish Match dominated the Scandinavian market during the period of these studies and the Swedish Match products in those studies conformed to the company's GOTHIA TEK® standard. By comparison, as shown in Table 1, cigarette smoking has been found to increase risk of CVD by a factor of about 1.5- to 3-fold. This most recent review provides additional clear evidence that the heart disease risks due to Swedish snus use are lower than the risks from cigarette smoking.

Stroke

FDA previously assessed the evidence pertaining to stroke and concluded that although the risk of stroke in exclusive snus users may be lower than in cigarette smokers, there was insufficient evidence to conclude that use of these products instead of smoking would result in substantially lower risk of stroke. The revised modified risk claim no longer uses the phrase "substantially lower."

The evidence related to stroke was summarized in the 2016 TPL review (p. 53):

The applicant stated that two case-control (Asplund et al., 2003; Koskinen and Blomstedt 2006) and four cohort studies (Bolinder et al., 1994; Haglund et al., 2007; Hansson et al., 2009; Janzon and Hedblad, 2009) reported relative risk estimates for stroke among both snus users and smokers in the same population. The applicant also stated that, among snus users, stroke (CVA) risk estimates from the individual studies and summary estimates from meta-analyses (Boffetta and Straif, 2009; Lee, 2007; Lee, 2011) were not statistically significantly increased. Among

smokers, risk estimates from most of the individual studies were statistically significantly increased and where increased, generally ranged from 1.4 to 3.0. Meta analyses and large US cohorts were generally consistent with the results from the individual studies. Overall, the stroke risk is consistently at least 40% greater among smokers compared to non-users of tobacco. The analyses in three of the four studies (Asplund et al. 2003; Bolinder et al., 1994; Hansson et al., 2009) controlled for hypertension, an important risk factor for stroke.

The findings for the association between Swedish snus and fatal stroke and post-stroke mortality have been mixed. In addition to the Hergens 2008 study as noted in the ENVIRON Snus Monograph, in which current Swedish snus use was associated with fatal ischemic stroke (RR=1.72, 95% CI=1.06-2.78), the older study of the same cohort by Bolinder 1994 observed an elevated, but non-significant risk of death due to stroke among current Swedish snus users, in younger men ages 35 to 54 (RR=1.9, 95% CI=0.6-5.7).

Boffetta and Straif (2009) reviewed three studies of any stroke (cerebrovascular disease or stroke) from Sweden and did not find a significant association between Swedish snus and stroke (RR = 1.02, 95% CI=0.93-1.13) or fatal stroke (RR=1.25, 95% CI=0.91-1.70). Lee (2007) reviewed two studies from Sweden and did not find a significant association between Swedish snus and stroke (RR = 1.17, 95% CI = 0.80-1.70).

In our independent systematic search of the literature, we identified an additional pooled analysis of 8 prospective cohort studies of Swedish snus and risk of stroke (Hansson et al., 2014). The analysis was restricted to never smokers and included the Swedish Construction Worker cohort. No association between Swedish snus and the overall risk of stroke or stroke subtypes was observed, but an elevated risk of 28 day case fatality (OR=1.42, 95% CI=0.99-2.04) and stroke mortality (HR=1.32, 95% CI=1.08-1.61) was observed, after adjusting for age, BMI, and year of diagnosis.

SMNA acknowledges that nicotine has hemodynamic effects that may increase the risk of vascular diseases – specifically elevations of heart rate and blood pressure. It is not clear whether these effects lead to increased stroke risk among snus users. In summary, while the negative effects of cigarette smoking on stroke risk are well established, the data for SLT, including Swedish snus, are less so. Nevertheless, recent evidence suggests an association between snus use and fatal stroke, which deserves further investigation. Although the risk of stroke in exclusive snus users may be lower than in cigarette smokers, there is insufficient evidence to conclude that use of these products instead of smoking would result in substantially lower risk of stroke.

The updated systematic review discussed above (Rostron et al., 2018) also found that risk for stroke was not increased in Swedish studies of current smokeless tobacco users who were never smokers (vs. non-users) (RR=1.04, 0.92-1.17, n=1) but was significantly increased in U.S. studies of smokeless tobacco users who were never smokers (RR=1.28, 95% 1.01-1.62, n=3). As described above and in the 2016 TPL review, the evidence derived from studies of Swedish smokeless tobacco users is particularly relevant to this assessment because products manufactured by Swedish Match dominated the Scandinavian market during the period of these studies and the Swedish Match products in those studies conformed to the company's GOTHIA TEK® standard. By comparison, as shown in Table 1, cigarette smoking has been found to increase risk of stroke by a factor of about 1.5- to 3-fold. This most recent review provides additional clear evidence that the risk of stroke due to Swedish snus use is lower than the risk from cigarette smoking.

Lung Cancer

In support of the revised modified risk claim, FDA's review of the evidence pertaining to lung cancer risk previously concluded that the use of Swedish snus does not have a significant effect on lung cancer risk. Therefore, and as clearly shown in Table 1, the risk of lung cancer is substantially lower in exclusive Swedish snus users than in cigarette smokers.

The evidence related to lung cancer was summarized in the 2016 TPL review (p. 50):

The observed relative risks reported by the individual studies and the summary estimates from the two meta-analyses suggest that the use of Swedish snus that are the subject of these applications does not have a significant effect on the risk of lung cancer.

The evidence related to lung cancer was summarized in the Epidemiology review (p. 24):

In section 6.1.1.3 of the applications, the applicant presented two Swedish studies that assessed the association between Swedish snus and lung cancer and estimated the association between smoking and lung cancer (Bolinder 1994; Luo 2007). A third study of Swedish snus and lung cancer, not mentioned in section 6.1.1.3 of the applications, was described in section 5.3.5 of Chapter 5 of the ENVIRON Monograph. The applicant concluded that "Swedish snus users are at no greater risk of developing lung cancer than non- or never-users of tobacco, while smokers are 7 to 30 times more likely to develop lung cancer." (p 406 section 6.1.1.3 of the applications)

Based on the evidence presented by the applicant, we agree with the applicant that there does not appear to be an elevated risk of lung cancer among exclusive Swedish snus users. Although use of snus exposes individuals to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen, the levels are lower than traditional smokeless tobacco products, which have not been conclusively linked to increased lung cancer risks. On the contrary, smokers are at greatly increased risk of lung cancer. Based on this evidence, we conclude that the risk of lung cancer is substantially lower in exclusive Swedish snus users than in cigarette smokers.

Emphysema and Chronic Bronchitis

In support of the revised modified risk claim, FDA's Epidemiology review of the evidence pertaining to respiratory disease, including emphysema and chronic bronchitis, previously concluded that the risk of respiratory disease is substantially lower in exclusive Swedish snus users than in cigarette smokers.

The evidence related to respiratory disease was summarized in the 2016 TPL review (pp. 50-51):

Snus is an oral SLT product and therefore is unlikely to cause respiratory disease or chronic obstructive lung disease (COPD), diseases commonly associated with cigarette smoking. Although there are harmful and potentially harmful constituents (HPHCs) found in SLT products, none have been linked to development of chronic lung disease unless inhaled. The pathobiology of COPD involves multiple injurious processes which are triggered by inhaled toxicants and modified by cellular senescence and infection.

The literature submitted by SMNA on the relationship between COPD and use of SLT products such as Swedish snus (Schivo et al. 2014) and various types of NRTs (Jimenez-Ruiz et al., 1998) suggests that there is no relationship, which is believed to be due to the lack of inhaled irritants being introduced directly into the lungs (Kirkham and Barnes, 2013; Stevenson et al., 2006).

Nicotine concentrations do not appear to be relevant to the development of COPD. Age seems to be the most important factor in the development of COPD in Swedish non-smokers (Hagstad et al., 2012) though SLT products were not analyzed as part of this study.

The primary risk factor for COPD and other chronic respiratory diseases is cigarette smoking. Since the 'tar' of cigarette smoke is the primary source of toxins, snus (a smokeless product) is much less likely to be a significant risk factor for COPD or other respiratory diseases. The large review articles and population studies confirm minimal, if any, increase in risk of respiratory disease related to use of the products which are the subject of these applications.

Summary and Conclusion

Swedish Match seeks MRTP orders for the eight General Snus products with the following 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." This revised modified risk claim addresses the issues that precluded a finding of scientific substantiation in FDA's 2016 review of the applications. In particular, the claim regarding mouth cancer risk is now in relative comparison with cigarette smoking, rather than an implied claim that the products cannot cause mouth cancer. Second, rather than a generalized claim about "lower risks to health than cigarettes", the revised claim names specific diseases/endpoints for which the evidence supports lower risks. Finally, whereas the original statement characterized the risk reduction as "substantial", the revised claim does not use this or any other modifier.

In sum, FDA's assessment of the scientific evidence supports the conclusion that exclusive users of snus have lower risk relative to cigarette smokers for each of the following health outcomes: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. This assessment supports the revised modified risk claim as scientifically accurate. Overall, the available scientific evidence demonstrates that the products that are the subject of these applications, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users.

2. Health Risks of Proposed MRTP Use Compared to Other Use Behaviors

In the original review of SMNA's applications, FDA evaluated the health risks of General Snus compared with a range of other products and use behaviors. As described in the 2015 TPL review for the General Snus premarket tobacco product applications (PMTAs) (FDA, 2015), General Snus products contain significantly lower levels of NNN and NNK than other smokeless tobacco products in the U.S. market. As a result, cancer risk is expected to be lower from the use of General Snus products compared to many other smokeless tobacco products. Although exposure to HPHCs, including nitrosamines, is lower than many other smokeless tobacco products, exposure is still elevated compared with non-use and, therefore, long-term use of Swedish snus is not without health risks. The 2016 TPL review concluded that Swedish snus use (compared with no use of tobacco) has been associated with increased risk of specific disease endpoints in individual epidemiological studies, including pancreatic cancer, fatal MI and stroke, diabetes, and adverse pregnancy outcomes. In addition, there are potential negative effects of nicotine exposure on the developing adolescent brain. Similarly, FDA previously concluded that "the health risks from the use of General Snus products that are the subject of the applications is greater than those posed by cessation" and "greater than those posed by FDA-approved cessation therapies." (FDA 2016, p. 58) In terms of dual use of General Snus and cigarettes, as opposed to exclusive use of General Snus products, FDA has concluded that "there is insufficient information to conclude that

smokers who use snus in conjunction with smoking will realize any reductions in risk of tobacco-related disease.” (FDA 2016, p. 59)

B. Effects of the Proposed MRTPs on Consumer Understanding and Perception

Consumer understanding and perceptions of the MRTPs, including of the claim, are psychological constructs considered precursors to intentions to use the product. Understanding—or comprehension of the claim content—is relevant to the potential population health impact of the marketing of the MRTPs to the extent that it affects who uses the products and how they use them. For instance, if an MRTP is shown to reduce tobacco users’ risk via exclusive use of the product, then consumers should understand they will not benefit from the risk reduction if they use the MRTP in conjunction with another tobacco product. Relatedly, Section 911(h)(1) requires that the modified risk communication enable consumers 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.

As discussed above, the applicant’s original consumer perception study suffered from methodological flaws that limited the utility of those data. Accordingly, FDA concluded that there was not sufficient information to conclude that participants comprehended the modified risk information. Because the claim has since been revised, and a new study conducted, the present evidence and assessment replaces the conclusions of the prior review.

As noted earlier, the revised proposed claim uses the phrase “instead of” – which could be interpreted to mean one can reduce his/her risk by using the General Snus products as a replacement for and to the exclusion of cigarettes. However, it is also possible that a consumer could interpret the phrase “instead of” to imply a situational, rather than complete, pattern of product substitution. This is of consequence because, if this latter interpretation of the claim led to users initiating the MRTPs while maintaining some level of smoking, such users would not experience a reduction in their individual risk and, in turn, the MRTPs would not benefit population health. Therefore, of particular interest in the assessment of consumers’ understanding of the claim is the extent to which they understand that the risk reduction is *not* achieved by partial switching (i.e., maintaining some level of cigarette smoking after initiating snus use).

1. Perception and Behavioral Intentions (PBI) Study

The applicant conducted one quantitative study, the PBI Study, to assess the proposed modified risk claim’s effects on consumer understanding, perceptions, and behavioral intentions related to tobacco products. Prior to conducting this study, the applicant initiated its claim development process with qualitative research, involving three phases of focus groups and triads.

The PBI Study was a between-subjects experimental study administered via computer, smartphone, or tablet. Characteristics of this study are presented in Table 2. Participants were randomized to view a video advertisement for General Snus that included either the proposed modified risk claim, one of two alternative test claims, or no test claim. The video is approximately one minute long and begins by introducing General Snus and describing its product features (i.e., smokeless, spitless, chilled, upper-lip pouch). It states that General Snus is made with “only the best” air-dried tobaccos; pure, clean water;

salt; and other natural and artificial flavors found in everyday food items. The video then describes the production process for General Snus, stating that it reduces “impurities found in other tobaccos” and that the product meets “strict Swedish food-grade standards.” Concurrently, the video depicts an image of an “APPROVED” stamp being applied. The video then provides the audio and text of the proposed 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.”

This is followed by a web address (“Learn more at GeneralSnus.com”) and an audio and textual display of one of the four currently required smokeless tobacco warning labels. The video in the control condition included the same information but without the proposed claim.⁴

Note, the video ad featured one General Snus product style (a 24-count portioned product) in two flavors (mint and wintergreen), even though the MRTPAs include products with other flavors (including unflavored) and styles (including a loose product). We do not consider this to be a major limitation of the study. The aim of the PBI Study was to evaluate the effects of the proposed claim on consumer understanding and intentions to use products. For these General Snus products, we do not expect that consumer understanding of the claim would vary based on the products’ flavor or product style. Intentions to use the product, on the other hand, may vary based on the flavor and product style. The applicant’s rationale for using mint and wintergreen products in the study stimuli was that these are popular variants, accounting for around 70% of General Snus sold in the U.S., which is a reasonable justification. In contrast, if the study had included unpopular product flavors or styles – such as unflavored products that most users do not initiate with – this could cause the study to underestimate the claim’s effects on use intentions (e.g., because consumers may not intend to use a product that they expect to dislike, even if the product confers reduced risk compared to other products).

After viewing the video, participants responded to items assessing the following key study outcomes: comprehension of the proposed modified risk claim, perceptions of absolute and relative health risks of using General Snus, intentions to buy General Snus, and intentions to quit smoking and using other tobacco products. While answering these questions, participants were able to re-watch the video by clicking a link on the page, though very few did so (0.5%; November 26, 2018 amendment, p. 24). This evaluation focuses on the condition in which participants viewed the ad with the proposed claim (i.e., Claim 1 in the PBI Study documentation) and the condition in which participants viewed the video advertisement with no test claim, which serves as an experimental control.

⁴ Note: As described above (pp. 17-18), the video advertisement the applicant proposes to use in their marketing (January 30 amendment) varies slightly from the version used in the PBI Study. In particular, the revised version does *not* reference reduced impurities; does not display the word “APPROVED”; and characterizes the Swedish food-grade standards as “tough” rather than “strict”. FDA does not expect these differences to affect the validity of the PBI Study’s results, given the findings and given that the additional text was included in both the control and test conditions.

Table 2: Characteristics of the applicant’s Perceptions and Behavioral Intentions (PBI) Study

Overview	Survey administered via computer, smartphone, or tablet. Participants viewed a General Snus video advertisement with or without the proposed modified risk claim and then responded to measures of perceptions and intentions.
Study Design	<p>Between-subjects experiment with stratified randomization across three factors:</p> <ul style="list-style-type: none"> • Modified risk test claim: one condition with the proposed modified risk claim; two conditions with alternative test claims; one control condition without a test claim.[‡] • Warning label: four currently required smokeless tobacco warning labels. • Product flavors: mint and wintergreen. <p>Analyses collapsed across warning labels and product flavors, except where noted.</p>
Sample	<p>10,532 adults recruited from a mix of online panels to reflect demographic characteristics of online U.S. adult population of legal age for tobacco use.</p> <p>Tobacco user groups[†] included:</p> <ul style="list-style-type: none"> • Young adult never tobacco users ($n = 1,914$) • Older adult never tobacco users ($n = 1,936$) • Young adult cigarette smokers ($n = 1,828$) • Older adult cigarette smokers ($n = 1,942$) • Adult former cigarette smokers ($n = 1,942$) • Adult smokeless tobacco users ($n = 970$) <p>This review focuses on the 5,289 participants in the proposed modified risk claim condition and the control condition, including 958 young adult never tobacco users, 977 older adult never tobacco users, 970 former smokers, 916 young adult smokers, 982 older adult smokers, and 486 smokeless users.</p>
Key Outcomes	<ul style="list-style-type: none"> • Intentions to buy General Snus • Intentions to use tobacco products • Intentions to quit cigarettes and other tobacco products • Perceptions of absolute and relative health risks • Comprehension of the proposed modified risk claim • Believability of the proposed modified risk claim

[‡] The three tested claims were: “Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.”; “Using General Snus products instead of cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users.”; “No tobacco is totally safe, but using General Snus instead of cigarettes puts you at a lower risk of chronic lung diseases and other tobacco-related ailments.”

[†] Note: Young adult refers to participants of legal age to use tobacco products to age 24 years. Older adult refers to participants over age 24 years. Adult refers to participants of legal age to use tobacco products or older.

Comprehension

Two items assessed recognition of information from the video advertisement, including claim text. Results show that the majority of participants were able to correctly answer these items (>75%). In particular, the item assessing participants’ processing of the claim’s message was a multiple-choice question about the effects of using General Snus instead of cigarettes on their risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. Response options included “puts you at lower risk...”, “does not affect your risk...”, “puts you at higher risk...”, and “None of the above.” The option defined as correct was the one that matched the proposed modified risk claim

(“puts you at lower risk...”). Among participants who viewed the video with the proposed claim, most selected the correct response (78-88% across all tobacco user groups; PBI Study Report, pp. 155-160). In contrast, among participants who viewed the video without the proposed claim, few selected the “lower risk” response option (9-19% across all tobacco user groups; PBI Study Report, pp. 155-160). As noted above, participants were able to review the video as they answered questions if they wanted, but few did so. These findings suggest that most consumers exposed to the proposed claim attended to the video stimulus and processed the claim itself.

Perceptions of Absolute Risks

Consumers’ perceptions of absolute risk are part of their overall assessment of risk and thus contribute to our assessment of their understanding of the claim in the context of total health. Moreover, because the proposed modified risk claim identifies specific disease endpoints, we would expect that the claim might lower perceptions of risk of those diseases. At the same time, whereas the claim conveys a risk reduction relative to cigarettes, this should not lead consumers to perceive the *elimination* of disease risk. The PBI Study examined participants’ perceptions of absolute risks of General Snus including whether, after viewing the video with the proposed modified risk claim, adult consumers understood that using General Snus causes health risks.⁵

Adding the proposed modified risk claim to the video advertisement reduced consumers’ perceptions of the absolute health risks of using General Snus for all eight health effects assessed. This was true among all tobacco user groups tested. However, though the absolute level of perceived risk was reduced after exposure to the claim, relative to no claim, consumers still perceived daily use of General Snus as causing substantial risks of the eight health effects assessed (Figure 1). Together these findings suggest the claim improved participants’ understanding of the products’ risks and are consistent with an appropriate understanding of the claim in the context of total health.

⁵ Note: In analyses of all risk perception items (PBI Study Report, pp. 87-209), the applicant disregarded “Don’t know” responses when calculating percentages. However, the Social Science review noted that visual inspection of the data tables suggested that the proposed claim may have affected participants’ likelihood of responding “Don’t know” on some risk perception items. Because “Don’t know” is a potentially meaningful response, the Social Science review included “Don’t know” responses in the denominators of the percentages for risk perception items. As a result, the percentages presented in this review differ slightly from those provided in the PBI Study Report.

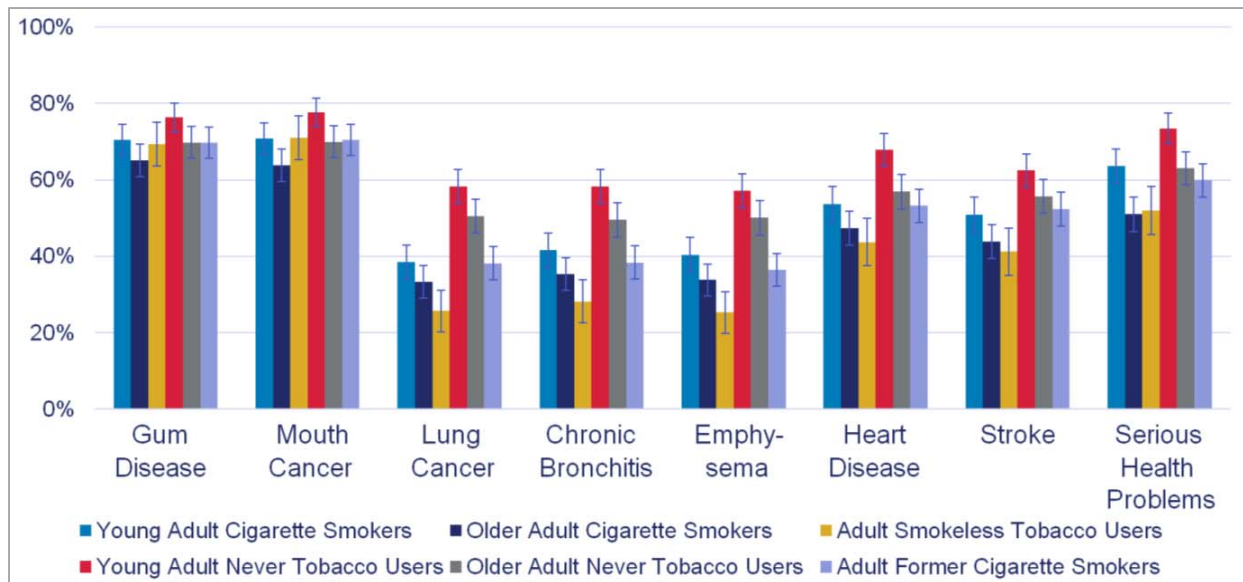


Figure 1. Percentages of participants in the PBI Study who perceived a “moderate,” “high,” or “very high” chance of health effects from using General Snus, after viewing the video ad with the proposed claim. The item asked, “If a typical person uses General Snus® every day and no other tobacco products, what is the chance that person would suffer from the following health conditions during his/her lifetime?” Options included: “very low chance,” “low chance,” “moderate chance,” “high chance,” “very high chance,” and “Don’t know.” Source: Based on data from the PBI Study Report. Error bars: 95% CIs.

Perceptions of Health Risks Compared to Cigarettes

The PBI Study also examined perceptions of the relative risk of the product as it compared to cigarettes. Because the proposed modified risk claim conveys a message that users can reduce their disease risk by using General Snus instead of smoking cigarettes, understanding of the claim would be reflected in their perceptions of relative risk.

Adding the proposed claim to the video advertisement for General Snus substantially increased the percentage of smokers who perceived General Snus as lower in specific health risks than cigarettes (Figure 2). As shown in Figure 2, smokers who viewed the video with the proposed claim, compared to without it, were statistically significantly more likely to perceive daily General Snus use as presenting a lower chance of all eight health effects tested compared to daily smoking. Adding the proposed claim had similar effects among smokeless tobacco users (not shown). This pattern of results suggests that participants’ perceptions were affected in the expected direction based on the message of the claim (i.e., General Snus poses lower risk of the diseases named compared to cigarettes). We note that this pattern held across all health effects assessed—which includes the diseases named in the claim as well as one that was not: gum disease. However, overall, the proposed claim brought participants’ perceptions into better alignment with current scientific evidence regarding the health risks of using General Snus, as reflected in the applicant’s proposed claim that using General Snus instead of cigarettes would put consumers at lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. These findings support the conclusion that participants had an appropriate understanding of the claim in the context of total health.

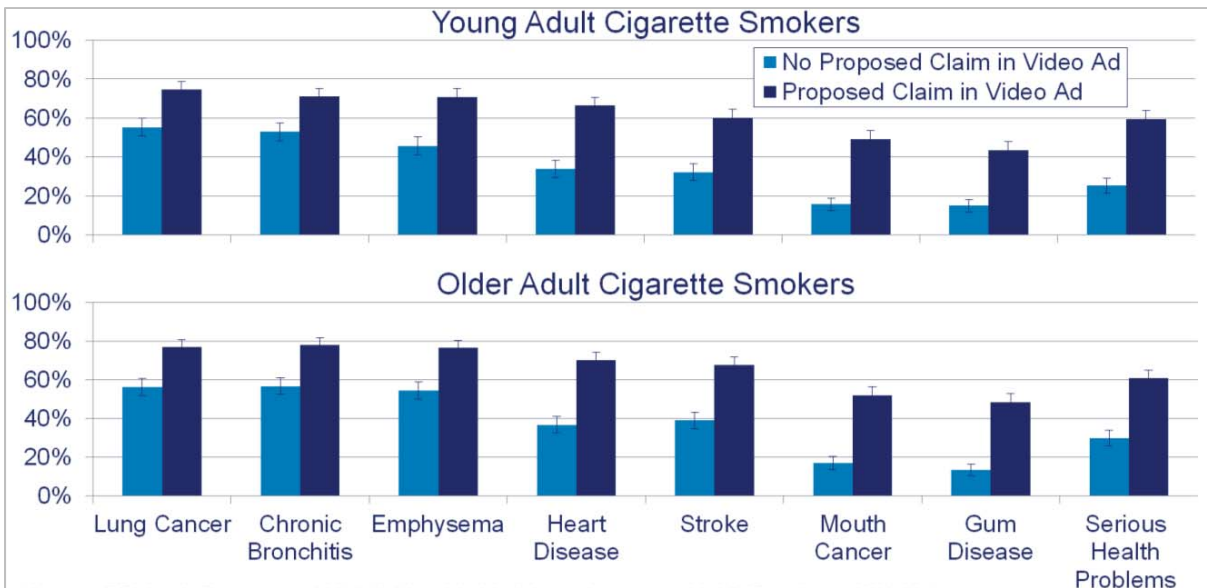


Figure 2. Percentages of cigarette smokers who perceived a “lower” or “much lower” chance of health effects from using General Snus daily compared to smoking cigarettes daily. The item asked, “Compared to the daily use of only cigarettes, the daily use of only General Snus® has...” Response options included “a much lower chance,” “a lower chance,” “the same chance,” “a higher chance,” “a much higher chance,” and “Don’t know.” Source: Based on data from the PBI Study Report and November 26, 2018 Amendment. Error bars: 95% CIs.

Understanding that the Proposed Claim Does Not Apply to Partial Switching

As discussed above, the applicant’s proposed claim states that using General Snus “instead of cigarettes” reduces health risks, which could be subject to interpretation. Consumers could interpret this as complete product substitution, or alternatively, as situational or partial product substitution. If the latter is true, this suggests that consumers could interpret the claim to mean there are health benefits of *partial* substitution—that is, using General Snus in place of some, but not all, of one’s cigarettes. The applicant did not provide evidence that there are health benefits of *partially* switching to General Snus. The health effects of partial switching may depend on a person’s smoking frequency, the extent to which the person cuts down on smoking, and the health endpoint. If consumers misunderstand the applicant’s proposed claim to mean that partially switching to General Snus reduces their disease risk, this could result in smokers continuing to smoke, which could prevent them from reducing their health risk.

The PBI Study examined whether, after viewing the video with the proposed claim, adult consumers understood the need to switch completely to General Snus to achieve the claimed reductions in disease risk. In particular, this can be assessed with consumer perceptions of how the risks of dual use of General Snus and cigarettes compare with both (a) exclusive General Snus use, and (b) exclusive smoking. With respect to the former, the results show that the proposed claim enabled consumers to understand that dual use of General Snus with cigarettes is more harmful than exclusively using General Snus. Among cigarette smokers who viewed the advertisement without the proposed claim, 41% of young adult smokers and 32% of older adult smokers perceived exclusive daily General Snus use as presenting a lower risk of “serious health problems” compared to daily use of both General Snus and cigarettes (Figure 3). In contrast, when the advertisement contained the proposed claim, substantially more smokers perceived exclusive use of General Snus as presenting lower health risks compared to dual use (60% of young adult smokers and 55% of older adult smokers). Similar effects were also

observed among smokeless tobacco users. For example, adding the proposed claim to the advertisement substantially increased the percentage of smokeless tobacco users who perceived exclusive General Snus use as presenting the a “lower” or “much lower” risk of “serious health problems” compared to dual use with cigarettes (from 49% to 66%) (Figure 3). These results show that the proposed claim improved adult smokers’ (and smokeless users’) perceptions that dual using General Snus with cigarettes presents greater risks of specific health effects than exclusively using General Snus. In turn, these findings support the conclusion that participants understood the claim.

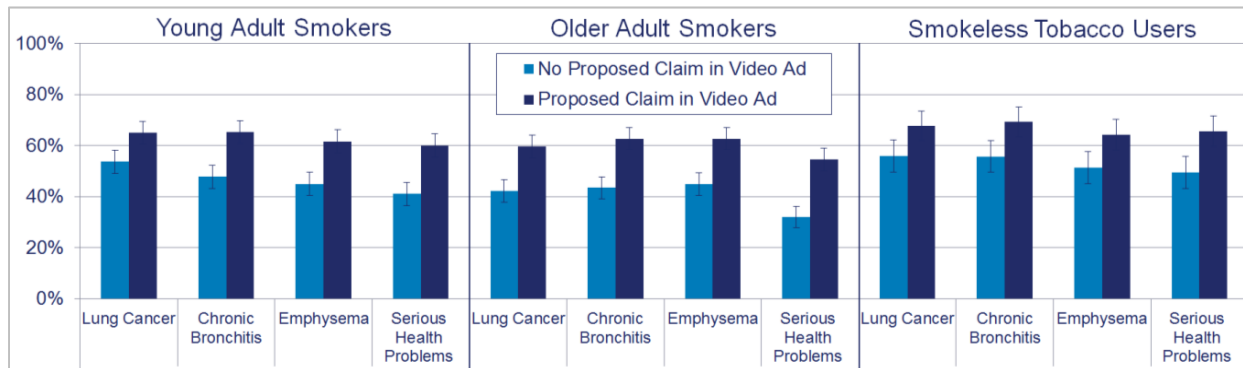


Figure 3. Percentages of cigarette smokers and smokeless tobacco users in the PBI Study who perceived a “lower” or “much lower” chance of health effects from exclusive daily *General Snus* use compared to daily use of both *General Snus* and cigarettes. The item asked, “Compared to the daily use of both cigarettes and *General Snus*®, the daily use of only *General Snus*® has...” Response options included, “a much lower chance,” “a lower chance,” “the same chance,” “a higher chance,” “a much higher chance,” and “Don’t know.” Source: Based on data from the PBI Study Report. Error bars: 95% CIs.

Whereas the study provided evidence suggesting the proposed claim led to consumers’ understanding of the health risks of dual use compared to exclusive General Snus use, it did not assess perceptions of risk from dual use (i.e., partial substitution) compared to exclusive cigarette smoking. However, additional insight into whether participants perceived the risk reduction to be attainable via partial substitution (vs. exclusive use) comes from an item that asked smokers about the number of cigarettes one could smoke per day on a day when they also used General Snus, while still achieving the lower disease risk. The results from this item showed that exposure to the claim increased the number of participants correctly responding that “zero” cigarettes could be smoked in addition to using General Snus while still reducing one’s risk (Figure 4). In particular, viewing the advertisement with the proposed modified risk claim, rather than without it, increased the proportion of young adult smokers who responded “zero” to 56% (with the claim) from 45% (without the claim); and among older adult smokers, to 44% (with the claim) from 34% (without the claim) (PBI Study Report, pp. 158-159). Importantly, adding the claim did not increase the proportions of smokers who selected the response options consistent with partial substitution (“Up to 5 cigarettes,” “Up to 20 cigarettes,” or “As many as you want to smoke”), suggesting that the proposed claim did not lead smokers to believe partial substitution would reduce their disease risk. Although “zero” was the most commonly reported response, this is likely an underestimate because the question was asked among respondents who, even after exposure to the modified risk claim, did not perceive that General Snus conveys lower risk of disease. For those respondents, it would be unclear how to respond to the item and is likely why there are sizeable proportions that selected “none of the above” and “don’t know.” In other words, the proportion of correct responses would have likely been higher had the question been asked only among those who indicated they perceived General Snus as lower risk compared to smoking (in line with the claim).

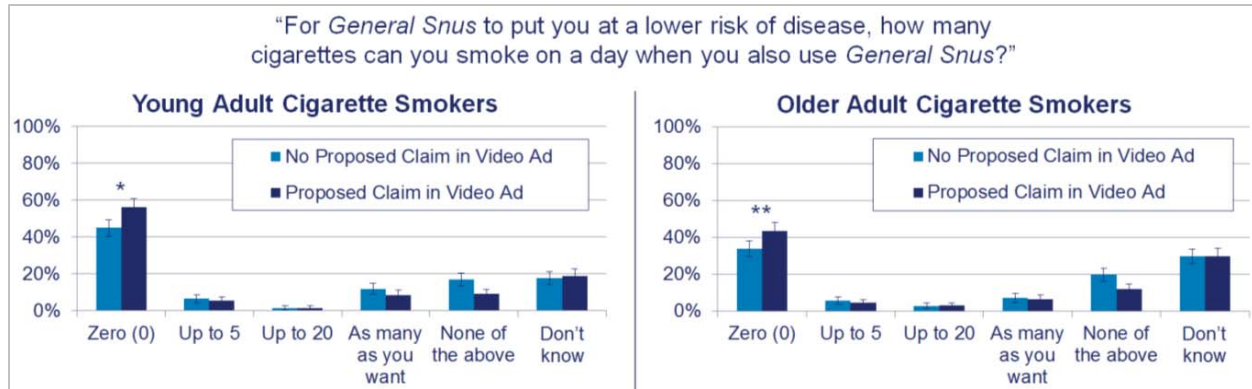


Figure 4. Smokers' responses to a PBI Study item about the number of cigarettes one can smoke on a day when they also use General Snus, for General Snus to put one at a lower risk of disease. Source: November 26, 2018 Amendment. Error bars: 95% CIs. * $p=.001$; ** $p=.005$.

Perceptions of Risk Compared to Cessation Aids and Quitting

The PBI Study also examined whether the proposed claim would enable adult smokers to understand that using General Snus presents greater risks of specific health effects than using cessation aids and quitting all tobacco use. Along with the results described above on perceptions of the absolute and relative health risks of using General Snus, this provides information about overall consumer understanding and could also be relevant to consumers' expected use patterns, including whether smokers would use General Snus instead of quitting all tobacco products.

After viewing the video without the proposed claim, the majority of participants perceived General Snus as having greater health risks compared to cessation aids, but some perceived General Snus to be lower in health risks. Specifically, across the eight health risks assessed, 16-27% of young adult smokers and 15-30% of older adult smokers perceived daily General Snus use as presenting a lower or much lower chance of negative health effects compared to daily use of cessation aids. These proportions were larger after smokers viewed the video with the proposed claim. After viewing the claim, 25-33% of young adult smokers and 32-42% of older smokers perceived General Snus as lower in risks than cessation aids across the eight health effects.

These findings are consistent with prior research finding that many U.S. smokers perceive nicotine replacement therapies (NRTs) to be just as harmful as cigarettes (Shiffman et al., 2008; Czoli et al., 2017), which may in part be due to beliefs that nicotine is the main cause of health harms from smoking (e.g., Keely O'Brien et al., 2017). In other words, because the claim communicates that General Snus reduces risks relative to cigarettes, for people who mistakenly believe the risks of NRT are similar to cigarettes, the claim inadvertently shifted their perceptions of General Snus as lower risk relative to NRT as well. Studies assessing perceptions of risk from smokeless tobacco compared to NRT are rare: a review of the literature (Czoli et al., 2017) uncovered only one study, which found that around half of U.S. adults who had heard of snus were "unsure" whether it was more harmful, less harmful, or as harmful as NRTs or non-nicotine medications (Regan et al., 2012). These results, along with the PBI Study findings, suggest that many U.S. consumers do not understand the safety of NRT compared to tobacco products. Indeed, such misunderstanding may partially explain why, in 2014-2016, only one in four adult cigarette smokers who tried to quit in the previous three months reported using nicotine patches or nicotine gum during their most recent quit attempt (Caraballo et al., 2017). Regardless of

these misperceptions related to NRT, there is no evidence that the MRTPs themselves are likely to impact perceptions of NRT or affect consumers' likelihood of initiating use of those products.

In addition, a minority of current cigarette smokers perceived that using General Snus would present lower health risks than quitting the use of all tobacco and nicotine products. After viewing the video with the proposed claim, 22-26% of young adult smokers and 29-38% of older adult smokers perceived a lower or much lower chance of health effects (across the eight effects tested) for someone who switches completely to General Snus than for someone who quits using all tobacco and nicotine products. These percentages were significantly higher than among smokers who viewed the video without the proposed claim (young adult smokers: 13-20%; older adult smokers: 14-26%). These responses may reflect participants' confusion about the survey item or response scale. According to the applicant, cognitive testing of a prior version of the survey instrument found that some people were confused about the comparison between switching to exclusive use of General Snus (i.e., quitting all other tobacco and nicotine products and using General Snus only) vs. quitting all tobacco and nicotine products. The applicant made changes to its survey items based on these cognitive testing results but may not have completely solved the problems. It is useful to note that these findings are in direct contrast to prior research on perceptions of health harm from using smokeless tobacco (e.g., in 2012-13, 93% of U.S. smokeless tobacco users perceived smokeless tobacco as harmful to health; Agaku et al., 2016) and findings from the PBI Study on *Perceptions of Absolute Health Risks*, which demonstrated that these participants perceived considerable risks from using General Snus, including after viewing the video with the proposed claim. Given the potential spurious nature of the above findings on perceptions of General Snus compared to quitting the use of all tobacco and nicotine products, I believe that these findings do not undermine the conclusion that consumers understood the claim, nor indicate a significant likelihood that the proposed modified risk products would negatively affect consumers quitting the use of all tobacco products.

Summary and Conclusion

Overall, these results provide evidence 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. This understanding is an important precursor to tobacco use behaviors that will reduce harm to individual tobacco users and benefit the health of the population as a whole. In addition, the evidence (discussed in the Social Science review) suggested that, though not the subject of the explicit modified risk claim, exposure to the claim could lead smokeless tobacco users to accurately perceive General Snus to be lower in health risks than other smokeless tobacco products, which in turn could lead to additional tobacco use behaviors that would reduce harm to individual tobacco users and benefit the health of the population as a whole. In terms of whether consumers understood how the product must be used to attain the purported risk reduction (i.e., exclusively), these data provide evidence that the proposed claim did *not* lead smokers to believe that partial substitution would reduce their disease risk. In particular, based on perceptions of the relative risk of exclusive snus use compared to dual use with cigarettes, and an item about the number of cigarettes one could smoke while using snus, the findings provide support that most consumers *do not* infer that partial substitution is associated with a reduction in risk. These results allay concerns that the phrase "instead of" will be interpreted by consumers to mean that one can dual use the product with cigarettes and still reap the benefit of the risk reductions described in the claim.

Although the evidence showed that exposure to the modified risk claim significantly impacted perceptions of the absolute and relative risk of the product—shifting perceptions towards greater accuracy, in line with the claim—this was not true for all participants. Rather, there remained a proportion of participants who were not affected by the claim and who continued to perceive the product as just as harmful as cigarettes. For instance, whereas ~60% of young adult smokers who were exposed to the claim correctly responded that General Snus presented lower risks of serious health problems compared to smoking, the remaining ~40% either perceived General Snus as posing the same or higher risk as cigarettes (or responded “don’t know”). Likewise, just as some participants did not perceive General Snus to be less harmful compared to cigarettes, they also did not understand that exclusive use of General Snus would be less harmful than dual use of General Snus plus cigarettes. Accordingly, when asked how many cigarettes one could smoke while using General Snus and still get the risk reduction, just over half (56%) of young adults exposed to the modified risk claim selected the correct response (“zero cigarettes”), whereas a proportion responded “don’t know” or “none of the above”. We evaluate these findings in the context of both the preexisting beliefs that participants bring with them into the study as well as the “dose” of their exposure. It is well-established in the literature that the majority of U.S. consumers (up to 90%) perceive smokeless tobacco products to be just as harmful as cigarettes (e.g., Song et al., 2009; Strong et al., 2019). This means that for most participants, the modified risk claim for General Snus needs to overcome (and reverse) established beliefs about the product category. In the course of a brief online study with a one-time exposure to a marketing video, it may be unsurprising that not all consumers will shift their perceptions to align with the claim. However, a real-world, appropriate marketing campaign would mean the intended audience would be exposed to the information more than once and in more than one way, increasing the likelihood that more of these users will shift their perceptions in line with the claim. Accordingly, it is important that postmarket surveillance and studies assess the impact of the marketing on users’ understanding of the products’ risks relative to cigarettes and their understanding that to reduce their risk, they should use the products exclusively, and not in conjunction with other tobacco products (e.g., dual use with cigarettes).

A few findings were contrary to expectations. For instance, addition of the claim reduced perceived risks across all seven disease endpoints assessed, not just the six endpoints that were specified in the claim, suggesting that the claim may have had a generalized effect of lowering perceptions of relative risk. Likewise, the study revealed that a proportion of smokers believe that General Snus might be less harmful than cessation aids—and exposure to the claim increased this proportion. As discussed above, there may be a number of reasons for these misbeliefs, including confusion about the harms of nicotine itself. Perhaps more unexpected is the finding suggesting that the claim increased the number of people perceiving General Snus as less harmful than quitting all tobacco use. As noted, given what we know about consumers’ perceptions of the harms of smokeless tobacco, including the PBI study results showing that participants continued to perceive General Snus as presenting substantial health risks, it is likely that this is a spurious finding. Finally, the concern about this misunderstanding of the relative harm of General Snus vs. cessation is that it could present a reason for consumers who were considering quitting all tobacco use to instead choose General Snus use. The results (discussed below) showing that exposure to the modified risk claim did *not* affect intentions to quit do not bear this out.

Finally, the Social Science review also notes that there were a few gaps in the PBI study, including measurement of perceived addiction risk and perceived risks of intermittent (i.e., non-daily) product use, which is a common use pattern among U.S. adult smokeless tobacco users generally and users of snus pouches in particular (Cheng et al., 2017).

Consumers' understanding of the modified risk claim, as reflected in their understanding of the products' risks in the context of total health, is a multifaceted construct. The assessment of understanding can be complicated by the fact that, in many cases, consumers have preexisting beliefs that are not aligned with scientific evidence (e.g., misconceptions related to the harms of NRT or the risks of smokeless tobacco relative to smoking). To inform this assessment of the proposed modified risk General Snus products, the PBI study assessed a number of different aspects of consumers' perceptions and understanding. On the whole, the pattern of results shows an improvement in the participants' understanding of the risks of the product. Taken together, 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 individual risk and benefit population health.

C. Effects of the Proposed MRTPs on Tobacco Use Behavior among Current Tobacco Users

As described above, FDA has determined that exclusive use of the eight General Snus products would pose lower risks to health than cigarette smoking for many smoking-related diseases. Accordingly, the primary behavioral impact of the MRTPs' marketing expected to result in a population health benefit is smokers completely switching to snus use. In addition, though not a subject of the proposed modified risk claim, evidence suggests that, compared to exclusive use of other smokeless tobacco products, exclusive use of these snus products pose reduced exposure to some HPHCs and offer the potential for reductions in oral cancer risk. FDA's scientific review of PMTAs for the eight products concluded that introducing the products to the market would give smokeless tobacco users "additional options for less toxic smokeless tobacco products" compared to other smokeless tobacco products sold in the U.S. market (FDA, 2015, p. 37). Thus, there could be additional population health benefits if current smokeless tobacco users switched to exclusive use of these products.

The original applications were determined to contain insufficient evidence demonstrating that the products would be used in a way that would result in a population health benefit. The applicant proposed that, as MRTPs, its products could have a similar impact in the U.S. as snus has had in Sweden. In particular, the applicant described a historical trend documented in Sweden, often called the "Swedish Experience," a grassroots movement wherein a large proportion of smokers transitioned to exclusive snus use, bringing rates of smoking to historically low levels and resulting in a population with a lower incidence of smoking-related diseases than comparable countries. Thus, the applications relied primarily on behavioral epidemiological data from Sweden and Norway. Ultimately, FDA's review of this evidence concluded that it had limited applicability to the potential impacts of marketing the MRTPs in the U.S. FDA pointed to the range of social and cultural differences between the two marketing contexts—including that snus is a traditional Swedish product—limiting the validity of extrapolating from one to the other. Moreover, snus was not marketed as a reduced risk product in Sweden, underscoring that adoption of the product was related to other factors. These limitations were also identified by TSPAC in the 2015 meeting.

In addition, the applicant's original consumer perception study was evaluated by FDA and found to suffer from several serious methodological flaws, including that the proposed modified risk information was not tested verbatim, as well as problematic measures. Although the original consumer perception study could have provided support for the potential behavioral impact of the modified risk information on the intended audience, ultimately the concerns with the study's methodology rendered the findings uninformative to the overall assessment. Thus, relying solely on the epidemiological evidence discussed

above, FDA concluded that the applicant had not demonstrated the likelihood that consumers would use the product in a way that would benefit individual users and population health.

To assess the revised proposed claim, the applicant conducted a new consumer perception study, the PBI study, which provides additional information on consumer perceptions, understanding, and behavioral intentions. These findings replace those of the former study which evaluated the original requests, and therefore are no longer relevant. The PBI study, and the findings relevant to behavioral intentions, are presented next.

Participants were asked, “How likely are you to buy General Snus for yourself if sold in a store where you usually shop?” The 11-point response scale ranged from 0 (no chance, almost none [1 in 100]) to 10 (certain, practically certain [99+ in 100]). Results show that adding the proposed claim to the advertisement statistically significantly increased older adult smokers’ intentions to buy General Snus ($M_{\text{WITHOUT CLAIM}} = 1.49$, $M_{\text{WITH CLAIM}} = 2.04$) and non-significantly increased young adult smokers’ ($M_{\text{WITHOUT CLAIM}} = 1.85$, $M_{\text{WITH CLAIM}} = 2.19$) and adult smokeless tobacco users’ ($M_{\text{WITHOUT CLAIM}} = 3.41$, $M_{\text{WITH CLAIM}} = 3.71$) intentions to buy it (PBI Study Report)(Figure 5). These patterns support the conclusion that that the proposed claim can positively impact intentions to buy among current tobacco users (cigarette smokers and smokeless tobacco users) who stand to benefit from completely switching to the product.

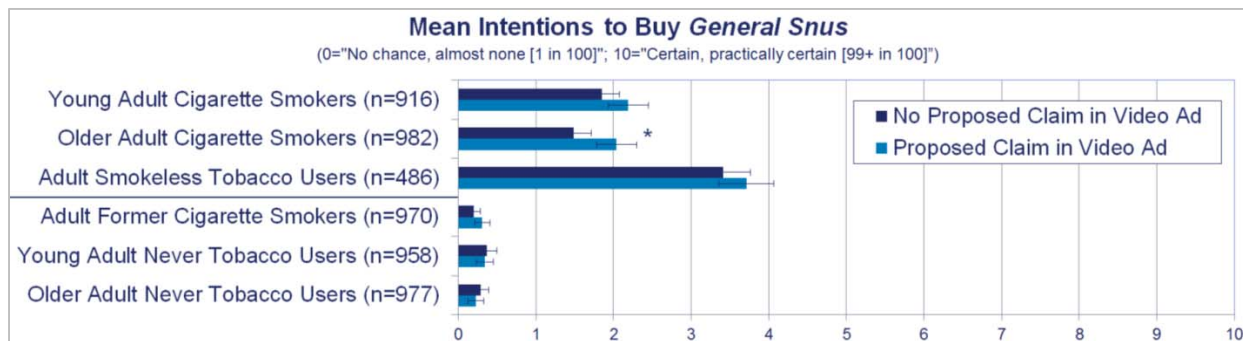


Figure 5. PBI Study participants’ mean self-reported likelihood of buying General Snus. The item asked, “How likely are you to buy General Snus® for yourself if sold in a store where you usually shop?” Response options ranged from 0 = “No chance, almost none [1 in 100]” to 10 = “Certain, practically certain [99+ in 100].” Source: PBI Study Report. Error bars: 95% CIs. * $p=.001$.

The applicant did not submit evidence regarding how those who intended to buy the product expected to use it: for instance, whether smokers would use General Snus as a complete substitute for smoking. We acknowledge, however, that such future behaviors could be difficult for consumers to predict before trying the product and thus challenging to assess in premarket research, which is one reason an actual use study may have provided useful information about the claim’s effects on use patterns.

The study did assess smokers’ intentions to quit smoking and all tobacco users’ intentions to quit using all tobacco products. Among current smokers and current tobacco users, adding the proposed claim to the video advertisement did not affect intentions to quit smoking or quit using all tobacco products. This is positive in that it appears the claim did not inadvertently depress smokers’ or smokeless tobacco users’ interest in quitting.

Summary and Conclusion

The design and conduct of the PBI study addressed the flaws previously identified by FDA’s review of the applicant’s previous consumer perception study, including testing the revised modified risk statement verbatim. The soundness of the study method, in addition to FDA’s statistical replication (described in Social Science Review), give us confidence to draw conclusions from this study. Accordingly, unlike the original assessment, we can now draw conclusions based on the data provided about potential behavioral effects of the proposed modified risk products.

In the 2016 TPL review, we noted that research had indicated that U.S. cigarette smokers may not find snus an appealing alternative to cigarette smoking (Biener et al. 2014; Sami et al. 2012; Hatsukami et al. 2011; O’Connor 2011). However, PBI study results provide supportive evidence that the addition of the proposed modified risk claim would positively impact intentions to use the product among older (25+) adult smokers. In particular, the addition of the claim to the video advertisement statistically significantly increased intentions to buy the product among adult smokers 25 years or older. Although this difference was statistically significant, it should be noted that the absolute mean ratings on the intentions scale were still relatively low (between 1 [“very slight possibility”] and 2 [“slight possibility”]). When interpreting these values, it’s worth noting a few things. First, because these are group means, they do not reflect variability within the group; this is particularly relevant when considering a consumer product about which people will naturally vary widely in terms of interest. Indeed, snus—as with other smokeless tobacco products—does not universally appeal to users of other tobacco products. Accordingly, just as snus currently has a very modest market share, it is likely that these MRTPs would appeal to a minority of smokers. Appealing to that group of smokers and persuading them to switch from cigarettes to a less harmful alternative presents an opportunity to benefit population health. Second, these results reflect the impact of a one-time exposure to an advertising video for a product. This type of study is critical for assessing understanding of the claim in a premarket context and is also informative of the potential effects on behavior. However, in the context of a single-session online study, it is hard to approximate the effects of a real-world marketing campaign. Thus, as mentioned above, it is reasonable to consider these study results as estimating a lower range of the potential impact of the real-world marketing of the products, where more frequent exposure to product marketing would have the potential to have a greater impact on levels of interest. In addition, although not statistically significant, the pattern of results for the other two user groups—young adult smokers and smokeless tobacco users—suggested that the claim also had a positive impact on their product interest. Moreover, perhaps unsurprisingly, smokeless users across conditions showed the highest mean levels of intentions to buy the product, suggesting that the addition of the claim could increase the likelihood of current smokeless users transitioning to a less toxic alternative (FDA, 2015). It is worth noting that the sample of smokeless users was around half the size of the smoker groups, which may be one reason why a significant effect was not detected for these users. Together, these findings provide support that the proposed modified risk claim could increase the likelihood of use of General Snus among adult tobacco consumers who could benefit from switching, including both smokers and smokeless tobacco users.

The applicant did not submit direct evidence that the proposed claim would encourage smokers to use General Snus as a complete substitute for smoking (e.g., the applicant did not submit an actual use study testing the claim’s effects on frequency of General Snus use or dual use with cigarettes). FDA previously noted relatively high rates of dual use among snus users (FDA, 2016); however, the findings described in the section on consumer understanding suggest that the proposed claim enabled consumers to

understand that dual use presents greater health risks than exclusive General Snus use, and this would provide users a reason to use the products exclusively.

The applicant elected to examine the effect of the claim in the format of a marketing video (e.g., rather than another form of marketing such as a print advertisement). As this format is likely more engaging than others (e.g., a print ad), these findings could reflect an upper bound of effectiveness in terms of impact on consumers. On the other hand, as mentioned above, the study findings estimate the effect of a one-time exposure: it is expected that an appropriate marketing plan that effectively reaches the intended audience (adult smokers) could have a larger impact than a single exposure (regardless of format).

D. Effects of the Proposed MRTPs on Tobacco Use Initiation among Non-Users

The impact on tobacco use behavior among current users must be considered alongside the potential effects on tobacco use initiation among non-users, such that a positive impact on population health is more likely when the benefits of the former are expected to outweigh the risk of the latter. Assessing potential impacts on behavior in a premarket setting is difficult, especially for non-users, particularly youth. As discussed above, the applications originally relied on Scandinavian behavioral epidemiological evidence to inform an assessment of the effect on non-users. FDA again concluded these data had limited applicability to the likely impact of the proposed MRTPs on non-users in the U.S. Similarly, though this question was addressed in the applicant's original consumer perception study, those data were determined to be uninformative due to flaws in the design and conduct of the study.

The PBI study was designed to address this issue by including adult non-users and assessing their interest in buying the product, including how the addition of a modified risk claim affected their interest in buying the product. In particular, the PBI study included three groups of non-users: adult former cigarette smokers, young adult never tobacco users, and older adult never tobacco users. The study found that mean levels of intentions to buy General Snus were low (<1) among all three groups of non-users, and the addition of the modified risk claim did not have a statistically significant effect: former smokers ($M_{\text{WITHOUT CLAIM}} = 0.20$; $M_{\text{WITH CLAIM}} = 0.31$), older adult never tobacco users ($M_{\text{WITHOUT CLAIM}} = 0.29$, $M_{\text{WITH CLAIM}} = 0.23$), and young adult never tobacco users ($M_{\text{WITHOUT CLAIM}} = 0.37$, $M_{\text{WITH CLAIM}} = 0.34$) (PBI Study Report, pp. 71-72) (Figure 5). 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.

Summary and Conclusion

The PBI findings show low levels of intentions to buy General Snus among non-user groups (adult former cigarette smokers; young adult never tobacco users; older adult never tobacco users), which were not affected by the addition of the modified risk claim.

Although youth are, in general, at risk for tobacco use initiation, surveillance data on U.S. youth tobacco use suggest snus is not a product category of particular interest among youth. Currently, snus use is relatively low among U.S. youth (0.5% and 1.9% among middle school and high school students in 2014, respectively; Arrazola et al., 2015; see Wang et al. [2018] for estimates of past-30 day use of any smokeless tobacco in 2017: 1.9% among middle school students and 5.5% among high school students). As described above, in the PBI study, the applicant stratified its recruitment and analyses of never

tobacco users to separately examine young adults (i.e., legal age to 24 years) and older adults (i.e., 25 years or older), finding results that were generally comparable across age groups. Though data on young adult non-users is informative, there is no direct evidence that this claim would affect youth non-users in the same way. In the absence of research on how the proposed claim affects youth perceptions and intentions, it is worth considering research on other modified risk statements, even though different claims may affect youth differently. One available study suggests that a modified risk claim similarly impacted risk perceptions among youth and adults and affected susceptibility to use the product only among adults (El-Toukhy et al., 2018). In particular, asking youth “Suppose the FDA approves a label saying that Swedish snus is less harmful than cigarettes” caused youth to perceive Swedish snus as exposing users to less harmful chemicals and as presenting a lower risk of serious health problems (El-Toukhy et al., 2018). Although generalizability may be limited, such research is the best available direct evidence we currently have on youth and shows that, just as with adults, when youth are exposed to modified risk information, it lowers their risk perceptions.

Studies suggest that perceptions of risk predict tobacco product use among youth (e.g., Song et al., 2009; Strong et al., 2019) and adults (e.g., Brose et al., 2015). For example, in a national sample of U.S. youth who had never used snus, youth who perceived snus as low or medium in risk were more likely to try it during the next year compared to youth who perceived snus as high in risk (Strong et al., 2019). Thus, even though the proposed claim did not increase never tobacco users’ intentions to use General Snus in the applicant’s study, it is still possible that exposing youth and young adult non-tobacco users to the proposed claim could increase their risk of initiating use of General Snus by lowering their risk perceptions. Accordingly, it is critical that an MRTP marketing plan target adult smokers and minimize exposure to youth, as discussed further in the next section.

E. Impact of the Proposed MRTPs to the Health of the Population as a Whole

An assessment of the impact of an MRTP on the population as a whole is primarily a function of the relative health risks of the proposed product and the likelihood of tobacco use behavior change, including behavior change due to the modified risk marketing. As described in the section on individual health risk, FDA has determined that exclusive use of the General Snus products that are the subject of these MRTPAs poses lower risk for many diseases than cigarette smoking and the revised claim being proposed by the applicant is scientifically substantiated. General Snus products also have been found to have lower levels of HPHCs than many other smokeless tobacco products on the market (FDA PMTA Review, 2015), suggesting that there would be a benefit to smokeless tobacco users switching completely to these products as well.

In its original submission, the applicant presented findings from a population model to estimate the potential impact of the proposed MRTPs on the population as a whole. In addition to concerns regarding the scientific substantiation of the originally proposed claims, FDA’s initial assessment determined that the applications contained insufficient information about the impacts of the proposed modified risk products on the behavior of current users and non-users of tobacco products and that the uncertainty about the impacts on behavior among these groups precluded the ability to determine, with any degree of certainty, that the products will benefit the health of the population as a whole. Although the applicant modeled a number of different scenarios of the impact to users and non-users, some resulted in population health benefits and some resulted in population health harms, and the applicant provided inadequate evidence as to which scenarios are more or less likely.

FDA's original assessment of the impact of the proposed MRTPs on likelihood of use among current users and non-users was based on evidence in the original applications from the applicant's consumer perception study and epidemiological behavioral evidence. In particular, the applications relied heavily on observational data from Sweden and Norway to support its argument that the phenomenon documented in Sweden could be replicated in the U.S. Ultimately, FDA and TPSAC did not find this argument compelling, concluding that there was limited applicability of the behavioral evidence from Sweden to the potential impact of the MRTPs on the U.S. population. The original applications did not contain studies of "actual use", and because of the flaws in the original consumer perception study, FDA ultimately concluded the applicant had failed to demonstrate that the product will benefit population health.

Swedish Match's amended applications provide new information that addresses this gap. In particular, the PBI study, designed in part to evaluate the revised proposed claim (and correct methodological flaws of the original study), provides evidence of the impact of the proposed MRTPs on behavioral intentions among users and non-users. These data showed that the addition of the revised modified risk claim to the marketing video had a positive, statistically significant effect on behavioral intentions to buy the product among adult smokers aged 25+ years. Among younger adult smokers (18-24 years), and smokeless tobacco users, the claim also increased intentions, though these changes were not statistically significant. On the other hand, among non-users, intentions to buy the product were low (<1 on the 0-10 scale) and, importantly, were not statistically significantly affected by the addition of the modified risk claim. FDA's review finds that the study's design was sound, and in sum, these findings support the conclusion that these MRTPs will benefit population health, particularly by (a) increasing interest and therefore likely uptake among those who could stand to benefit (adult smokers), and (b) having no effect on the interest and therefore likely uptake among current non-users, including young adult never users and former users.

The PBI study provided information about intentions to buy the products but did not examine how consumers might use the products, including whether smokers who were interested in the products would be interested in switching to exclusive use or would intend to dual use. These questions may be less meaningfully addressed via self-report (e.g., in the absence of any product trial) and better suited to an actual use study that can examine patterns of product uptake/use. However, the applicant did not conduct an actual use study. A key to the population health benefit of these MRTPs is not only that smokers will adopt the products, but that they will switch to exclusive use of them and cease smoking. Accordingly, confirming that the marketing of the MRTTP has the intended effect on behavior (including uptake and patterns of use) will be a priority question to be evaluated in postmarket surveillance and studies (see Section IV).

A priority for the assessment of consumer understanding was to examine the extent to which smokers will understand that they are to use the product exclusively and not in addition to cigarettes. As noted, it is possible to interpret the phrase "instead of" in the revised modified risk claim in different ways, and this concern was also raised by TPSAC members. The evidence provided in the PBI study found that, overall, the addition of the modified risk claim to the marketing video improved consumers' understanding of the relative risks of snus compared to cigarette smoking and that people had an appropriate understanding of the claim. Moreover, addressing the potential ambiguity of the phrase "instead of", these data provided evidence that the proposed claim did *not* lead smokers to believe that partial substitution would reduce their disease risk.

Finally, the assessment of the population impact must also consider the potential risks to youth, a population vulnerable to initiating the use of tobacco products. The applicant assessed the impact of the

modified risk products on non-users, including young adult non-users, but did not include youth in its study. Snus products, including General Snus, are currently on the U.S. market and use by youth is relatively low compared to other types of tobacco products. However, this is in the absence of marketing a product as lower risk and although data on young adult non-users (included in this study) is helpful and informative, there is no direct evidence to determine whether this claim would affect youth non-users in the same way. FDA is aware of one published study evaluating the impact of a modified risk claim about snus on youth, which found that a modified risk claim similarly impacted risk perceptions among youth and adults, but affected susceptibility to use the product only among adults (El-Touhky et al., 2018). Nonetheless, given that lower risk perceptions can predict tobacco use initiation, it is possible that exposing youth and young adult non-tobacco users to the proposed claim could increase their risk of initiating use of General Snus. In addition, it is well-documented that exposure to marketing impacts youth initiation. For this reason, it is critical that a marketing plan for any products that receive MRTTP orders be designed to target tobacco users and prioritize preventing youth exposure. I recommend that postmarket restrictions include requirements focused on minimizing youth exposure, including age- and identity-verification and age-restriction controls for digital marketing and reporting metrics that will enable FDA to monitor the effectiveness of targeted marketing efforts. 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 MRTTP continues to benefit the population as a whole.

IV. Conclusions and Recommendation

The applicant has requested risk modification orders under Section 911(g)(1) of the FD&C Act for eight General Snus products with the following claim:

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"

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 the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;

- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons.

Furthermore, FDA must require that the advertising and labeling of the MRTPs 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 (section 911(h)(1) of the FD&C Act).

To the extent possible, the assessment integrates the various threads of evidence regarding the product and its potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the product on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population.

1. Review Conclusions

After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from TPSAC; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the Agency from other sources, I conclude that:

- The applicant **has demonstrated** that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

The 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" is scientifically accurate. The available scientific evidence, in particular the long-term epidemiological studies, reviewed under the original submission and summarized again in this review, substantiates that relative to cigarette smoking, exclusive use of the eight General Snus products poses lower risk of the above-named health outcomes. The applicant provided sufficient justification to determine that the epidemiological evidence from Sweden and Norway, although not specific to the products that are subjects of these applications, provides a reasonable characterization of the risks that would be expected to be observed among General Snus users in the U.S. if they used the products in a similar manner.

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 individual tobacco users. As described above, exclusive use of these products poses lower risks than cigarette smoking for many of the major causes of tobacco-related disease. In addition to these lower risks relative to cigarette smoking, FDA has previously determined that the levels of NNN and NNK, two potent carcinogens in smokeless tobacco products, in these General Snus products are lower than those in the vast majority of

smokeless tobacco products on the U.S. market, and when used exclusively instead of other smokeless tobacco products, the General Snus products offer the potential for reductions in oral cancer risk.

Although exposure to HPHCs is lower than many other smokeless tobacco products, exposure is still elevated compared with non-use and, therefore, long-term use of General Snus is not without health risks. FDA's 2016 TPL review concluded that Swedish snus use (compared with no use of tobacco) has been associated with increased risk of specific disease endpoints in individual epidemiological studies, including pancreatic cancer, fatal MI and stroke, diabetes, and adverse pregnancy outcomes. In addition, there are potential negative effects of nicotine exposure on the developing adolescent brain.

The additional evidence provided in the amendment also supports that, as actually used by consumers, the eight General Snus MRTPs will benefit the health of the population as a whole. The PBI study demonstrated that exposure to the claim positively impacted relative risk perceptions and intentions to buy the product among smokers aged 25 years and older, a group who stands to benefit the most from the marketing of the products. For instance, among adult smokers aged 25 years and older, participants who were exposed to a marketing video with the modified risk claim reported significantly higher intentions to buy the product compared to those who did not see the modified risk claim. Smokers under age 25 years showed a similar pattern, although the impact of the claim on intentions was not statistically significant for this group. Similarly, although not statistically significant, the pattern of results also suggested the claim may have a positive impact on smokeless tobacco users' intentions to buy the product. In addition, smokeless tobacco users across conditions showed the highest mean levels of intentions to buy the product, suggesting that the marketing of the products with the claim could increase the likelihood of current smokeless users transitioning to the eight General Snus products, which are likely to be a less toxic alternative. The applicant also provided evidence to show that consumers can understand the claim and its significance in the context of total health, including understanding that the risk reduction is not achieved via partial switching (i.e., dual use of General Snus with continued use of cigarettes). In fact, the proposed claim improved consumers' understanding of the risks of General Snus relative to cigarettes and their understanding that dual use presents greater health risks than exclusive General Snus use, thereby increasing the likelihood that consumers who use the products will do so exclusively. Together, the demonstrated impact of the claim on understanding, perceptions, and behavioral intentions, even in the context of a relatively brief exposure, supports that the proposed MRTPs will benefit the population as a whole.

The PBI study provided sufficient evidence to support product authorization. However, the results were not without limitations. In particular, although the evidence showed that exposure to the modified risk claim significantly impacted perceptions of the absolute and relative risk of the products—shifting perceptions in line with the claim, towards greater accuracy—this was true, on average, but not necessarily for all participants. In fact, a proportion of participants was not affected by the claim and continued to perceive the product as just as harmful as cigarettes, for instance. Likewise, just as some participants did not perceive General Snus as less harmful compared to cigarettes, a proportion also did not understand that exclusive use of General Snus would be less harmful than dual use of General Snus with cigarettes. Considered in the context of the totality of the evidence, these results do not undermine my conclusion that the product meets the standard in Section 911(g)(1) of the FD&C Act. However, given their relevance to the population health impact of these MRTPs, these are areas that need to be monitored through postmarket surveillance and studies (PMSS).

Finally, the new evidence supports that the population health benefits gained by cigarette smokers (and potentially other smokeless tobacco users) switching to these products will not be outweighed by the

risks of initiating new tobacco use. The PBI study found low levels of intentions to buy the product among non-users of tobacco (including young adults) and, importantly, found that the inclusion of the modified risk claim did *not* affect these intentions. Prevention of youth initiation of tobacco products is a key consideration in FDA's evaluation. Although the available evidence from epidemiological studies does not demonstrate significant youth initiation of snus products at this time, it is possible that marketing the product as a modified risk product could change this. In fact, some studies suggest that risks perceptions predict tobacco product use among youth (e.g., Song et al. 2009; Strong et al. 2019). Thus, it is essential that modified risk marketing be targeted to current tobacco users and disseminated in ways to minimize exposure among youth. Based on these conclusions, the postmarket requirements described below include measures to limit youth exposure to the products' labeling, advertising, and marketing. In addition, reporting requirements will enable FDA to monitor, among other things, the degree to which the implementation of the marketing plans is effectively targeting the intended audience and limiting exposure to youth.

Section 911(h)(4) of the FD&C Act requires an MRTP order to be for a specified time period. I recommend authorization for a period of five years, given that these would be the first MRTP authorizations issued by the Agency. Although this review has found that the products will benefit the health of the population as a whole, that determination may change over time as a function of how the product is actually used by consumers. Therefore, monitoring use of the eight General Snus products that are the subject of these applications in terms of uptake, dual use, and complete switching is required. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and understanding at multiple time points. A five-year period is a reasonable amount of time for trends in use behavior to emerge to evaluate in postmarket surveillance and studies and assess whether the standard continues to be met and whether the order should be renewed.

2. Environmental Impact

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on October 3, 2019. The FONSI was supported by an environmental assessment prepared by FDA on October 3, 2019.

3. Postmarket Surveillance and Studies

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."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the eight General Snus products that are

the subject of these applications, as actually used by consumers, continue to benefit the health of the population as a whole is likely to be driven by use behavior. Therefore, monitoring use of the eight General Snus products that are the subject of these applications in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were non-users, smokers, or other tobacco product users before initiating the MRTPs and the extent to which new users of the MRTPs become exclusive users or dual users with cigarettes or other tobacco products over time. Relatedly, such surveillance must include an assessment of consumers' understanding of the claim and perceptions of the products. In particular, PMSS must assess the extent to which users of these products understand that, to reduce their risk of disease relative to smoking as described in the modified risk information, they must use General Snus exclusively. **To adequately assess these impacts, you must conduct PMSS that include assessing users' behavior and consumer understanding at multiple time points.**

In addition, FDA has determined that assessing the impact of your MRTP orders on uptake of the products requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the products are sold (e.g., 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 tobacco products by quarter since the granting of your modified risk granted orders (for the initial reporting period) or the previous reporting period (for all reports that follow), including, for each MRTPA STN, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were 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 tobacco products for each MRTPA STN, post-MRTP authorization.

MRTP Use and Adverse Experiences

In order for FDA to determine whether the eight General Snus products that are the subject of these applications, 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. 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. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported adverse experiences for the tobacco products, which includes a listing of all 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 products including nature, frequency, and potential aggravating factors.

In addition, the PMTA orders for your General snus products, issued on November 10, 2015, require you to report to the FDA all adverse experiences that are both serious and 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 STN(s) PM0000010-PM0000017 and MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029.**

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

- Death;
- A life-threatening adverse event;
- 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, *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 PMTA (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 the MRTPs and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the eight General Snus products that are the subject of these applications, as actually used by consumers, 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 findings both in your own studies (i.e., studies conducted by you or on your behalf) and in publications including any new scientific data (published or otherwise) regarding the MRTPs and consumer perception, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco products from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this

order. A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the MRTPs and consumer perception, behavior, or health.

II. 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 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) requires that the results of PMSS be submitted on an annual basis. These reports must be identified as “PMSS Report”, and the MRTPA STNs should be referenced 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 agreed upon 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.

4. Postmarket Advertising and Promotion Requirements, Recordkeeping and Retention, and Manufacturing Information

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

Advertising and Promotion Requirements

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, 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;
 - 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 adult audiences by age-range(s), including young adult audiences, ages 18-24, and other demographic and/or psychographic characteristics that reflect your intended target audience;
 - Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
 - Use of owned, earned, shared, and/or paid social media to create labeling for, advertise, market, and/or promote the products;
 - Use of partners, influencers, bloggers, and/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/or
 - Use of earned media and/or public-relations 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 youth, ages 17 years and under, 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 for the first six months after the date of your modified risk order you provide FDA a 30-day notification for all labeling, advertising, marketing, and/or promotional materials for which you plan on disseminating to the public. These notifications are not for pre-approval, but are required so that FDA can have timely access to your marketing plans and materials, and if needed, 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 providing notification to FDA. 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. The notification must include:

- 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 advertisement 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 and media buys;
 - Target specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and psychographic characteristics that reflect your intended target audience(s), including how the target audience(s) are defined and the insights used to develop the target audience profile(s) and the source of such insights;
 - Restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
 - Use owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;
 - Use partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
 - Conduct any consumer engagements – whether by you, on your behalf, or at your direction – including events at which the products will be demonstrated; and/or
 - Use public-relations outreach to create labeling for, advertise, market, and/or promote the

products.

III. Periodic Reporting

Under sections 911(h)(5) of the FD&C Act, these orders require that you submit periodic reports 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. For the six-month reporting period, the report must include:

- A cover letter that includes the following text in your subject line: **PERIODIC REPORT for MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029**. The cover letter should include the STN(s) and corresponding tobacco product name(s), applicant name, date of report, and reporting period.
- 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. 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**. The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, reporting period.
- A description of the implementation of all advertising and marketing plans, including strategic creative briefs and paid media plans – whether conducted by you, on your behalf, or at your direction – by channel and by product, and the 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 adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and/or psychographic characteristics that reflect the intended target audience(s), how the target audience(s) were defined and the insights used to develop the target audience profiles(s) and the source of such insights;
 - Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
 - Use of owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;
 - Use of partners, influencers, bloggers, and/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/or
 - Use of public-relations 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 location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under), not previously submitted. This analysis should be verified against post-launch delivery-verification reports submitted to you 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 location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures, not previously submitted.

V. 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 consumer 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 least of federal minimum legal age to purchase 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 least of federal minimum legal age to purchase 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) – 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 least of federal minimum legal age to purchase 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 location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to youth, ages 17 and under. Such monitoring also requires post-launch delivery verification reports be submitted to you 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 General Snus 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 legal age to purchase 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.

Recordkeeping and Retention

The risk modification orders for your modified risk tobacco products are effective for 5 years from the issue date of the orders. If you wish to renew your orders, we recommend you submit a request for renewal 360 days prior to the end of your effective timeframe. In order to help ensure that your risk modification orders meet the standard for renewal and to help expedite the review of any renewal applications, we request that you establish and maintain the records listed below. The records should be retained for a period of not less than four years from the date of distribution of the last batch of the tobacco products listed in your orders under section 911(g)(1). The records should be legible, written in English, and upon request, available for inspection and copying by officers or employees duly designated by the Secretary. Please note that Appendices B and C require you to periodically submit some of these records to FDA (e.g., in PMSS reports and/or advertising and promotion-related reports). Additionally, we remind you that the PMTA orders for your General snus products issued on November 10, 2015, also require you to establish and maintain records, some of which overlap with the records listed below:

- The MRTPAs submitted prior to the orders
- Postmarket reports, as described in the Required PMSS Appendix, including adverse experience

- reports and all relevant documentation associated with the experience
- Records of all nonclinical or clinical studies, including:
 - Source data;
 - Study protocols (including statistical analysis plan);
 - Amendments showing the dates and reasons for any protocol revisions;
 - Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals or non-approvals;
 - Informed consent forms;
 - Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC;
 - Investigator financial disclosure statements;
 - Progress reports;
 - Monitoring reports;
 - Adverse experience reports;
 - Case report forms/subject diaries/medical records/laboratory reports;
 - Subject data line listings/observation records;
 - Test article accountability records;
 - Study results/protocol summaries/study reports; and
 - Certifications and amendments to certifications
 - Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls), packaging, storage, and stability monitoring and testing (including protocol and results) of the products
 - Records pertaining to the sale, distribution, or other disposition of the products, specifically:
 - A list of distributors and retailers of the products, including brick-and-mortar and digital⁶;
 - Any available information (not to include personally identifiable information) about product purchases, such as purchasers' demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use);
 - Policies and procedures regarding verification of the age and identity of purchasers of the products; and
 - Policies and procedures regarding restrictions on youth access to the products
 - Health hazard analyses, if performed voluntarily or directed by FDA
 - Records pertaining to any and all complaints associated with any of the products that you receive or of which you are aware

Manufacturing Information

The PMTA orders for your General Snus 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. 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**

⁶ For the purposes of this order, here and throughout the document, "digital" includes internet/online and mobile.

MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029. The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, 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 MRTPAs;
 - 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 products and the basis for concluding that each manufacturing change did not result in any modification to the products.⁷
- 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 General snus products, issued on November 10, 2015, require that, for products that have been distributed, if the deviation may negatively impact public health, you promptly identify and report that deviation to CTP. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products.

Discontinuation and Reintroduction

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

⁷ 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.

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V. Appendix – The Public Health Rationale for Recommended Restrictions on Modified Risk Tobacco Product Labeling, Advertising, Marketing, and Promotion

I. Background

Most tobacco use is established in adolescence and age of initiation plays a significant role in the progression from tobacco experimentation to regular use (HHS 2012). It is well established that industry practices, such as tobacco product labeling, advertising, marketing and promotion, substantially impact youth trial and uptake of tobacco product use. Part of FDA's premarket review of a modified risk tobacco product (MRTP) application is aimed at determining whether the applicant has demonstrated that the modified risk tobacco product will or is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

Firms seeking a marketing order for an MRTP may not have robust data on the degree to which its labeling, advertising, marketing, and promotion may influence youth perception or appeal to youth. This memo describes FDA's authorities under the Family Smoking and Tobacco Control Act (Tobacco Control Act) to monitor and restrict tobacco product marketing and related activities in the context of MRTP application review and authorization. The MRTP application review process includes an evaluation of product labeling and advertising, as well as evidence concerning consumer comprehension of the proposed modified risk information. Given FDA's statutory mandate to protect young people from the dangers of tobacco use and ensure that the marketing of an MRTP will or is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products (e.g., youth or minors), the agency can request and review any changes to labeling, advertising, marketing, and promotional materials and plans for MRTPs that have received modified risk authorization to ensure that there are no grounds for withdrawing authorization and restrict the marketing of such products as appropriate to continue satisfying the requirements of Section 911 of the Federal Food Drug and Cosmetic Act. This will help FDA evaluate the potential impact of such materials on the likelihood of initiation and use of the MRTPs by youth or others who do not use tobacco products and provide the firm and/or the agency an opportunity to prevent or mitigate any related potential harms to the public health.

II. The Food, Drug, and Cosmetic Act, as Amended by the Tobacco Control Act: Congressional Findings and FDA Authorities Related to Tobacco Product Labeling, Advertising, Marketing, and Promotion

The Tobacco Control Act makes clear the harmful influence of tobacco product labeling, advertising, marketing and promotion on youth tobacco use, and the intent of Congress to give FDA the authority to restrict these activities. In the Tobacco Control Act, Congress finds that, "[t]obacco advertising and marketing contribute significantly to the use of nicotine-containing tobacco products by adolescents," and "[b]ecause past efforts to restrict advertising and marketing of tobacco products have failed adequately to curb tobacco use by adolescents, comprehensive restrictions on the sale, promotion, and distribution of such products are needed." TCA §2(5) and (6). Thus, Congress concludes, "[c]omprehensive advertising restrictions will have a positive effect on the smoking rates of young people," and "[r]estrictions on advertising are necessary to prevent unrestricted tobacco advertising

from undermining legislation prohibiting access to young people and providing for education about tobacco use.” TCA §2(25) and (26).

These findings are underscored by section 906(d) of the FD&C Act, which grants FDA the authority to “require restrictions on the sale and distribution of a tobacco product, including restrictions on the access to, and the advertising and promotion of, the tobacco product, if [...] such regulation would be appropriate for the protection of public health,” and section 910(a)(2) of the FD&C Act, which grants FDA the authority to require premarket review and authorization of a new tobacco product before such product may be legally marketed in the United States. Further, as part of premarket application review, FDA may require “information relevant to the subject matter of the application” to assist the agency in determining “whether the marketing of a tobacco product [...] is appropriate for the protection of public health” (section 910(b)(1)(G) and 910(c)(4) of the FD&C Act). In an order authorizing the marketing of a new tobacco product FDA may also restrict the sale and distribution of the tobacco product to the extent that the sale and distribution of a tobacco product may be restricted under section 906(d) of the FD&C Act. FD&C Act §910(c)(1)(B).

Similarly, with respect to MRTPs, Congress found that “[i]t is essential that the [FDA] review products sold or distributed for use to reduce risks or exposures associated with tobacco products and that it be empowered to review any advertising and labeling for such products.” TCA §2(36). Congress also found that “[t]he [FDA] is a regulatory agency with the scientific expertise to... evaluate the impact of labels, labeling, and advertising on consumer behavior in order to reduce the risk of harm and promote understanding of the impact of the product on health.” Accordingly, under section 911 of the FD&C Act, Congress gave FDA authority to require premarket review and authorization of MRTPs before such products may be legally marketed in the United States. §911(a). As part of the MRTP application review process, FDA reviews the proposed product labeling and advertising and may require any other information to assist the agency in determining whether the MRTP will or is expected to “benefit the health of the population as a whole, taking into account both users of tobacco products and those persons who do not currently use tobacco products.” §911(d)(1), (4), (7) and § 911(g)(1)-(2). In making these determinations, the agency specifically evaluates the likelihood that persons who do not use tobacco products, including youth, will start using the MRTP that is the subject of the application. §911(g)(4)(C). In addition, under section 911(h)(1), FDA must require that any advertising or labeling concerning MRTPs 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. Finally, under section 911(h)(5), FDA has broad authority to require that the MRTP for which an applicant obtained an order under section 911(g)(1) “comply with requirements related to advertising and promotion of the tobacco product.”

III. Effects of Youth-Exposure to Tobacco Product Labeling, Advertising, Marketing, and Promotion on Youth-Appeal, -Perception, and -Use of Tobacco Products

A. Influence of Tobacco Product Marketing on Youth Tobacco Use, in General

As noted in the FD&C Act, as amended by the Tobacco Control Act, a key consideration in determining whether the marketing of an MRTP will or is expected to benefit the health of the population as a whole is the increased or decreased likelihood that persons who do not use tobacco products, especially youth, will start using the MRTP. In addition to Congress’ findings in the Tobacco Control Act, there is a large body of scientific evidence that documents the potential harm of tobacco product labeling, advertising, marketing and promotion on youth tobacco use.

In one of the first comprehensive reviews on the subject—the National Cancer Institute’s (NCI) 19th monograph, *The Role of the Media in Promoting and Reducing Tobacco Use*—authors conclude that “the total weight of evidence—from multiple types of studies, conducted by investigators from different disciplines, and using data from many countries—demonstrates a causal relationship between tobacco advertising and promotion and increased tobacco use” (NCI 1998). As such, the direct role of tobacco product marketing and related activities in increasing tobacco use in the United States, especially among youth, and the high rates of youth-exposure to tobacco marketing due to its ubiquity, are two key rationales cited by NCI for restricting tobacco product marketing and related activities.

The 2012 Surgeon General’s report, *Preventing Tobacco Use Among Youth and Young Adults*, synthesizes more than 30 years of research on the topic. This report outlines similar findings—tobacco product labeling, advertising, marketing, and promotion influence a wide range of established risk factors for youth tobacco use by shaping attitudes, beliefs, and risk perceptions, and promoting pro-tobacco social and cultural norms. The report states, “there is strong empirical evidence, along with the tobacco industry’s own internal documents and trial testimony, as well as widely accepted principles of advertising and marketing that support the conclusion that tobacco manufacturers’ advertising, marketing, and promotions recruit new users as youth and continue to reinforce use among young adults” (HHS 2012). This evidence is sufficient to conclude that “marketing efforts and promotion by tobacco companies show a consistent dose-response relationship in the initiation and progression of tobacco use among young people” (HHS 2012).

To illustrate these points, the report cites findings of studies that demonstrate “advertising and promotion by the tobacco industry are effective in raising awareness of smoking, increasing brand recognition, and creating favorable beliefs regarding tobacco use. There is strong and consistent evidence that marketing influences adolescent smoking behavior, including selection of brands, initiation of smoking, and overall consumption of cigarettes” (HHS 2012). Further, “research conducted by the tobacco industry consistently demonstrates that the brand imagery portrayed on packages is particularly influential during youth and young adulthood—the period in which smoking behavior and brand preferences develop,” and “displays of packages in retail outlets, commonly referred to as ‘powerwalls,’ have high visibility among youth and help to establish brand imagery and social norms at an early age” (HHS 2012). “Young people who are more familiar with tobacco advertising can identify specific advertisements, have a favorite tobacco advertisement, or possess cigarette promotional items are more likely to begin smoking than their peers who do not have these characteristics,” and “adolescents who both owned cigarette promotional items and had a favorite cigarette advertisement” were more likely to progress from initiation of smoking to established smoking (HHS 2012).

Research has found that a key tactic of tobacco companies seeking to attract and recruit youth users is to use advertising with aspirational imagery and themes known to resonate with younger audiences, such as independence, popularity, rebelliousness, attractiveness, and being “cool” (HHS 2012). Even tobacco advertising that purportedly targets adult users can have a profound influence on adolescent tobacco use behaviors if it creates positive feelings in youth toward the product; pleasant feelings motivate actions that consumers anticipate will reproduce those feelings (Slovic & Peters 2006). As such, youth are more likely to mimic behavior portrayed as favorable in advertising, such as tobacco use. Furthermore, youth often misjudge the risks and benefits of advertised products based on how they feel about them (Slovic & Peters 2006). If youth feel positively toward a product, they are more likely to perceive it as having lower risks and higher benefits.

In addition, adolescents are “uniquely susceptible to social and environmental influences to use tobacco” given their developmental stage and are heavily influenced by peers, family members, prominent members of their community, celebrities, and other cultural icons and adult role models—

especially those they perceive to be popular, attractive, and “cool” (HHS 2012). As such, images of tobacco use in various types of media are “a potentially powerful socializing force among adolescents, in part because they are communicated by people who are identified by youth as media stars,” and “adolescents actively rely on external information as they seek to shape their own identities, often looking to media stars as models of what to wear and what to do” (HHS 2012). These marketing campaigns may be misleading in that they imply positive, pervasive and/or pro-tobacco social norms that are inaccurate or overstated. The misleading impression can be enhanced by failing to disclose a sponsor’s relationship with a company or failing to reveal that the content was not organically generated independently of the sponsoring company. Because youth have a heightened sensitivity to normative influences, sponsored tobacco marketing content may encourage youth uptake of tobacco use (HHS 2012).

B. Influence of Tobacco Product Marketing on Youth Tobacco Use in the Context of Tobacco Products Other Than Cigarettes

Much of the research spanning the past few decades has focused on the influence of tobacco product marketing on cigarette smoking in particular; however, companies that sell other types of tobacco products engage in the same labeling, advertising, marketing, and promotional practices used by cigarette companies. “[T]he traditional division of products, brand identities, and marketing between cigarette and smokeless tobacco companies has all but become nonexistent in recent years as major U.S. cigarette companies, including RJR and Altria, have acquired smokeless tobacco companies and have developed new smokeless tobacco products” (HHS 2012). Some of these products are even marketed with popular cigarette brand names (e.g., Camel Snus).

Beyond cigarette-specific marketing, research has found that youth exposed to in-store marketing of e-cigarettes, hookah, cigars, smokeless tobacco, and pipe tobacco were two to three times more likely to use those products as well as to initiate cigarette use (Cruz et al. 2018). Further, research exploring the influence of tobacco marketing on youth use of novel tobacco products, such as e-cigarettes, confirms that exposure and receptivity to tobacco advertising is significantly associated with tobacco initiation among adolescents. The 2016 Surgeon General’s report, *E-cigarette Use Among Youth and Young Adults*, concluded “e-cigarette products are marketed in a wide variety of channels that have broad reach among youth and young adults,” and themes in e-cigarette marketing are “parallel to the themes and techniques that have been found to be appealing to youth and young adults in conventional cigarette advertising and promotion” (HHS 2016).

The report also summarizes the results of several studies looking at the relationship between e-cigarette marketing and youth tobacco use. For example, an analysis of the 2011 National Youth Tobacco Survey (NYTS) found that “adolescents who reported frequent exposure to protobacco advertising at the point of sale and on the Internet (e.g., seeing ads most of the time or always) had significantly higher odds of ever using e-cigarettes, and there was a dose-response association between the number of marketing channels to which they were exposed and ever use” (HHS 2016; Agaku & Ayo-Yusuf 2014). Two analyses of 2014 NYTS data assessing exposure to e-cigarette advertising in different channels (i.e., internet, print, television and movies, retail stores) found that “exposure to each type of e-cigarette marketing was significantly associated with increased likelihood of ever having used and current use of e-cigarettes among middle and high school students. Exposure was also associated with susceptibility to use e-cigarettes among current nonusers. In multivariate models, as the number of channels of e-cigarette marketing exposure increased, the likelihood of use and susceptibility also increased” (HHS 2016; CDC 2016; Mantey et al. 2016). These findings are particularly relevant in the context of more recent NYTS data showing a substantial increase in youth use of e-cigarettes from 2017 to 2018 (Gentzke et al. 2019).

This uptick in youth e-cigarette use also contributed significantly to the first increase in overall youth tobacco use in recent years (Gentzke et al. 2019).

Recent studies have also assessed the influence of e-cigarette marketing on youth use of conventional cigarettes. For example, an analysis of data collected between 2013-2015 via the Population Assessment of Tobacco and Health study found youth receptivity was highest for e-cigarette advertising (compared to conventional cigarette, cigar, and smokeless tobacco product advertising), and receptivity to e-cigarette advertising was also associated with initiation of conventional cigarette smoking (Pierce et al. 2018). Another study had similar findings concluding that exposure to any e-cigarette advertising may play a role in teens' decision to initiate e-cigarette and conventional cigarette use (Padon, Lochbuehler, et al. 2017). These findings further underscore the powerful influence of tobacco product labeling, advertising, marketing, and promotion within and between product types, and the need for marketing restrictions for novel tobacco products.

C. Influence of Digital Tobacco Marketing on Youth Tobacco Use

While all tobacco product labeling, advertising, marketing, and promotion has the potential to significantly influence youth tobacco use, digital⁸ labeling, advertising, marketing, and promotion is particularly concerning given that it is transforming traditional marketing practices and is highly targeted to young people. The Pew Research Center reports that a vast majority of teens have access to a home computer or smartphone and nearly half of teens report using the internet "almost constantly" (2018), which means that many youth are constantly being exposed to marketing of a variety of different products, including tobacco products. While there is overwhelming evidence that children, teens, and young adults are exposed to and influenced by marketing of unhealthy products in traditional media, the internet provides marketers with new, relatively inexpensive channels and tools for disseminating their messages (Dunlap et al. 2016). Research examining online engagement with tobacco marketing among youth found a sizable increase of engagement over time (Soneji, Yang, Knutzen, et al. 2018) and that the number of engagements is associated with tobacco use initiation, frequency of use, and progression to poly-product use (Soneji, Yang, Moran, et al. 2018). According to the 2012 Surgeon General's report, "the techniques of digital marketing are part of sophisticated behavioral targeting in which the marketer collects data on the users' every move (e.g., every click of the mouse, sign-up for a contest, forwarding to a friend) to enable ever more precisely targeted marketing" (HHS 2012). This precision marketing also represents an opportunity to limit youth-exposure to the digital marketing of tobacco products.

Via social media applications, marketers gain access to detailed profiles of users and their friends. Social media has fundamentally altered the marketing landscape by moving young audiences from passive recipients of advertising to active participants in the co-creation and dissemination of marketing messages (Dunlap et al. 2016). Corporate brands leverage the use of social media by adolescents and young adults to target and engage with young audiences (Dunlap et al. 2016). Unlike traditional forms of advertising that target potential customers with ads, companies that join in the "complex network of relations" of social media "befriend" their customers, which is a particularly appealing approach for companies wanting their consumers to express their personality through brand association (Dunlap et al. 2016). "Marketers seek to create 'brand ambassadors,' [i.e., social-media influencers] who promote the product in the context of their online communications, whether or not such promotions are recognized by the users or receivers as marketing. The effect is to blur the distinction between marketing communications and market research" (HHS 2012).

⁸ For the purposes of this memo, here and throughout the document, "digital" includes internet/online and mobile.

For example, a study examining message content on Twitter concluded that Twitter serves as an important platform for e-cigarette marketing (Chu et al. 2015). Whenever a message posted by an e-cigarette brand is “retweeted” by another user, the message has reached a new network of users. Additional retweets can provide a cascading spread within and outside an original poster’s network and cause the message to go viral. This exposure through a retweeting network allows rapid diffusion of messages across groups (Chu et al. 2015). However, Twitter content often reaches unintended audiences, including youth and other vulnerable populations, due to the platform’s exponential reach and relatively limited control over what types of people are exposed to specific messages (Chu et al. 2015). With more than 30% of today’s youth reporting they use Twitter, marketing and promotion of tobacco products through Twitter can influence youth (Pew Research Center 2018). In addition, a recent study found that sales growth of JUUL was accompanied by a variety of innovative, engaging, and wide-reaching campaigns on social media platforms popular among youth, such as Twitter, Instagram, and YouTube (Huang et al. 2018).

IV. The Public Health Rationale for Requiring Submission of Modified Risk Tobacco Product Labeling, Advertising, Marketing, and Promotional Materials and Plans and for Placing Restrictions on the Marketing of Modified Risk Tobacco Products to Limit Youth-Exposure to Such Marketing

A. Purpose of Marketing Requirements and Restrictions for Modified Risk Tobacco Products, in General

As noted in the introduction, FDA has a statutory mandate to authorize the marketing of a modified risk tobacco product only if the applicant has demonstrated that such tobacco product will or is expected to benefit the health of the population as a whole, taking into account the relative health risks to individuals, the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the MRTP, the increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP, and the risks and benefits of the MRTP as compared with using smoking cessation products. Thus, FDA’s premarket review under the MRTP application pathway is aimed, in part, at determining if marketing an MRTP would increase or decrease the likelihood that those who do not currently use tobacco products will start using them. Among non-users, youth are a significant population of concern as their current stage of brain development makes them especially susceptible to nicotine addiction (HHS 2012). Prior sections of this memo have illuminated the powerful impact of tobacco product labeling, advertising, marketing, and promotion on youth-perceptions of tobacco products, youth-appeal of tobacco products, the likelihood of youth initiation and use of tobacco products, even when said marketing is purportedly targeted or designed to appeal to adults. In addition, MRTP marketing will likely include claims that are intended to lower perceptions of risk. Indeed, recent studies have demonstrated that when youth are exposed to modified risk statements about a product, they perceive it as less harmful. For instance, asking youth “Suppose the FDA approves a label saying that Swedish snus is less harmful than cigarettes” caused youth to perceive Swedish snus as exposing users to less harmful chemicals and as presenting a lower risk of serious health problems (El-Toukhy et al., 2018). Given that risk perceptions predict tobacco product use among youth (e.g., Song et al., 2009; Strong et al., 2019), if youth are exposed to modified risk advertising and labeling, this could increase their likelihood of initiation. For example, in a national sample of U.S. youth who had never used snus, youth who perceived snus as low or medium in risk were more likely to try it during the next year compared to youth who perceived snus as high in risk (Strong et al., 2019). Thus, for FDA to help ensure that the continued marketing of an MRTP will benefit the health of the population as a whole, it is critical for FDA to conduct ongoing review and evaluation of the

product's labeling, advertising, marketing, and promotional materials and plans to assess any possible effects on perceptions, appeal, intentions, and behaviors among intended and unintended audiences, and to place appropriate restrictions on the product's marketing and related activities from the outset to limit youth-exposure to such marketing.

Additionally, requiring a firm that receives marketing authorization for its MRTPs to provide labeling, advertising, marketing, and promotional materials and plans in advance of their use is not for pre-approval, but will provide FDA timely access to such materials and plans and, if needed, allow FDA to provide advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and on the likelihood that the marketing of the products will continue to benefit the health of the population.

B. Reducing Youth-Appeal of Tobacco Product Marketing

Generally, firms receiving marketing authorization for an MRTP should seek to reduce the youth-appeal of the tobacco product's labeling, advertising, marketing, and promotional materials, including avoiding the use of imagery and themes known to resonate with youth, such as aspirational content depicting tobacco use as "cool," attractive, rebellious, and/or risky, or as a means to make one more popular, desirable, or independent (HHS 2012). Other potential strategies for limiting youth-appeal of labeling, advertising, marketing, and promotional materials include focusing marketing content on instructional demonstrations and product comparisons and avoiding bright, bold, cheerful designs and colors, which can influence youths' product choices because these characteristics affect their perception of the products, draw attention to them, and influence purchase decisions (Padon, Mahoney, et al. 2017; Akcay 2012; Lempert & Glantz 2016).

Instead, labeling, advertising, marketing, and promotional materials should be clearly tailored to appeal to adults by using personalization strategies that make the content relevant and meaningful to adult recipients and should depict individuals who are similar to the target audience in terms of attributes, beliefs, and interests, in relatable situations that make it easier for adult viewers to engage with and connect to the advertising (Hawkins et al. 2008; Nielsen 2014). For example, advertising tailored to adult tobacco users would likely use headline and body copy that is relevant only to adults who might be considering switching products; would use models that are obviously older adults (ages 35-54) who look like and/or explicitly state they are tobacco users; and would portray people in realistic situations for tobacco users without making them look highly appealing or aspirational to other non-targeted populations, such as youth.

C. Limiting Youth-Exposure to Tobacco Product Marketing

Given the association between tobacco product marketing and youth initiation of tobacco use detailed in Section III, to help ensure the marketing of the products receiving marketing authorization under the MRTP application pathway continues to benefit the health of individuals and of the population as a whole, it is critical to limit youth-exposure to the products' marketing, advertising, labeling, and promotion. Placing certain marketing restrictions⁹ on the newly authorized MRTPs from the outset, such as the media channels through which the firm markets its products, are essential components of limiting youth-exposure, and are thus critical to ensuring the products will benefit the health of the population as a whole.

⁹ For the purposes of this memo, this section focuses on restrictions related to digital tobacco product marketing. Considerations for other types of marketing restrictions may be addressed in the future, and the contents of this memo should not be viewed as an exhaustive list.

1. Restrictions on Paid Digital Tobacco Product Marketing

The rise of digital marketing has changed media consumption habits over the past decade and created an increasingly complex media landscape where it is not yet possible to completely eliminate youth-exposure to tobacco marketing. However, the data sources, methodologies, and technologies used to deliver and track digital media consumption have also evolved, enabling product marketers to create sophisticated, highly targeted digital marketing plans and paid media buys designed to reach their intended audiences based on specific demographics, psychographics, and media passion-points while also limiting reach or “spill” to unintended audiences. Thus, it is possible, efficient, and necessary for firms to take advantage of these technologies to help ensure that tobacco product marketing is targeted to adults and that “spill” to youth audiences is minimal.

For example, paid digital advertising targeting capabilities have evolved such that it is possible, if not standard practice, to target paid advertising using sophisticated data management systems and algorithms connecting individuals to a range of data points, including their demographic characteristics, purchase behaviors, preferences, political opinions, internet search terms, browsing history, interactions with digital content (e.g., liking a social media post, following a specific influencer, sharing a video), digital accounts, connected devices, physical location, and information about other members of their household. Consumers are also increasingly digitizing and sharing detailed information about their personal beliefs, experiences, and behaviors, giving marketers ever-growing capabilities to track and target individuals who meet the exact demographic and psychographic profiles of their ideal consumers. As a result, targeting advertising based on a “digital destination,” such as placing advertising on a specific website, is becoming largely obsolete and economically inefficient in comparison to targeting advertising based on specific digital profiles connected to actual consumers who can thus be reached in almost any digital location and time (IAB 2018).

This is especially significant when considering the need to limit youth-exposure to tobacco marketing appearing in the digital environment, which is exponentially more vast, ever-changing, and difficult to categorize than more traditional media channels like broadcast television and radio and print, making it difficult to accurately determine the audience composition of a specific digital property (i.e., what percent of visitors to a specific website are within a certain age-range), or even assess where one digital property ends and another begins. Fortunately, paid digital advertising targeting capabilities offer tobacco marketers the ability to target adults who meet specific age criteria through the use of first- and/or second-party age-verified data (see table) on any digital property accepting paid tobacco advertising, while also restricting youth-access to such advertising. Marketers can also layer on additional demographic and psychographic data (e.g., tobacco product purchase behaviors) to further enhance the efficiency of their paid digital media buys.¹⁰

¹⁰ In addition to first- and second-party age-verified data, firms can use 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 to enhance first- and second-party age-verified audience targeting data. However, such data is not considered age-verified and should only be used in combination with first- and/or second-party age-verified data.

Table. Definitions of first- and second-party age-verified data

First-party age-verified data	Data owned by a firm (e.g., a firm’s customer registration data collected via site traffic to the firm’s company-owned website; data the firm uses in direct marketing to its adult smoking customers) that the firm has age-verified through independent, competent, and reliable data sources.
Second-party age-verified data	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 a firm has access. This data must be age-verified by the second party and not through data aggregators.

Using targeting through the use of first- and/or second-party age-verified data (see table) does not mean that a firm will not be able to advertise at all in certain digital platforms, for example on certain websites that do not have age-restriction measures in place. Rather, even if a website does not have its own first-party age-verified data, tobacco advertising could still show up on that site. For example, if an adult that a tobacco marketer has age- and identity-verified as meeting the federal minimum legal age to purchase tobacco products through independent, competent, and reliable data sources visits TeenVogue.com, that adult could be delivered a tobacco ad on the site using the marketer’s first-party age-verified targeting data (regardless of whether TeenVogue.com has its own first-party age-verified data to share with the tobacco marketer), but an age-verified teen on TeenVogue.com would not be delivered the same tobacco ad as a result of this targeting. Therefore, through the use of targeting data, different individuals can see different ads when visiting the same website at the same time. This allows for a highly targeted approach to tobacco advertising delivery, which can help ensure that youth exposure is minimized, while at the same time not restricting access to adults.

2. Restrictions on Tobacco Product Social Media Marketing and the Use of Influencers, Bloggers, Brand Ambassadors, etc.

Although paid digital advertising can be effectively targeted using first- and second-party age-verified data to reach adults, there are other types of digital marketing that cannot be targeted using this approach. For example, product-branded social media accounts essentially operate as both mini websites and “free” advertising channels offering a range of effective means of directly reaching and engaging consumers. In fact, “the ability to influence a large number of individuals, the minimal effort required to make influence attempts, and the flexibility to deploy a variety of influence strategies through information technologies are a potent combination making influence in online social networks considerably more compelling and pervasive than in conventional interpersonal interactions,” highlighting the need for close scrutiny of these methods (Subramani & Rajagopalan 2003). Further, one of the most effective digital marketing practices today—especially among youth who are particularly susceptible to social influences—is the use of “organic” depictions of tobacco use and endorsements of tobacco products by cultural icons and other influencers through their own social media accounts (HHS 2012).

Thus, as part of ensuring digital media plans and buys for tobacco products are highly targeted to adults while limiting spill to youth, it is critical to mitigate against the incredible reach and influence of social media, including “organic” influencer promotion. Currently, there are no universal age-restriction controls on social media platforms and some do not offer any age-restriction options; however, many social media platforms are beginning to offer branded-account owners the option to age-restrict some

or all of their account pages, followers, and content, including even specific posts, photos, videos, events, etc. These options still face a few additional limitations; for example, most social media platforms allow users to establish their own account profile settings, including self-reported age, and users are not age- or identity-verified. However, users are increasingly prompted to “link” digital profiles and accounts (e.g., option to sign-up for a new account using an existing email account or social media account), increasing the likelihood of more accurate self-reporting.

As part of these restrictions, firms must ensure that their own social media accounts as well as those of any influencers promoting a tobacco product on a firm’s behalf use the available age-restriction controls to restrict youth access to any product promotion disseminated through social media accounts. Firms must also ensure the disclosure to consumers or viewers, via the use of statements such as “sponsored by [firm name],” of any relationships between the firm and entities that creating labeling for, advertise, market and/or promote the product on the firm’s behalf to help prevent misleading marketing, which is especially likely to influence youth.

V. Proposed Marketing Restrictions in MRTP Authorization Orders

In this context, FDA should consider including detailed marketing restrictions and requirements, in addition to other requirements, for any MRTP receiving market authorization. FDA should determine such marketing restrictions and requirements on a case-by-case basis when issuing a modified risk order. Information that should be considered in these determinations includes, but is not limited to, information submitted to FDA by a firm seeking authorization under the MRTP application pathway regarding the firm’s intended labeling, advertising, marketing, and promotion of the product; use of industry practices known to substantially impact youth trial and uptake of tobacco product use; new and emerging technologies, media, and marketing practices; and existing applicable laws and legal agreements affecting the sales, distribution, marketing, advertising, labeling, and/or promotion of certain tobacco products.

Generally, firms seeking marketing authorization for MRTPs should seek to limit youth-exposure to the products’ labeling, advertising, marketing, and promotion. Restrictions in a marketing order should be aimed at the following with respect to advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product:

- 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 adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and psychographic characteristics that reflect the intended target audience(s), including how the target audience(s) are defined and the insights used to develop the target audience profile(s);
- Actions taken to restrict youth-access and limit youth-exposure to the products’ labeling, advertising, marketing, and/or promotion;
- Use of owned, earned, shared/social, and/or paid media to create labeling for, advertise, market, and/or promote the products;
- Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
- Consumer engagements, including events at which the products will be demonstrated; and/or
- Use of public-relations outreach to create labeling for, advertise, market, and/or promote the products.

Firms should 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 **digital sales** of the products to individuals who are under the federal minimum legal age to purchase tobacco products.

Firms should establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare consumer information against independent, competent, and reliable data sources, such as public records, at the first point of access to any **owned digital properties** (e.g., the firm's company-owned, consumer-directed, product-branded website(s) and/or mobile applications), to restrict access to any of the products' labeling, advertising, marketing, and/or promotion appearing in such properties to only individuals who are at least of federal minimum legal age to purchase tobacco products.

Firms should 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 the firm's behalf through the influencer's account), at the first point of access to any **shared digital properties** (e.g., the firm's product-branded social media accounts, pages and associated content; content promoting the products on the firm's behalf disseminated through another entity's social media accounts), to restrict access to any of the products' labeling, advertising, marketing, and/or promotion appearing in such properties to only individuals who are at least of federal minimum legal age to purchase tobacco products.

Firms should establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of 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), to restrict access to such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products. Such targeting must use only first- and/or second-party age-verified data (see table). Firms should restrict advertising practices that are not and/or cannot be targeted using such data (e.g., tactics like "Run-of-Site," "homepage takeovers," "splashy buys").

Firms should 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) 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 location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). Such monitoring should require real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to youth, ages 17 and under. Such monitoring also should require post-launch delivery verification reports be submitted to the firm from an accredited source (e.g., Media Ratings Council).

Firms should **disclose to consumers or viewers any relationships between the firm and entities** that create labeling for, advertise, market, and/or promote the products, on the firm's behalf or at the firm's direction, via the use of statements such as "sponsored by [firm name]" in any such labeling, advertising, marketing, and/or promotional materials.

It is vital to the continued protection of public health that FDA take these and other marketing-related considerations seriously when evaluating marketing plans to ensure they are sufficiently targeted to limit youth-exposure to tobacco product labeling, advertising, marketing, and promotion. The evaluation of these marketing plans, including evaluation of their potential impact on youth tobacco use, will help

FDA determine whether the marketing, and continued marketing, of an MRTP will benefit the health of the population as a whole.

VI. Conclusion

Given the level of evidence indicating the direct and powerful impact of tobacco marketing on youth tobacco use, and FDA's statutory mandate to protect young people from the dangers of tobacco use, it is both reasonable and critical for firms to submit planned labeling, advertising, marketing, and promotional materials and plans for MRTPs that have received authorization, and for FDA to place restrictions on the marketing of such products. This important safeguard will help FDA ensure, on an ongoing basis, that the continued marketing of MRTPs will benefit the health of the population as a whole.

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