FDA Briefing Document

February 6, 2019
Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC)

Modified Risk Tobacco Product Applications (MRTPAs)
MR0000020-22; MR0000024-25; MR000027-29
Swedish Match North America

Office of Science
Center for Tobacco Products
Food and Drug Administration

DISCLAIMER STATEMENT

The attached briefing document contains information prepared by the Food and Drug Administration (FDA) for the members of the Tobacco Products Scientific Advisory Committee (TPSAC). The FDA background package includes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are referring Swedish Match North America's Modified Risk Tobacco Product Applications (MRTPAs) for eight General Snus products to TPSAC in order to gain TPSAC's insights and recommendations. This briefing package may not include all issues relevant to FDA's decision on the applications and instead is intended to focus on issues identified by FDA for discussion by TPSAC. FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments has been considered and all FDA reviews have been finalized. FDA's determination may be affected by issues not discussed at the TPSAC meeting. The information in these materials does not represent agency position or policy. The information is being provided to TPSAC to facilitate its evaluation of the issues and questions referred to the Committee.

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Memorandum

To:	Members, Tobacco Products Scientific Advisory Committee (TPSAC)
From:	Matthew R. Holman, Ph.D., Director, Office of Science, Center for Tobacco Products, United States Food and Drug Administration
Subject:	Overview of the FDA Briefing Document for February 6, 2019 discussion of Swedish Match North America MRTPAs for eight General Snus tobacco products (FDA Submission Tracking Numbers MR0000020-22; MR0000024-25; MR000027-29)

Introduction

We would like to thank the TPSAC members in advance for their efforts to provide recommendations to FDA on the Modified Risk Tobacco Product Applications (MRTPAs) submitted by Swedish Match North America (SMNA). SMNA is seeking risk modification orders under Section 911(g)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for its General Snus tobacco products. See Appendix A for information on the statutory requirements for Modified Risk Tobacco Products (MRTPs).

In June 2014, SMNA submitted applications to market ten[1] General Snus products as modified risk tobacco products. FDA issued a Response Letter summarizing the findings of its scientific review of the applications on December 14, 2016. On September 17, 2018, FDA received an amendment to the MRTPAs, providing responses to the three deficiencies and two recommendations outlined in the FDA Response Letter.

The eight MRTPAs cover both loose and portioned varieties of General Snus. The applicant describes General Snus as a moist (50-60% moisture) to semi-moist (30-45% moisture) oral smokeless tobacco product that is traditionally produced and used in Sweden and manufactured using a heat treatment process. The applicant states that the products are typically placed between the upper lip and the gum and do not require expectoration during use (Section 3.1.2 of the MRTPAs).

As part of its evaluation of the amendment to these MRTPAs, FDA is reviewing the applicant's revised 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 focus of the TPSAC meeting, as described below, will be the information provided in the applicant's amendment, namely: the revised modified risk claim and the new consumer perception study used to evaluate this claim in terms of consumer understanding, perception, and behavioral intentions.

[1] Although ten applications were initially submitted, two applications were subsequently withdrawn.

Draft Topic for TPSAC Discussion

FDA is reviewing the scientific information submitted in the amendment and evaluating its responsiveness to the deficiencies previously identified by FDA. The amendment submitted by the applicant includes the request for a revised modified risk claim, as well as a new consumer perception study to evaluate the revised claim in terms of consumers' understanding, perceptions, and behavioral intentions. FDA is also reviewing public comments submitted in accordance with Section 911(e).

FDA intends to present its preliminary assessment of the following matters for TPSAC discussion:

- **Revised modified risk claim**: The amendment proposes a revised modified risk claim[2] to be used in the marketing of these products: "Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis." FDA will review the epidemiological evidence available to assess the scientific accuracy of this statement.

- **New consumer perception study**: The applicant conducted the Perceptions and Behavioral Intentions (PBI) study to evaluate the revised modified risk claim. FDA will present an overview of the study, including relevant findings and improvements that address previously identified deficiencies.

FDA will ask TPSAC to discuss its preliminary assessment of these matters and any concerns raised by the revised modified risk claim and its potential impact on: (a) consumer understanding; or (b) population health.

[2] The express modified risk claim requested in the original submissions was to 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."

Background

I. REVIEW OF REGULATORY HISTORY

This section describes the regulatory history of these MRTPAs including the initial submissions, FDA's response, and the new amendment that is the subject of this TPSAC Meeting.

A. MRTPAs: Initial Submissions

On June 10, 2014, FDA received applications from Swedish Match North America, Inc. 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 products 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);
- 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).

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 911(g)(1).

Modified Risk Information: SMNA 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. Maintain "WARNING: Smokeless tobacco is addictive."

2. Remove "WARNING: This product can cause gum disease and tooth loss."

3. Remove "WARNING: This product can cause mouth cancer."

4. 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, wherein the removal of the warning would suggest to consumers that the product would *not* cause the health outcomes named (gum disease and tooth loss; mouth cancer). Each of the three requests was assessed individually, per Section 911(g)(1), to determine whether SMNA 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.

B. TPSAC Meeting, April 2015

Pursuant to Section 911(f) of the FD&C Act, FDA referred the MRTPAs to TPSAC, and TPSAC reported its recommendations on the applications during an open public committee meeting held on April 9-10, 2015. At the meeting, the Committee discussed the ten submitted MRTPAs, including the adequacy of the scientific evidence to support the proposed implied modified risk claims. 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.

The TPSAC discussion was summarized in the Technical Project Lead (TPL) Review (p. 27-28) as follows:

> The TPSAC recommendations are consistent with the FDA's review and evaluation of the MRTPAs. With respect to tooth loss and gum disease, the Committee expressed similar concerns with the quality of scientific evidence on the associations between snus use and these health outcomes. Unanimously, the Committee voted that the scientific evidence was insufficient to conclude that these products do not pose risks of gum disease or tooth loss in users of these products.
>
> With respect to oral cancer, some members of the Committee expressed concerns with the limitations of the available scientific evidence to make any conclusions about the association between snus use and oral cancer. Others expressed concerns with the lack of scientific evidence on female users of these products. When voting on the issues, three members voted that the scientific evidence was insufficient to conclude that these products do not pose risks of oral cancer in users of these products; three members voted that the scientific evidence was sufficient to conclude that these products do not pose risks of oral cancer; and two members abstained.
>
> With respect to the risks as compared to smoking cigarettes, the Committee expressed concerns with making general statements about the relative risks of use of these products as compared to

cigarettes, which may not address all relevant health outcomes. Some members expressed concerns with the use of the term "substantially" within the comparison. Specifically, the Committee discussed the need to emphasize that the reduction in risks would occur from exclusive use of the eight products (in lieu of smoking), to convey the risk of other health outcomes, such as those experienced during pregnancy, and to ensure comprehension of the risks on the part of individuals with low levels of literacy. Voting on the issues, the members split evenly (4 to 4) on whether the evidence supports the statement that health risks to individual users from using these snus products *exclusively*, are "substantially lower" than the health risks from smoking cigarettes. All members voted that evidence did not support that the statement proposed by SMNA adequately communicates the potential risks to individual users of these products.

With respect to behavioral outcomes, the Committee did not believe that behaviors among the U.S. population would mimic those observed in Sweden and expressed a need for evidence on the abuse liability of these General Snus products. Six members of the Committee voted (versus one against and one abstention) that evidence from Sweden was not relevant for assessing the likelihood that U.S. tobacco users would switch to the use of the General Snus products; five (versus three abstentions) voted that the evidence was not relevant for assessing the likelihood that non-users will initiate use of the General Snus products. Additionally, seven members of the Committee voted (versus one abstention) that the applications did not include sufficient information on the behavioral aspects of the use of these snus products among the U.S. population.

Finally, with respect to the provision of modified risk information within the context of the warning, six of the Committee members (versus 2 abstentions) voted that it was not appropriate to provide the information within the warning labels. In particular, the Committee members expressed concerns that providing this information within a warning may have undue impacts on comprehension and that the study did not provide evidence on the potential effectiveness of this manner of information provision.

C. FDA's Evaluation of the SMNA MRPTAs

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 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 standards of 911(g)(1), but believed 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. Regarding the request to remove the "mouth cancer" warning, FDA stated that it was not issuing a modified risk order based on the proposed claim in its current form because (a) the scientific evidence did not support the implied claim resulting from removal of the warning, and (b) the applicant did not provide evidence regarding how the removal of the warning would impact consumers' understanding and behavior. However, FDA noted that the evidence provided may support "other claims about relatively lower risk of mouth cancer for these products as compared to other tobacco products", suggesting that the applicant consider:
    - A revised claim "more precisely tailored to the supporting science" regarding risk of mouth cancer relative to other tobacco products; and
    - A revised claim that would appear outside of the health warning.

2. Regarding the request to replace the "not a safe alternative" warning with the express modified risk claim, ".... this product presents substantially lower risks to health than cigarettes", FDA concluded that the statement may be substantiated, but only in part. In particular, FDA found that the evidence supports that the 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. However, the generality of the statement language connotes that use of the product could substantially reduce all tobacco related diseases. In addition, FDA found that the evidence was insufficient to (a) determine that the products would benefit the population as a whole taking into account, for example, smokers who switch completely, non-users who initiate use, and dual use by current tobacco users; or (b) be comprehended by the public, particularly in the context of a warning. Accordingly, FDA suggested that the evidence in the applications might support another claim about the relative health risks compared to cigarettes and suggested the applicant consider a revised claim that:
    - Was "more precisely tailored to the supporting science" and that would provide consumers with information about differences in specific health risks between snus and cigarettes; and
    - Would appear outside of the warning label.

3. FDA concluded that the applicant's Consumer Perception Study was deficient because of a failure to use appropriate stimuli and because the measures were problematic. FDA suggested that if the applicant chose to conduct a new consumer perception study (i.e., as part of addressing the deficiencies discussed in 1 and 2), the applicant should address the deficiencies of its initial study, including:
    - Ensuring that the study stimuli test the proposed modified risk information verbatim;
    - If the applicant decided to keep the modified risk information in the warning itself (despite the recommendations not to), then the applicant should examine the impact of this context on consumer perception and comprehension; and
    - Consider assessing consumer perception, understanding, and intentions in the context of an actual use study designed to address behavioral outcomes.

Finally, in addition to the above deficiencies, the Response Letter included the following request and recommendation, respectively, for any potential future submission: (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.

D. Amendment

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

- Deficiencies 1 and 2: The applicant has proposed a revised modified risk claim that conveys specific health risks that are reduced relative to cigarette smoking. The modified risk claim is independent of the warning label. There is no request to change or remove warning labels.

- Deficiency 3: The applicant has conducted a new consumer perception study to (a) evaluate the revised modified risk claim and (b) 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.

Preliminary FDA Review

I. PROPOSED MODIFIED RISK CLAIM

Proposed modified risk claim under review: **"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 section summarizes FDA's assessment regarding the scientific accuracy of the revised 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." This assessment comes from the Epidemiology and TPL reviews of the original submissions. Evidence relevant to the scientific accuracy of the modified risk claim was provided in the initial MRTPA submissions; no additional information related to the health risks of the product was provided in the amendment. To evaluate the revised modified risk claim, we review FDA's assessment of the evidence regarding the risks of snus as they compare to smoking cigarettes for each of the health outcomes identified: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.

Note, the intended meaning of the claim may be subject to interpretation; in particular, the phrase "instead of" might be intended to connote complete replacement of one product for another (i.e., use of snus to the exclusion of cigarettes). Alternatively, the phrase might connote a discrete instance of substitution—i.e., substituting snus for one cigarette. The assessment of scientific accuracy is based on a comparison of exclusive snus use to cigarette smoking. The issue of interpretation is addressed separately, in the context of the consumer perception study, including the degree to which consumers

understand that exclusive use of snus is the means by which the described risk modification is achieved (see below).

In its initial 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. Accordingly, FDA assessed the scientific accuracy of the implied claim that snus did not cause mouth cancer. In the revised claim, the question is not whether or not 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 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.

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. Epidemiology 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.

In characterizing the health risks of the products that are the subject of these applications, 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.

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 GOTHIATEK® standard; and that any observed health effects are the result of use of products that meet the GOTHIATEK® standard. FDA's review of the eight General Snus products confirms that the eight General Snus products also conform to the GOTHIATEK® standard. Thus, FDA concluded that 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.

What follows is a summary of FDA's findings, as reported in the TPL and Epidemiology Reviews, regarding the risk of snus use compared to cigarette smoking, for each of the health outcomes included in the revised modified risk claim. In addition, for context, 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, lung cancer, and emphysema and chronic bronchitis compared with non-users of tobacco. The exception is the Roosaar et al. (2008) study, which is not a meta-analysis, because it 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.

Table 1. Results from published studies[1] of health effects for oral cancers, heart disease, stroke, lung cancer, and emphysema and chronic bronchitis associated with Swedish snus use or smoking compared to non-users of tobacco (Data Source: Appendix VI of Appendix 6a 2013 Environ Snus Monograph of MRTPAs; 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

[1]All but one study (Roosaar et al. 2008) are meta-analyses

*Male current smokers

†RR estimate is for never smokers

‡Nonmalignant respiratory disease death (which includes chronic obstructive pulmonary disease (COPD), bronchitis, emphysema, pneumonia, and influenza)

§RR estimate includes a pooled study of 8 cohorts from Hansson et al. 2012

‖RR estimate includes a pooled study of 8 cohorts from Hansson et al. 2014

A. 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 did not cause mouth cancer.

The conclusions related to mouth cancer were summarized in the 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 risk of mouth cancer from snus was likely lower than that from other tobacco products, and Deficiency 1 suggested that the applicant consider a revised modified risk claim about the risks of mouth cancer relative to other tobacco products. The revised modified risk claim from the applicant does not claim a lack of mouth cancer risk, but instead refers to the General Snus product having lower risk for mouth cancer than cigarettes. In support of the revised modified risk claim, the 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" (Epidemiological Review, p. 29) This is clearly seen by comparing the relative risks for Swedish snus and cigarette smoking compared to non-users, shown in Table 1.

B. Heart Disease

In support of the revised modified risk claim, FDA's review of the evidence pertaining to heart disease concluded that the risk may be lower among users of snus compared to cigarette smokers.

The evidence related to CVD (ischemic heart disease, coronary heart disease, myocardial infarction, and overall CVD) was summarized in the 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). By comparison, as shown in Table 1, cigarette smoking has been found to increase risk of cardiovascular disease by a factor of about 1.5- to 3-fold. This most recent review provides clear evidence that the heart disease risks due to Swedish snus use are lower than the risks from cigarette smoking.

C. Stroke

In support of the revised modified risk claim, FDA's review of the evidence pertaining to stroke concluded that risk of stroke may be lower among snus users compared to cigarette smokers.

The evidence related to stroke was summarized in the TPL Review (p. 53) as follows:

> 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.

As described above, the updated systematic review (Rostron et al., 2018), 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). 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 clearer evidence that the risk of stroke due to Swedish snus use is lower than the risk from cigarette smoking.

D. Lung Cancer

In support of the revised modified risk claim, FDA's review of the evidence pertaining to lung cancer risk concluded that the use of Swedish snus does not have a significant effect on lung cancer risk and, therefore, that 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 TPL Review (p. 50) as follows:

> 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) as follows:

> 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.

E. Emphysema and Chronic Bronchitis

In support of the revised modified risk claim, FDA's review of the evidence pertaining to respiratory disease, including emphysema and chronic bronchitis, concluded that the risk of respiratory disease is substantially lower in exclusive Swedish snus users than in cigarette smokers (Epidemiology Review, p. 27).

The evidence related to respiratory disease was summarized in the TPL Review (pp. 50-51) as follows:

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.

F. Summary and Conclusions

The revised modified risk claim addresses the issues that precluded substantiation in FDA's initial review of the applications. In particular, the claim regarding mouth cancer risk is now in comparison with cigarette smoking, rather than an implied claim of no risk. Second, rather than a generalized claim about "lower risks to health than cigarettes", the revised claim names specific diseases/endpoints. 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 these health outcomes: mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis. This assessment supports the revised modified risk claim as scientifically accurate.

II. CONSUMER UNDERSTANDING AND INTENTIONS

To communicate modified risk information to consumers, the applicant proposes to use the following claim in the marketing of its eight products, under Section 911(g)(1) of the Food, Drug, & Cosmetic (FD&C) Act: "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 retain all currently mandated smokeless tobacco warning labels on its label, labeling, and advertising (LLA) materials, which includes the warnings about: mouth cancer; gum disease and tooth loss; "not a safe alternative"; and addiction. The applicant has indicated that it does not plan to employ the claim on the product's label or labeling, but would include it in advertisements using the following platforms: the branded website, print and online advertising, earned media/public relations, direct mail, email, social media, and consumer activation selling events.

The section below reviews the research the applicant conducted to develop and evaluate its revised modified risk claim in terms of its effects on consumer understanding and intentions to use tobacco products.

SMNA's Consumer Perceptions and Behavioral Intentions Research

Qualitative Research. The applicant conducted qualitative research, involving three phases of focus groups and triads, to develop its proposed modified risk claim and marketing materials. Each phase informed the next, with the goal of developing a believable presentation of an accurate claim. Participants were adult tobacco users, primarily cigarette smokers plus some smokeless tobacco and e-cigarette users. Some participants were skeptical about the idea of a modified risk tobacco product (e.g., because they did not believe risks could be reduced by switching from one tobacco product to another, because they did not highly value a risk reduction if it did not *eliminate* risk, because they did not trust the tobacco industry or government). Participants seemed more receptive to modified risk information after first being introduced to a product and its characteristics. Participants appeared to view the

applicant's proposed 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.") as more believable and motivating than similar claims that mentioned reductions in one specific risk (mouth cancer or lung cancer) plus "diseases caused by using tobacco." Participants were shown marketing information in the form of brochures and videos. Some participants reported that they felt more informed and motivated by a video advertisement – particularly when it included the proposed claim – compared to a brochure advertisement.

Quantitative Research. The applicant also conducted one quantitative study (the Perceptions and Behavioral Intentions [PBI] Study; SMNA 17-01GEN) to assess the proposed modified risk claim's effects on consumer understanding and intentions to use tobacco products. This was a between-subjects experimental study administered via computer, smartphone, or tablet. Characteristics of this study are presented below 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. After that, participants responded to items assessing the following key study outcomes: intentions to buy General Snus, intentions to quit smoking and use other tobacco products, perceptions of absolute and relative health risks of using General Snus, and comprehension of the proposed modified risk claim (see Appendix B).

The video was approximately one-minute long. The video introduced General Snus, described its product features (smokeless, spitless, chilled, upper-lip pouch), provided information about how it is manufactured, followed by audio and text of the proposed claim. The video provided a web address (GeneralSnus.com) and ended with an audio and textual display of one of the four mandatory smokeless tobacco warning labels.

The PBI Study's experimental design allowed the applicant to compare consumer understanding and behavioral intentions after participants viewed the video advertisement with the proposed claim, with one of two alternative test claims, or with no test claim. Our 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 ad with no test claim, which serves as an experimental control. Results of the PBI Study were generally similar across the three claims that were tested, although the proposed claim appeared to have larger effects on smokers' intentions and perceptions compared to the other two claims (as the applicant notes in the Executive Summary, p. 1).

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	Between-subjects experiment with stratified randomization across three factors: • 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 mandated smokeless tobacco warning labels. • product flavors: mint and wintergreen. Analyses collapsed across warning labels and product flavors, except where noted.
Sample	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. Tobacco user groups† included: • 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) 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.
Key Outcomes	• 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 24 years old. Older adult refers to participants over 24 years old. Adult refers to participants of legal age to use tobacco products or older.

Consumer Understanding

The PBI Study provides evidence that the proposed modified risk claim would improve consumers' understanding of the health risks of using General Snus. First, adding the proposed claim to the video advertisement for General Snus substantially increased the percentage of smokers who perceived General Snus as lower in health risks than cigarettes (see Table 3). For example, after viewing an advertisement that did not include the proposed claim, 25% of young adult smokers and 30% of older adult smokers perceived daily General Snus use as presenting a lower risk of "serious health problems" compared to daily smoking. In contrast, among smokers who viewed the advertisement *with* the proposed claim, these percentages were over twice as high: 60% for young adult smokers and 61% for older adult smokers. Second, adding the proposed claim to the advertisement had similar effects on risk perceptions among smokeless tobacco users. For example, among smokeless tobacco users who viewed the advertisement without the proposed claim, 44% perceived daily General Snus use as presenting a lower risk of "serious health problems" than daily cigarette smoking, compared to 71% of smokeless tobacco users who viewed the advertisement *with* the proposed claim. Similarly, when asked about emphysema, chronic bronchitis, and lung cancer, after viewing the advertisement without the claim, 68-75% of smokeless users perceived daily General Snus use as presenting lower risk relative to daily cigarette smoking, whereas after exposure to the claim, these percentages ranged from 77-84%. These findings are noteworthy given that between one-third and one-half of U.S. adult smokeless tobacco users also currently smoke cigarettes, depending on the subtype of smokeless tobacco (Cheng et al., 2017). Third, after viewing the advertisement with the proposed claim, consumers continued to perceive daily General Snus use as presenting substantial health risks, particularly for mouth cancer and gum disease (see Table 4). This was true among the products' intended users (i.e., cigarette smokers, smokeless tobacco users) as well as unintended users (i.e., former smokers, never tobacco users).

Table 3. Percentages of smokers in the applicant's PBI Study who perceived "a lower chance" or "a much lower chance" of health effects from using *General Snus* compared to cigarettes, after viewing the *General Snus* advertisement (Source: MRTPAs Section 13.4.3.2 and November 26, 2018 Amendment, pp. 33-36)

Tobacco User Group[†]	Proposed Claim Absent or Present on Advertisement	Percentage Responding "A lower chance" or "A much lower chance"							
		Gum Disease	Mouth Cancer	Lung Cancer	Chronic Bronchitis	Emphy-sema	Heart Disease	Stroke	Serious Health Problems
Young Adult Cigarette Smokers	Absent	15.0	15.7	55.3	53.0	45.8	33.9	32.2	25.3
	Present	43.4	49.1	74.6	71.2	70.9	66.4	60.0	59.5
Older Adult Cigarette Smokers	Absent	13.4	16.9	56.3	56.7	54.5	36.7	39.1	29.9
	Present	48.4	52.0	77.1	78.2	76.6	70.3	67.8	60.8

Note: The study item stated: "Compared to the daily use of only cigarettes, the daily use of only *General* Snus has [a much lower chance; a lower chance; the same chance; a higher chance; a much higher chance; don't know] of causing [health effect]." Note that the applicant excluded "Don't know" responses in its analyses of risk perception items (PBI Study Report, pp. 87-209). However, because the proposed claim may have affected participants' likelihood of responding "Don't know" on some risk perception items, and because "Don't know" is a potentially meaningful response (e.g., Waters et al., 2013), we include "Don't know" responses in the denominators of the percentages we report for risk perception items in this document.

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

Table 4. Percentages of participants who perceived a "moderate," "high," or "very high" chance of health effects from using *General Snus*, after viewing the *General Snus* advertisement with the proposed modified risk claim (Source: MRTPAs Section 13.4.2.1)

	Percentage Responding "Moderate Chance," "High Chance," or "Very High Chance"							
Tobacco User Group[†]	Gum Disease	Mouth Cancer	Lung Cancer	Chronic Bronchitis	Emphy-sema	Heart Disease	Stroke	Serious Health Problems
Young Adult Cigarette Smokers	70.4	70.8	38.5	41.6	40.4	53.6	50.9	63.7
Older Adult Cigarette Smokers	65.1	63.8	33.3	35.3	33.8	47.4	43.9	51.0
Adult Smokeless Tobacco Users	69.4	71.0	25.7	28.2	25.3	43.7	41.2	52.0
Young Adult Never Tobacco Users	76.3	77.7	58.2	58.2	57.2	67.9	62.5	73.5
Older Adult Never Tobacco Users	69.8	70.0	50.5	49.5	50.1	56.9	55.7	63.0
Adult Former Cigarette Smokers	69.7	70.5	38.2	38.4	36.5	53.2	52.3	59.9

Note: The study 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"; "Don't Know." Note that the applicant excluded "Don't know" responses in its analyses of risk perception items (PBI Study Report, pp. 87-209). However, because the proposed claim may have affected participants' likelihood of responding "Don't know" on some risk perception items, and because "Don't know" is a potentially meaningful response (e.g., Waters et al., 2013), we include "Don't know" responses in the denominators of the percentages we report for risk perception items in this document.

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

The applicant's proposed claim states that using General Snus "instead of cigarettes" reduces health risks, which some consumers may interpret as implying complete product substitution (i.e., switching), or alternatively, to mean that there are health benefits of *partial* substitution (i.e., using General Snus in place of some but not all of one's cigarettes). Thus, to examine this, we consider consumer perceptions of how the risks of dual use of General Snus and cigarettes compare with both (1) exclusive General Snus use, and (2) exclusive smoking. With respect to the former, the proposed claim improved consumers' understanding 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, many perceived exclusive General Snus use as presenting the same or higher risks compared to dual use with cigarettes. For example, 56% of young adult smokers and 64% of older adult smokers perceived exclusive daily General Snus use as presenting an equal or higher risk of "serious

health problems" compared to daily use of both General Snus and cigarettes. In contrast, when the advertisement contained the proposed claim, substantially fewer smokers held these perceptions (e.g., for "serious health problems," 36% of young adult smokers and 39% of older adult smokers) and instead more of them perceived that exclusive General Snus use presents lower health risks compared to dual use (e.g., for "serious health problems," 41% of young adult smokers who viewed the advertisement without the proposed claim, and 60% who viewed the advertisement with the proposed claim). Similar effects were also observed among smokeless tobacco users: for example, adding the proposed claim to the advertisement substantially reduced the percentage of smokeless tobacco users who perceived exclusive General Snus use as presenting the same or higher risk of "serious health problems" compared to dual use with cigarettes (from 48% to 30%). Thus, the proposed claim improved consumers' understanding that dual use presents greater health risks than exclusive General Snus use.

Although the proposed claim improved consumers' understanding of the health risks of dual use compared to exclusive General Snus use, it is less clear whether the claim would help consumers understand the risks of dual use compared to exclusive smoking. The applicant did not assess participants' perceptions of risk from partial substitution compared to exclusive cigarette smoking. However, one item asked smokers how many cigarettes they could smoke per day on a day when they also used General Snus, while still achieving the lower disease risk (see Table 5). Viewing the advertisement with the proposed modified risk claim, rather than without it, increased the proportion of smokers who responded "Zero (0) cigarettes," which the applicant defined as correct (young adult smokers: 56% with the claim, 45% without the claim; older adult smokers: 44% with the claim, 34% without the claim) (PBI Study Report, pp. 158-159). At the same time, adding the claim did not increase the proportions of smokers who responded "Up to 5 cigarettes," "Up to 20 cigarettes," or "As many as you want to smoke," which provides suggestive evidence that the proposed claim did not mislead smokers to believe that partial substitution would reduce their disease risk. However, we note that this study item only asked about smoking cigarettes on the *same day* that one also uses *General Snus*. Thus, it is unknown whether smokers who responded "Zero (0) cigarettes" believe that they can reduce their disease risk by substituting *General Snus* for cigarettes on some days and continuing to smoke on others.

Table 5. Smokers' beliefs about the number of cigarettes they can smoke on a day when they also use *General Snus* to put them at a lower risk of disease (Source: November 26, 2018 Amendment, pp. 38-39)

Tobacco User Group[†]	Proposed Claim Absent or Present on Advertisement	Number of Cigarettes: %					
		Zero (0)	Up to 5	Up to 20	As many as you want	None of the above	Don't know
Young Adult Cigarette Smokers	Absent	45.0	6.6	1.5	12.0	17.0	17.9
	Present	56.2	5.5	1.5	8.6	9.1	19.0
Older Adult Cigarette Smokers	Absent	33.9	5.8	3.0	7.4	20.0	29.9
	Present	43.7	4.6	3.1	6.7	12.1	29.9

Note: The study item asked, "For *General Snus* to put you at a lower risk of disease, how many cigarettes can you smoke on a day when you also use *General Snus*?" The applicant defined "Zero (0) cigarettes" as correct.
[†] Note: Young adult refers to participants of legal age to use tobacco products to 24 years old. Older adult refers to participants over 24 years old.

The PBI Study also provides evidence that the proposed modified risk claim would lead smokeless tobacco users to perceive General Snus as lower in health risks than other smokeless tobacco products. First, adding the proposed claim to the advertisement substantially increased the percentage of smokeless tobacco users who perceived General Snus as lower in health risks than moist snuff (see Table 6). For example, adding the claim nearly doubled the percentage of smokeless tobacco users who perceived daily General Snus use as presenting a lower risk of mouth cancer compared to daily use of moist snuff (25% without the claim; 48% with the claim). Second, adding the proposed claim to the advertisement had similar effects on smokeless tobacco users' perceptions of risk from General Snus compared to other brands of snus (see Table 6). For example, 19% perceived daily General Snus use as presenting a lower risk of mouth cancer than other brands of snus after viewing the advertisement without the claim, compared to 34% after viewing the advertisement with the claim. This suggests that the proposed claim could encourage switching to these General Snus products among current users of other smokeless tobacco products, which is informative given that FDA's scientific review of premarket tobacco applications (PMTAs) for these products concluded that they could serve as "additional options for less toxic smokeless tobacco products" compared to other smokeless tobacco products sold on the U.S. market (FDA, 2015, p. 37).

Table 6. Percentages of adult smokeless tobacco users in the applicant's PBI Study who perceived "a lower chance" or "a much lower chance" of health effects from using *General Snus* compared to moist snuff tobacco and other brands of snus, after viewing the *General Snus* advertisement (Source: November 26, 2018 Amendment, pp. 26-31)

Comparator Product	Proposed Claim Absent or Present on Advertisement	Percentage Responding "A lower chance" or "A much lower chance"							
		Gum Disease	Mouth Cancer	Lung Cancer	Chronic Bronchitis	Emphy-sema	Heart Disease	Stroke	Serious Health Problems
Moist Snuff Tobacco	Absent	22.0	25.1	30.3	31.1	31.5	27.8	27.0	24.1
	Present	45.3	48.2	45.3	51.8	49.8	49.4	50.6	45.7
Other Snus Brands	Absent	15.0	18.8	27.4	29.0	29.0	24.9	25.3	19.1
	Present	35.1	33.6	42.0	43.3	43.7	41.2	38.0	34.7

Note: Adult smokeless tobacco users were of legal age to use tobacco products or older. The study items stated: "Compared to the daily use of only moist snuff, the daily use of only *General* Snus has [a much lower chance; a lower chance; the same chance; a higher chance; a much higher chance; don't know] of causing [health effect]" and "Compared to the daily use of only other brands of snus, the daily use of only *General* Snus has [a much lower chance; a lower chance; the same chance; a higher chance; a much higher chance; don't know] of causing [health effect]." Note that the applicant excluded "Don't know" responses in its analyses. However, because the proposed claim may have affected participants' likelihood of responding "Don't know" on some risk perception items, and because "Don't know" is a potentially meaningful response (e.g., Waters et al., 2013), we include "Don't know" responses in the denominators of the percentages we report for risk perception items in this document.

Behavioral Intentions

The PBI Study provided evidence that the proposed modified risk claim would increase the likelihood of use of General Snus among adult tobacco consumers who could benefit from switching (see Table 7). Specifically, the PBI Study found that adding the proposed claim to the advertisement 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, pp. 74-75). In contrast, intentions to buy General Snus remained low among 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) after viewing the advertisement with the proposed modified risk claim (PBI Study Report, pp. 71-72).

Table 7. Intentions to buy General Snus among participants in the applicant's PBI Study (Source: MRTPAs Sections 13.4.1.1 and 13.4.1.2).

	Mean (SD) Intentions to Buy General Snus (0-10 scale, 10= "Certain, practically certain [99+ in 100]")	
Tobacco User Group[†]	Proposed Claim Absent	Proposed Claim Present
Young Adult Cigarette Smokers	1.85 (2.53)	2.19 (2.80)
Older Adult Cigarette Smokers	1.49 (2.55)*	2.04 (2.86)*
Adult Smokeless Tobacco Users	3.41 (2.79)	3.71 (2.86)
Young Adult Never Tobacco Users	0.37 (1.43)	0.34 (1.23)
Older Adult Never Tobacco Users	0.29 (1.17)	0.23 (1.14)
Adult Former Cigarette Smokers	0.20 (0.90)	0.31 (1.11)

Note: The study item asked, "How likely are you to buy *General* Snus for yourself if sold in a store where you usually shop?" The response scale ranged from 0 ("No chance, almost none [1 in 100]") to 10 ("Certain, practically certain [99+ in 100]").
* $p = .001$.
[†] Note: Young adult refers to participants of legal age to use tobacco products to 24 years old. Older adult refers to participants over 24 years old. Adult refers to participants of legal age to use tobacco products or older.

The applicant did not submit evidence that smokers would use General Snus as a complete substitute for smoking. Among current smokers, adding the proposed claim to the video advertisement did not affect intentions to quit smoking. However, it is unknown whether adding the proposed claim may have increased or decreased intentions to quit smoking among the subset of smokers who became more likely to buy General Snus after viewing the proposed claim, as the applicant's research was not designed to assess this. The applicant's research also did not assess intended patterns of use (e.g., intended frequency; intentions to dual use with cigarettes) among participants who indicated that they were likely to buy General Snus. We acknowledge that such future behaviors would be difficult for consumers to predict before trying the product and thus challenging to assess in premarket research. Finally, the applicant also did not study the effects of the proposed modified risk claim in an actual use study that would have provided direct evidence of the claim's effect on the frequency of General Snus use and dual use with cigarettes.

Assessment of Youth and Young Adults

Youth and young adult never tobacco users are at increased risk of initiating tobacco use with General Snus, compared to older never users, given that most tobacco use initiation occurs during youth and young adulthood. 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. The applicant did not submit research

evaluating whether the proposed modified risk claim would increase youth uptake of General Snus. We note that use of snus is currently low among U.S. youth. For instance, an analysis of data from the 2014 National Youth Tobacco Survey (NYTS)—which was the most recent survey year reporting snus use separately from other smokeless tobacco products—found that past 30-day use of any snus product among U.S. high school and middle school students was 1.9% and 0.5%, respectively, compared to 5.5% and 1.6% for chew/snuff/dip use, respectively (Arrazola et al., 2015). Additionally, an analysis of the 2017 NYTS reported a decrease in smokeless tobacco product use among high school students from 7.9% in 2011 to 5.5% in 2017 (Wang et al., 2018). Also, the applicant submitted plans for how it would limit youth exposure to its modified risk marketing and promotions for the eight products. These plans include disseminating modified risk information on a third-party age-verified branded website, in direct mail and email to age-verified legal-age tobacco users, at adult-only consumer events, on Facebook pages restricted to self-identified adults, and in print publications and websites with 85%+ adult readership (for more details, see the November 26, 2018 Amendment, pp. 5-21). If authorized to market the products as modified risk products, we recommend that the applicant monitor uptake by youth in its postmarket surveillance and studies and inform FDA immediately of any increases.

Summary and Conclusions

In sum, the applicant's new consumer perceptions and intentions research provides evidence that the proposed modified risk claim would improve U.S. consumers' understanding of the products' health risks relative to cigarettes, smokeless tobacco, and dual use of the products with cigarettes. In addition, the study provides evidence suggesting that the proposed modified risk claim is likely to increase use of General Snus among adult tobacco consumers who could benefit their health by switching; whereas the claim is not likely to impact use among never and former users.

In addition, the design and conduct of the PBI Study addressed deficiencies identified by FDA's review of the consumer perception study submitted in the original 2014 submission, including:

- Proposing a claim outside the context of the warning label
- Testing the revised modified risk statement verbatim
- Including an "attention check" in the study
- Employing established measures to assess most study outcomes
- Defining user groups of interest (e.g., differentiating between smokers and smokeless users rather than combining them into a single "tobacco user" group)

References

Arefalk G, Hambraeus K, Lind L, Michaëlsson K, Lindahl B, Sundström J. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. *Circulation.* 2014 Jun 23.;130(4):325-32.

Arrazola R, Singh T, Corey C, Husten C, Neff L, Apelberg B, Bunnell R, Choiniere C, King B, Cox S, McAfee T, Caraballo R; Centers for Disease Control and Prevention (CDC).*MMWR Morb Mortal Wkly Rep.* 2015 Apr 17;64(14):381-5.

Asplund K, Nasic S, Janlert U, Stegmayr B. Smokeless tobacco as a possible risk factor for stroke in men. *Stroke.* 2003 May 29;34(7):1754-9.

Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol.* 2008 Jul 1;9(7):667-75.

Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *Bmj*. 2009 Aug 19;339:b3060.

Bolinder G, Alfredsson L, Englund A, de Faire U. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health.* 1994 Mar 1;84(3):399-04.

Bolinder G, Ahlborg B, Lindell J. Use of smokeless tobacco: blood pressure elevation and other health hazards found in a large-scale population survey. *Journal Inter Med.* 1992 Oct 1;232(4):327–34.

Cheng Y, Rostron B, Day H, et al. Patterns of use of smokeless tobacco in US adults, 2013-2014. *Am J Public Health.* 2017 Sep 1;107(9):1508-14.

FDA. Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review for PM0000010-PM0000017. *Department of Health & Human Services.* 2015.

Haglund B, Eliasson M, Stenbeck M, Rosen M. Is moist snuff use associated with excess risk of IHD or stroke? a longitudinal follow-up of snuff users in Sweden. *Scand J Public Health.* 2007 Dec 1;35(6):618-22.

Hagstad S, Ekerljung L, Lindberg A, Backman H, Rönmark E, Lundbäck B. COPD among non-smokers - report from the obstructive lung disease in Northern Sweden (OLIN) studies. *Respir Med.* 2012 Jul 1;106(7):980-8.

Hansson J, Pedersen N, Galanti M, et al. Use of snus and risk for cardiovascular disease: results from the Swedish Twin Registry. *J Intern Med.* 2009 Jun 1;265(6):717-24.

Hansson J, Galanti M, Hergens M, et al. Use of snus and acute myocar**d**ial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol.* 2012 Oct 1;27(10):771-9.

Hansson J, Galanti M, Hergens M, et al. Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. *J Intern Med.* 2014 Jul 1;276(1):87-95.

Hergens M, Ahlbom A, Andersson T, Pershagen G. Swedish moist snuff and myocardial infarction among men. *Epidemiology*. 2005 Jan 1;16(1):12-6.

Hergens MP, Lambe M, Pershagen G, Terent A, Ye W. Smokeless tobacco and the risk of stroke. *Epidemiology.* 2008 Nov 1;19(6):794-9.

Huhtasaari F, Asplund K, Lundberg V, Stegmayr B, Wester P. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *BMJ.* 1992 Nov 21;305(6864):1252-6.

Huhtasaari F, Lundberg V, Eliasson M, Janlert U, Asplund K. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based studying middle-aged men. *J Am Coll Cardiol.* 1999 Nov 15;34(6):1784-90.

Janzon E, Hedblad B. Swedish snuff and incidence of cardiovascular disease. A population-based cohort study. *BMC Cardiovasc Disord.* 2009 May 27;9(21).

Jiménez-Ruiz C, Kunze M, Fagerström K. Nicotine replacement: a new approach to reducing tobacco-related harm. *Eur Respir J.* 1998 Feb 1;11(2):473-9.

Johansson S, Sundquist K, Qvist J, Sundquist J. Smokeless tobacco and coronary heart disease: a 12-year follow-up study. *Eur J Cardiovasc Prev Rehabil.* 2005 Aug 1;12(4):387-92.

Kirkham P, Barnes P. Oxidative stress in COPD. *Chest.* 2013 Jul 1;144(1):266-73.

Koskinen L, Blomstedt P**.** Smoking and non-smoking tobacco as risk factors in subarachnoid haemorrhage. *Acta Neurol Scand.* 2006 Jul 1;114(1):33-37.

Lee P. Circulatory disease and smokeless tobacco in Western populations: a review of the evidence. *Int J Epidemiol. 2007 Aug 1;36*(4):789-04.

Lee P, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med.* 2009 Jul 29;7(36).

Lee P. Summary of the epidemiological evidence relating snus to health. 2011 Mar 1; *Regul Toxicol Pharmacol.* 2011 Mar 1;59(2):197-14.

Luo J, Ye W, Zendehdel K, et al. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet.* 2007 Jun 16;369(9578);2015-20.

Roosaar A, Johansson A, Sandborgh-Englund G, Axéll T, Nyrén O. Cancer and mortality among users and nonusers of snus. *Int J Cancer.* 2008 Jul 1;123(1):168-73.

Rostron B, Chang J, Anic G, Tanwar M, Chang C, Corey C. Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis. *Open heart*. 2018 Oct 8;5(2):e000846.

Schivo M, Avdalovic MV, Murin S. Non-cigarette tobacco and the lung. *Clin Rev Allergy Immunol.* 2014 Feb 1;46(1):34-53.

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

Timberlake D, Nikitin D, Johnson N, Altekruse S. A longitudinal study of smokeless tobacco use and mortality in the United States. *Int J Cancer. 2017 Jul 15;141(2):264-70.*

Wang T, Gentzke A, Sharapova S, Cullen K, Ambrose B, Jamal A. Tobacco product use among middle and high school students – United States, 2011-2017. *MMWR Morb Mortal Wkly Rep.* 2018 Jun 8;67(22):629-33.

Waters EA, Hay JL, Orom H, Kiviniemi MT, Drake BF. "Don't know" responses to risk perception measures: implications for underserved populations. *Medical decision making*. 2013 Feb;33(2):271-81.

Wennberg P, Eliasson M, Hallmans G, Johansson L, Boman K, Jansson J. The risk of myocardial infarction and sudden cardiac history of smoking. *J Intern Med.* 2007 Sep 1;262(3):360-7.

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

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

1) the label, labeling, or advertising of which represents, either implicitly or explicitly, that:
    a) the tobacco product presents a lower risk of tobacco-related disease or is less harmful than one or more other commercially marketed tobacco products;
    b) the tobacco product or its smoke contains a reduced level of a substance or presents a reduced exposure to a substance; or
    c) the tobacco product or its smoke does not contain or is free of a substance;
2) the label, labeling, or advertising of which uses the descriptors "light", "mild", "low", or similar descriptors; or
3) for which the tobacco product manufacturer has taken any action directed to consumers through the media or otherwise, other than by means of the tobacco product's label, labeling, or advertising, after June 22, 2009, respecting the product that would be reasonably expected to result in consumers believing that the tobacco product or its smoke may present a lower risk of disease or is less harmful than one or more commercially marketed tobacco products, or presents a reduced exposure to, or does not contain or is free of, a substance or substances. [Section 911(b)(2)]

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

To request a Section 911(g) order from FDA, a person must file a modified risk tobacco product application (MRTPA) under Section 911(d). The MRTPA should include, among other things, information about the various aspects of the tobacco product as well as information to enable FDA to assess the impacts of the proposed MRTP on individual health outcomes and population-level outcomes, such as initiation or cessation of tobacco product use. In March 2012, FDA published a draft guidance for public comment, entitled "Modified Risk Tobacco Product Applications," which discusses the submission of applications for an MRTP under Section 911 of the FD&C Act and considerations regarding studies and analyses to include in an MRTPA (https://www.congress.gov/111/plaws/publ31/PLAW-111publ31.pdf).

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

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

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

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

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

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

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

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

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

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

- The relative health risks the MRTP 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 MRTP;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the MRTP;
- The risks and benefits to persons from the use of the MRTP 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.

Once an MRTPA is submitted, FDA performs preliminary administrative reviews to determine whether to accept and file it. In general, after filing an application, FDA begins substantive scientific review. As part of this scientific review, FDA will seek and consider public comments on the application as well as recommendations from the FDA Tobacco Products Scientific Advisory Committee (TPSAC). FDA intends to review and act on a complete MRTPA within 360 days of FDA filing an application. An order authorizing an MRTP refers to a specific product, not an entire class of tobacco products (e.g., all smokeless products).

An FDA order authorizing an MRTP is not permanent; it is for a fixed period of time that will be determined by FDA and specified in the order. To continue to market an MRTP after the set term, an applicant would need to seek renewal of the order and FDA would need to determine that the findings continue to be satisfied. Also, if at any time FDA determines that it can no longer make the determinations required for an MRTP order, FDA is required to withdraw the order. Before FDA withdraws an MRTP order, it will provide an opportunity for an informal hearing as required under the law.

APPENDIX B: Key Outcomes and Items in the Perceptions and Behavioral Intentions (PBI) Study

Comprehension of Modified Risk LLA Materials

Item: Using *General* Snus® instead of cigarettes…

Options:

- puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
- does not affect your risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
- puts you at higher risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis
- none of the above

Item: For *General* Snus® to put you at a lower risk of disease, how many cigarettes can you smoke on a day when you also use *General* Snus®?

Options:

- Zero (0) cigarettes
- Up to 5 cigarettes
- Up to 20 cigarettes
- As many as you want to smoke
- None of the above

Item: Fill in the blank: *General* Snus® production process was created to reduce ____ found in other tobaccos.

Options:

- impurities
- bitterness
- flavors
- sugar
- none of the above
- don't know

Perceived Absolute Risks of Daily *General Snus* Use

Item: 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:

- very Low Chance
- low Chance

- moderate Chance
- high Chance
- very High Chance
- don't Know

Repeat for: chronic bronchitis, emphysema, gum disease, heart disease, lung cancer, mouth cancer, stroke, serious health problems

Perceived Relative Risks of Daily *General Snus* Use

Item: Compared to the **daily use of only cigarettes**, **the daily use of only *General* Snus®** has…

Item: Compared to the **daily use of only moist snuff**, **the daily use of only *General* Snus®** has…

Item: Compared to the **daily use of only other brands of snus**, **the daily use of only *General* Snus®** has…

Item: Compared to the **daily use of only aids that help stop smoking**, **the daily use of only *General* Snus®** has…

Item: Compared to the **daily use of both cigarettes and *General* Snus®**, **the daily use of only *General* Snus®** has…

Item: Compared to **never having used any tobacco or nicotine products, the daily use of only *General* Snus®** has…

Options:

- a much lower chance
- a lower chance
- the same chance
- a higher chance
- a much higher chance
- don't know

Repeat for: chronic bronchitis, emphysema, gum disease, heart disease, lung cancer, mouth cancer, stroke, serious health problems

Perceived Risks of Switching to *General Snus* vs. Quitting

Item: Compared to the person **who has quit** all tobacco and nicotine products and uses nothing, **the person who has quit all tobacco and nicotine products except for the daily use of *General* Snus® has…**

Options:

- much lower chance
- lower chance

- the same chance
- higher chance
- much higher chance
- don't know

Repeat for: chronic bronchitis, emphysema, gum disease, heart disease, lung cancer, mouth cancer, stroke, serious health problems

Intention to Buy *General Snus*

Item: How likely are you to buy *General* Snus® for yourself if sold in a store where you usually shop?

Options:

- No chance, almost none [1 in 100]
- Very slight possibility [1 in 10]
- Slight possibility [2 in 10]
- Some possibility [3 in 10]
- Fair possibility [4 in 10]
- Fairly good possibility [5 in 10]
- Good possibility [6 in 10]
- Probable [7 in 10]
- Very probable [8 in 10]
- Almost sure [9 in 10]
- Certain, practically certain [99+ in 100]

Intention to Quit Smoking

Item: Which of the following describes you?

Options:

- I don't want to stop smoking
- I think I should stop smoking but don't really want to
- I want to stop smoking but haven't thought about when
- I REALLY want to stop smoking but I don't know when I will
- I want to stop smoking and hope to soon
- I REALLY want to stop smoking and intend to in the next 3 months
- I REALLY want to stop smoking and intend to in the next month
- don't know

Intention to Quit Using Other Products

Item: Which of the following describes you?

Options:

- I don't want to stop using [PRODUCT]
- I think I should stop using [PRODUCT] but don't really want to
- I want to stop using [PRODUCT] but haven't thought about when
- I REALLY want to stop using [PRODUCT] but I don't know when I will
- I want to stop using [PRODUCT] and hope to soon
- I REALLY want to stop using [PRODUCT] and intend to in the next 3 months
- I REALLY want to stop using [PRODUCT] and intend to in the next month
- don't know

Repeat for: e-cigarettes; moist snuff; chewing tobacco; Snus; aids that help stop smoking; cigars, cigarillos, or filtered cigars; pipes filled with tobacco; hookahs or water pipes filled with tobacco

Intended Product Use

Item: How will you use [PRODUCT] moving forward?

Options:

- quit completely
- cut back use
- use the same amount
- use more
- don't know

Repeat for: cigarettes; e-cigarettes; moist snuff; chewing tobacco; Snus; aids that help stop smoking; cigars, cigarillos, or filtered cigars; pipe tobacco; hookahs or water pipe tobacco

Believability of Proposed Claim

Item: How believable do you find each of the following statements about *General* Snus®? Using *General* Snus® instead of cigarettes puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.

Options:

- not at all believable
- a little believable
- somewhat believable

- very believable
- don't know