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1 OVERVIEW

Swedish Match North America, Inc. (hereafter referred to as Swedish Match) seeks to amend the eight Modified Risk Tobacco Product applications (MRTPAs) originally submitted on 10 June 2014 for the following products:

- MR0000020, General Loose
- MR0000021, General Dry Mint Portion Original Mini
- MR0000022, General Portion Original Large
- MR0000024, General Classic Blend Portion White Large – 12 ct
- MR0000025, General Mint Portion White Large
- MR0000027, General Nordic Mint Portion White Large – 12 ct
- MR0000028, General Portion White Large
- MR0000029, General Wintergreen Portion White Large

This amendment addresses the three deficiencies and the two requests/recommendations mentioned in the scientific review referenced in the letter from the Center for Tobacco Products (CTP) dated 14 December 2016.

The responses provided in this amendment, in addition to data included in the original applications from 2014, demonstrate conclusively that use of the eight General Snus products instead of cigarette smoking significantly reduces harm and the risk of certain tobacco-related diseases to individual users. Moreover, the submitted evidence also demonstrates that marketing of the products with the following health claim will most likely benefit the population as a whole considering both current users of tobacco products (particularly cigarette smokers) and those who do not currently use such 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."

Swedish Match therefore believes that the mentioned eight General Snus products meet the criteria for modified risk tobacco product orders, and that they should be marketed with the above health claim.

As explained in more detail below, the mentioned claim has been rigorously tested in a consumer perception study alongside the currently mandated health warnings for smokeless tobacco products.

2 RESPONSES

2.1 Deficiency 1

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

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

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

you meet with the Office of Science in FDA's Center for Tobacco Products to discuss how your applications could be amended.

Swedish Match's response

Swedish Match accepts CTP's request to retain the "WARNING: This product can cause mouth cancer" label.

After consultations with CTP (Food and Drug Administration [FDA] Meeting Minutes, 19 April 2017 – TC0002213 and FDA Meeting Minutes, 12 October 2017 – TC0002533), Swedish Match developed three modified risk health claims to be potentially used alongside the currently mandated health warnings for smokeless tobacco products. The claims were rigorously tested in a new consumer perception study entitled "Perceptions and Behavioral Intentions Study." The design of that study addresses the issues related to consumer perception and behavioral research raised in the scientific review referenced in the letter from CTP dated 14 December 2016. Results of the study are provided below in the response to Deficiency 2 (Section 2.2).

2.2 Deficiency 2

You request to revise the currently required "WARNING: This product is not a safe alternative to cigarettes" on the label and advertising, by replacing it with an express modified risk claim "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes."

Our review concluded that the claim that the eight General snus products present substantially lower risks to health may be substantiated, but only in part. That is, there is evidence to support that the eight General snus products, as actually used by consumers in Sweden and Norway, as compared to smoking cigarettes may substantially reduce the risks of some, but not all, tobacco-related diseases to individual tobacco users. The scientific evidence is insufficient to support that substantial reductions would be observed across the full range of risks posed by tobacco products, as implied by a generalized statement about health risks as compared to smoking (i.e., "substantially lower risks to health than cigarettes"). The evidence is also insufficient that U.S. consumers would use the products in the same manner as consumers in Sweden and Norway (e.g., frequency or intensity of usage; exclusive snus use versus dual use with cigarettes); therefore, we cannot conclude that, as actually used by U.S. consumers, the products would substantially reduce the risks to smokers. In addition, FDA assessed the potential benefits and harms to the health of the population and concluded that the evidence is insufficient to determine that the products will benefit the population as a whole, taking into account, for example, smokers who switch completely to the General snus products, non-users who initiate use, and dual use by current tobacco users. Furthermore, the scientific evidence is not sufficient to conclude that the modified risk information would be comprehended by the public in the context of total health and in relation to all tobacco-related disease, particularly in the context of a

warning. As a result, we are not issuing modified risk orders based on the proposed claim in its current form.

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

Swedish Match's response

Swedish Match accepts CTP's request to retain the "WARNING: This product is not a safe alternative to cigarettes" label.

As noted in the MRTPA partial decision Technical Project Lead (TPL) review (page 22), "…there is evidence to support that exclusive use of the eight General Snus products as compared to smoking cigarettes may significantly reduce harm and the risk of *certain* tobacco-related disease to individual tobacco users." Based on this and feedback from the face-to-face meeting on 22 March 2017 (FDA Meeting Minutes, 19 April 2017 – TC0002213), Swedish Match developed three modified-risk health claims to be used together with the currently mandated warning statements for smokeless tobacco products. The three proposed claims listed below were selected based on a review of the scientific literature (including epidemiological research), qualitative research performed by Swedish Match, and statements made by CTP in the TPL reports for the General Snus Premarket Tobacco Application (PMTA) order and the MRTPA partial decision. The factual content of all three claims is clearly supported by the weight of the submitted evidence.

Specifically, claim 1 is based on the compelling, analytical epidemiological evidence from Sweden (originating from cohort studies and population-based case-control studies) showing no association between long-term use of snus and various types of cancer (notably including oral and lung cancer) or cardiovascular disease (myocardial infarction and stroke). The lack of an association between use of snus and pulmonary conditions like chronic bronchitis and emphysema is based on mechanistic considerations: tobacco smoke increases the risk through chronic irritation of the airways and pulmonary exposure to various combustion products. As use of smokeless tobacco including snus does not involve inhalation of tobacco smoke, it is generally accepted that such products are unassociated with chronic lung conditions. Also, it was considered reasonable to focus the claim wording on the diseases that make up most of the

excess risk experienced by smokers, namely smoking-related cancers, cardiovascular diseases, and chronic obstructive pulmonary diseases.

- Claim 1: Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.

- Claim 2: Using General Snus instead of cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users.

- Claim 3: No tobacco is totally safe, but using General Snus instead of cigarettes puts you at a lower risk of chronic lung disease and other tobacco-related ailments.

The wording of these proposed claims reflects the language in the MRTPA partial decision TPL review of "lower risk" or "reduction in risk" rather than "no risk" or "unassociated with."

The three claims were rigorously tested in qualitative focus groups and triads and in cognitive interviews, and were modified accordingly based on feedback before being tested in the large, quantitative consumer perception study. In addition, the protocol for the quantitative study was reviewed by CTP, and CTP's feedback was implemented into the study protocol (FDA Meeting Minutes, 12 October 2017 – TC0002533). Key study design features are provided in the response to Deficiency 3 in Section 2.3; also see the full protocol (Study SMNA 17-01GEN Report Section 17.3).

The three claims were tested in the form of short videos providing background information on snus (eg, production technique, how snus differs from other smokeless tobacco products, and how it is used) followed by one of the health claims and one of the mandated warnings (test groups), or the same video without any health claim (control groups).

Overall, all three claims performed well in the quantitative survey in terms of comprehension, perceptions of absolute and relative health risks, and lack of effect on behavioral intentions among current non-users of tobacco products. Specifically, non-users exposed to any of the three health claims demonstrated no increased interest in buying General Snus compared to the non-using control subjects. None of the claims impacted initiation (ie, among never users) or re-initiation (ie, former smokers) of tobacco/nicotine product (TNP) use through General Snus among non-TNP users (Study SMNA 17-01GEN Report Sections 1-16, Table 17).

However, claim 1 was the most impactful in terms of behavioral intentions among current cigarette smokers: those exposed to the claim showed a significant increase in their likelihood to buy General Snus compared to those who were not exposed to the claim (Table 1). Claim 1 was therefore selected to be the only claim for which Swedish Match seeks modified risk orders. Accordingly, only data relating to Claim 1 are presented in this document. Results for all three claims are detailed in the full study report (Study SMNA 17-01GEN Report Sections 1-16).

Table 1: The Likelihood to Buy General Snus by Test versus Control in Current Cigarette Smokers

Age	Claim 1			Control			P-value
	N	Mean	SD	N	Mean	SD	
Legal age to 24 years	454	2.19	2.80	462	1.85	2.53	0.030[a]
>24 years of age	483	2.04	2.86	499	1.49	2.55	0.001[b]

Source: Study SMNA 17-01GEN Report Sections 1-16, Table 18
N=number of respondents; SD=standard deviation.
Note: P-values provided in the table are based on one-tailed independent two-sample t-tests. Likelihood to buy was assessed using an 11-point Juster scale where 0=no chance, almost none [1 in 100] to 10=certain, practically certain [99+ in 100].
[a] p>0.05 when adjusted for multiple comparisons.
[b] p<0.017 when adjusted for multiple comparisons.

Current smokers in the claim 1 test group consistently viewed daily General Snus use as being associated with a lower risk of serious health conditions than daily cigarette smoking compared to the control group. Specifically, compared to current smokers in the control group, current smokers who viewed the claim 1 video perceived "a much lower chance/lower chance" of each of the following: chronic bronchitis, emphysema, lung cancer, and "serious health problems" (Study SMNA 17-01GEN Report Sections 1-16, Table 23 [d and e]).

Compared to current smokers in the control group, current smokers who viewed the claim 1 video had a similar perception of "the same chance/a much lower chance/a lower chance" of the following non-respiratory-related health conditions: gum disease, mouth cancer, heart disease, and stroke (Study SMNA 17-01GEN Report Sections 1-16, Table 23 [d and e]):

Among current smokers (legal age to 24 years, >24 years), believability was higher in the claim 1 test group (ranging from 48.4% to 54.0%) than in the control group (ranging from 33.0% to 35.1%) (Study SMNA 17-01GEN Report Sections 1-16, Table 32 [d and e]). In never tobacco users and former cigarette smokers, believability for claim 1 was low in the test and control groups (Study SMNA 17-01GEN Report Sections 1-16, Table 32 [a, b, and c]), which was unsurprising since never and former users expressed no interest in buying General Snus (Study SMNA 17-01GEN Report Sections 1-16, Table 17).

Claim 1 had no impact on the intention to quit cigarettes among current cigarette smokers as measured by the validated Motivation to Stop Scale (test versus control mean scores for the legal age to 24 years: 3.39 versus 3.28; >24 years: 3.59 versus 3.67) (Study SMNA 17-01GEN Report Sections 1-16, Table 20).

Based on the totality of evidence, claim 1 (*"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis")* was clearly the most impactful. Swedish Match therefore proposes to use this claim in marketing/advertising.

2.3 Deficiency 3

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

Although a well-designed study on consumer perception and comprehension will provide indirect information on potential impacts on behavior, we recommend that you also consider assessing consumer perception, comprehension, and intentions in the context of an actual use study designed to address behavioral outcomes, particularly among current users of tobacco products.

Swedish Match's response

Swedish Match has conducted a new consumer perception study entitled "Perceptions and Behavioral Intentions Study" to address this deficiency. As noted in Section 2.1, the protocol was reviewed and amended based on CTP feedback provided at a 13 September 2017 teleconference (FDA Meeting Minutes, 12 October 2017 – TC0002533). The purpose of this study was to determine how the three proposed modified risk claims impacted various cohorts of adult consumers' perceptions of health risks of using General Snus and their behavioral intentions regarding tobacco. The study utilized a test versus control methodology to assess the impact of three General Snus videos, each containing one modified risk claim (serving as the test), versus one General Snus video not containing a modified risk claim (serving as the control). Key features of the study are detailed below. For additional study details, see the full protocol (Study SMNA 17-01GEN Report Section 17.3).

Objectives of the Study

The primary objectives of the study were:

1. To compare the likelihood of various usage intentions and behaviors related to General Snus and other TNP between test and control sample groups. Specifically, after having viewed a single General Snus video, to compare:

- Within current TNP non-user groups:
  - The likelihood to initiate TNP use with General Snus between test and control sample groups, focusing on TNP non-user groups
  - The likelihood to re-initiate TNP use with General Snus between test and control sample groups, focusing on former TNP groups
- Within current TNP user groups:
  - The likelihood to use General Snus between test and control sample groups
  - Among current smokers, the likelihood to use cigarettes between test and control sample groups
  - The intention to quit current TNP between test and control sample groups

2. To examine perceptions of absolute risk associated with using General Snus, smoking cigarettes, and never having used any TNP, between test and control sample groups among all respondents. The health conditions under consideration when assessing absolute risk were:

- Respiratory conditions: chronic bronchitis, emphysema, lung cancer, serious health problems
- Non-respiratory conditions: gum disease, heart disease, mouth cancer, stroke

3. To compare perceptions of the relative risks* associated with using General Snus to using the following between test and control sample groups among all respondents:

- Cigarettes
- Cigarettes and General Snus
- Quitting all TNP
- Never having used any TNP

The health conditions under consideration when assessing relative risk were:

- Respiratory conditions: chronic bronchitis, emphysema, lung cancer, serious health problems

- Non-respiratory conditions: gum disease, heart disease, mouth cancer, stroke

4. To assess the comprehension of the General Snus modified risk claims between test and control sample groups

Secondary objectives of the study included:

5. To compare the likelihood of various usage intentions and behaviors related to General Snus and other TNP (e-cigarettes, moist snuff, chewing tobacco, snus, cigars, cigarillos, or filtered cigars filled with tobacco, pipe tobacco, and hookah or water pipe tobacco) between test and control sample groups. Specifically, among TNP user groups, compare the likelihood to use current TNP between the test sample and the control sample (after having viewed a single General Snus video).

6. To compare perceptions of the relative risks associated with using General Snus with using the following between test and control sample groups among all respondents:

- Moist snuff

- Other brands of snus

- Aids that help stop smoking

7. To assess the believability of the General Snus modified risk claims between test and control sample groups.

Study Design

Video content – Selection and Appropriateness

To identify appropriate video messages, the following elements were considered:

- Videos had to include mandatory government warnings regarding smokeless tobacco.

- All information in claims had to be scientifically substantiated.

- Videos should provide a background on snus (eg, what snus is, how it differs from other smokeless tobacco products, and how to use it appropriately).

- Videos had to communicate why General Snus differed from other types of smokeless tobacco products marketed as “snus.”

- Messages had to have stopping power so that a consumer would pay attention and digest all information provided.

- Video content was reworked and modified to minimize the reading level required to comprehend claims.

To ensure that the video content was appropriate and clear, multiple phases of testing were performed. First, three phases of qualitative research, composed of both focus groups (eight to ten people in size) and triads (three people in size), covering seven major United States (US) markets (Chicago, Seattle, St. Louis, Charlotte, Minneapolis, Denver, and Washington, D.C.), resulted in a total of 119 respondents providing input over a four-month window (May to August 2017).

Ultimately, key decision criteria used during the qualitative research were:

- Comprehension: Did the respondent understand the information?

- Believability: Did the respondent find the information credible?

- Motivation: Was the respondent motivated to try General Snus in place of cigarettes?

Subsequently, two rounds of qualitative, in-depth, in-person, cognitive interviews were conducted in 19 respondents prior to initiation of the quantitative study. Interviews were conducted utilizing a methodology where respondents were interviewed question by question rather than retrospectively after completion of the full survey. Results from the cognitive interviews are provided in the Cognitive Testing Report (Study SMNA 17-01GEN Report Section 17.5).

Quantitative Study Design

Respondents were invited to evaluate a single General Snus description provided in a one-minute video and answer a web-based survey intended to measure the impact of the modified risk claim on TNP usage behaviors and perception of health risks associated with TNP. A between-groups test versus control design was utilized to assess the impact of the modified risk claims. Respondents within each of six cohorts were randomly assigned into one of three test cells (one for each modified risk claim) or a control cell (same video but without a health claim). Within each test/control cell, each respondent was then randomly assigned into one of eight General Snus video advertisements as shown in Table 2.

A video format was chosen, with each video being approximately one minute in length. All information presented to respondents in each video was identical, with the following key exceptions:

1. Each of the three test videos included one of the three MRTP marketing claims. The control video omitted any test claims but was otherwise identical.

2. All four videos had variants that allowed for balanced, randomized usage of:

    a. Government warning statements – each video included one of the following:

        i. WARNING: General Snus is not a safe alternative to cigarettes.

        ii. WARNING: General Snus can cause mouth cancer.

        iii. WARNING: General Snus can cause gum disease and tooth loss.

        iv. WARNING: General Snus is addictive.

    b. General Snus flavors – Videos rotated evenly between mint and wintergreen flavors, which were chosen because they comprise roughly 70% of General Snus product sold in the US (internal sales data on file).

Table 2: Study Design – Random Assignment into Test/Control Cells

	Test			Control
WARNING:	**Claim 1**	**Claim 2**	**Claim 3**	
General Snus is not a safe alternative to cigarettes.	Mint flavor	Mint flavor	Mint flavor	Mint flavor
	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor
General Snus can cause mouth cancer.	Mint flavor	Mint flavor	Mint flavor	Mint flavor
	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor
General Snus can cause gum disease and tooth loss.	Mint flavor	Mint flavor	Mint flavor	Mint flavor
	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor
General Snus is addictive.	Mint flavor	Mint flavor	Mint flavor	Mint flavor
	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor	Wintergreen flavor

Source: Study SMNA 17-01GEN Report Sections 1-16, Table 1

Data Analysis

The analyses focused on test versus control using independent measures. Descriptive analyses (summary statistics) were performed for all variables. Independent sample t-tests and two-sample binomial proportion tests were conducted to examine statistical significance between test claims versus control groups. Based on the FDA's draft guidance document on multiple endpoints (FDA Guidance for Industry 2017), a multiplicity adjustment was applied to the statistical tests performed for each hypothesis. Detailed information for the descriptive analyses, bivariate

analyses, and multiplicity adjustment is provided in the Statistical Analysis Plan (Study SMNA 17-01GEN Report Section 17.4).

Study Cohorts

The study population consisted of US adults of legal age for TNP use. Eligible respondents, who met inclusion and exclusion criteria (as detailed in Study SMNA 17-01GEN Report Section 17.3, Section 8.4.2 and Section 8.4.3) were included from the following six study cohorts:

1. Never tobacco users from legal age to 24 years of age
2. Never tobacco users >24 years of age
3. Former cigarette smokers from legal age and older
4. Current cigarette smokers from legal age to 24 years of age
5. Current cigarette smokers >24 years of age
6. Current smokeless tobacco users from legal age and older

Detailed definitions (eg, definition of former smokers) for each cohort are provided in Study SMNA 17-01GEN Report Sections 1-16, Table 2.

The study population was sourced from established on-line consumer panels. A stratified sampling framework was used based on socio-demographic characteristics of the adult population from the Population Assessment of Tobacco and Health (PATH) study data (ICPSR 36231 2017). In addition, in accordance with guidance from CTP (FDA Meeting Minutes, 19 April 2017 – TC0002213), this study oversampled the young adult population (ie, from legal age to 24 years of age) among never users and current cigarette smokers.

There were 10,532 respondents who met eligibility criteria, were randomized, and were included in the data analysis. The number of respondents from each cohort randomized to each test/control claim is shown in Table 3. Overall, 99.8% of respondents stated they understood the survey content (Study SMNA 17-01GEN Report Sections 1-16, Statistical Table 3a).

The demographics were generally similar among the three test claims and control groups within each cohort. Respondents' mean age was 39.8 years (range: 18 to 99 years) (Study SMNA 17-01GEN Report Sections 1-16, Statistical Table 3b). Overall, 36.8% of respondents were 18 to 24 years of age (Study SMNA 17-01GEN Report Sections 1-16, Table 12).

Table 3: Study Design – Summary

	Total sample		Cohort											
			Never tobacco users legal age (per state) - age 24 years		Never tobacco users aged older than 24 years		Former cigarette smokers legal age (per state) and older		Current cigarette smokers legal age (per state) - 24 years		Current cigarette smokers aged older than 24 years		Current smokeless tobacco users legal age (per state) and older	
	N=10,532		N=1,914		N=1,936		N=1,942		N=1,828		N=1,942		N=970	
	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Claim 1	25.0%	2,631	25.1%	480	24.7%	478	25.3%	491	24.8%	454	24.9%	483	25.3%	245
Claim 2	24.9%	2,621	25.2%	482	24.4%	473	25.0%	486	25.0%	457	24.7%	480	25.1%	243
Claim 3	24.9%	2,622	24.8%	474	25.1%	486	25.0%	486	24.9%	455	24.7%	480	24.8%	241
Control	25.2%	2,658	25.0%	478	25.8%	499	24.7%	479	25.3%	462	25.7%	499	24.8%	241

Source: Study SMNA 17-01GEN Report Sections 1-16, Table 11

Key Findings

All of the claims performed well in terms of comprehension and perceptions of absolute and relative risks of General Snus. However, claim 1 was the most impactful of the three claims in terms of behavioral intentions among current smokers; key results are summarized as follows:

- None of the claims tested within the consumer research motivated non-users of TNP to start using General Snus (Study SMNA 17-01GEN Report Sections 1-16, Table 17).
- When examining the whole body of evidence, across study objectives and cohorts, claim 1 consistently achieved the most support for the study hypotheses.
  - Claim 1: *Using General Snus instead of cigarettes puts you at lower risk for mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis*.
- Focusing exclusively on claim 1:
  - Research demonstrated that consumers comprehended claim 1 (Study SMNA 17-01GEN Report Sections 1-16, Table 27).
  - Respondents who viewed the claims compared with those who did not view the claims perceived lower absolute risk for health conditions from the daily use of only General Snus and no other TNP (Study SMNA 17-01GEN Report Sections 1-16, Table 22).
  - Among respondents who viewed claim 1 compared with control, perceptions of relative risk for General Snus were lower than smoking cigarettes (Study SMNA 17-01GEN Report Sections 1-16, Table 23).
  - Claim 1 demonstrated consistently higher believability among test respondents versus control (Study SMNA 17-01GEN Report Sections 1-16, Table 32).
  - For current cigarette users >24 years of age, viewing claim 1 resulted in statistically significantly higher intent to try General Snus compared with control (Table 1).
  - For current cigarette users above legal age for tobacco use but ≤24 years of age, viewing claim 1 resulted in directionally higher intent to try General Snus compared with control (Table 1).

Data for all claims and hypotheses are detailed in the full study report (Study SMNA 17-01GEN Report Sections 1-16).

Conclusions

The study demonstrated that all of the claims performed well in terms of comprehension and perceptions of absolute and relative risks of General Snus. TNP non-users had little interest in General Snus irrespective if they were exposed to any of the tested claims. In particular, claim 1 did not influence behavioral intentions in this subset whereas current smokers were more interested in buying General Snus if exposed to claim 1.

One key strength of the study was that the video content was rigorously tested in qualitative research prior to the initiation of the quantitative, web-based survey. Also, the study had sufficient sample size for most cohorts to ensure reasonable statistical power to test the primary research hypotheses. One limitation was the inability to enroll enough current smokeless tobacco users, which resulted in limited statistical power to draw conclusions in this particular subset.

In summary, claim 1 produced a net positive benefit to public health by encouraging smokers to try General Snus in lieu of smoking, while properly communicating the risks of General Snus in the context of all TNP. Therefore, based on the totality of evidence, Swedish Match believes that claim 1 (*"Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis")* is the most impactful and proposes to use this MRTP claim in marketing/advertising.

Swedish Match considered doing an actual use study in addition to the quantitative, premarket study. However, it was concluded that such a study would not provide meaningful additional information as it could not, in reality, be conducted in a real-life situation in which General Snus is marketed with a modified risk claim. Swedish Match believes that any meaningful real-life data can only be obtained in a post-market situation where a modified risk message is permitted and used in marketing. If modified risk orders are issued for the eight General Snus products, Swedish Match looks forward to presenting a post-market surveillance program that will generate valid, real-life data on actual use behaviors and perceptions.

2.4 Request/Recommendation 4

"You did not provide a clear description of the Dynamic Population Model and its use, including detailed explanations of how all data inputs were derived from the original data sources and a complete listing of all tobacco use behaviors that were used in this implementation of the model along with their transition probabilities. Given the uncertainty around those impacts, as indicated above, we are unable to ascertain the direction and magnitude of the effect, if any, the proposed MRTPs would have on U.S. population health. In future submissions, if a model is provided, you should provide detailed information about the construction of the model and the underlying parameters used as inputs in the model in order for FDA to assess the model's validity."

Swedish Match's response

The Dynamic Population Model (DPM) was developed by Ramboll Environ, primarily with funding from R. J. Reynolds Tobacco Company (RJR) but with additional financial support from Swedish Match. Details of the DPM have been published in two peer-reviewed journals (Bachand et al 2018; Bachand and Sulsky 2013).

The DPM estimates the difference in population-level survival between a counterfactual scenario that allows the use of a higher risk product and/or a lower risk product, and a base case scenario that only allows the use of the higher risk product. It allows for modeling of current, former, and never users of cigarettes and/or an MRTP. It can be used to examine the magnitude of beneficial consequences required to offset the potential for population-level survival deficits associated with harmful consequences of increased MRTP availability (Bachand et al 2018). The DPM was successfully validated and calibrated, whereby appropriate input data were used to define a base case and a counterfactual scenario (Bachand et al 2018; Bachand and Sulsky 2013). For the purposes of the General Snus MRPTAs, a variant of the model was used in which only one tobacco product (cigarettes) is available for use in the base case and one new product (General Snus) was added in the counterfactual scenario. Details are provided in Appendix 1.

The findings in the consumer perception study confirm and extend the previously submitted conclusions based on the tested DPM scenarios. It shows that current smokers are more likely to buy General Snus and use it instead of cigarettes if exposed to Claim 1 (Section 2.3). The tested modeling scenarios clearly illustrated that even a small increase in the proportion of current smokers who switch completely to General Snus is likely to result in a net population benefit (under reasonable assumptions about potential adverse effects of a modified risk designation for snus). The consumer perception study showed that such potential adverse effects are likely to be minimal (such as, an increased uptake of General Snus by current non-users of tobacco products or a decreased interest in quitting among current smokers). In fact, the study showed that current non-users were consistently uninterested in General Snus irrespective of any of the tested health claims. The claims also did not decrease the interest in quitting among current smokers. These results and observations underscore the conservative nature of the estimates of population benefit that was previously presented based on the DPM.

2.5 Request/Recommendation 5

"We recommend following best practices for the conduct of systematic reviews and meta-analyses when identifying and synthesizing evidence from the open scientific literature to provide greater confidence in the conclusions drawn from the reviews and analyses. When comparing health risks against other tobacco products, you should include all relevant studies and study results to most accurately reflect the potential risks associated with the product. In synthesizing the evidence, you should consider and explain the factors that may influence the interpretation of study findings, such as the impact of study design, exposure and outcome assessment, inadequate sample size, and the potential for bias and confounding."

Swedish Match's response

Swedish Match thanks CTP for their best practices recommendation and will take it into consideration for future projects.

3 REFERENCES

Bachand et al 2018

Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. Regulatory Toxicology and Pharmacology 2013;67(2):246-51.

Bachand and Sulsky 2013

Bachand AM, Sulsky SI, Curtin GM. Assessing the likelihood and magnitude of a population health benefit following the market introduction of a modified-risk tobacco product: enhancements to the Dynamic Population Modeler, DPM(+1). Risk Analysis 2018;38(1):151-62.

FDA Guidance for Industry 2017

FDA Guidance for Industry. Multiple endpoints in clinical trials. January 2017. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf.

SAMHSA 2016

Substance Abuse and Mental Health Services Administration (SAMHSA). Key substance use and mental health indicators in the United States: results from the 2015 National Survey on Drug Use and Health. September 2016. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf. Accessed 30 January 2018.

ICPSR 36231 2017

United States Department of Health and Human Services. National Institutes of Health. National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug Administration. Center for Tobacco Products. Population Assessment of Tobacco and Health (PATH) Study. ICPSR36231-v13. Ann Arbor, MI: Interuniversity Consortium for Political and Social Research, 19 June 2017. https://doi.org/10.3886/ICPSR36231.v13.

APPENDIX 1. DYNAMIC POPULATION MODEL

The Dynamic Population Model (DPM) is capable of modeling any combination of behaviors, and the analyses in the General Snus Modified Risk Tobacco Product applications (MRTPA) focused on four behaviors that are most directly related to the Food and Drug Administration (FDA) MRTPA Draft Guidance:

- Smokers who switch to the Modified Risk Tobacco Product (MRTP) instead of continuing to smoke
- Smokers who switch to the MRTP instead of quitting smoking
- MRTP users who switch to conventional cigarettes
- Never smokers and former smokers who initiate tobacco use with the MRTP

Other behaviors are available in the DPM and could have been incorporated in the analyses. The analyses presented in the General Snus MRTPA assigned current and formal dual use to have the same mortality risk as current and former cigarette smoking, respectively. Therefore, the transition to dual use of both products by current smokers instead of smoking cessation was identical to continued smoking by current smokers instead of smoking cessation, which is a conservative approach that likely overestimates the risks associated with dual use of conventional cigarettes and General Snus.

To address which scenarios are more or less likely, the scenarios used for tipping point analyses and the likelihood that these scenarios will occur in practice are summarized below. By presenting a range of possible scenarios, including some that results in harm, the FDA may consider the characteristics of each scenario and judge the likelihood of that scenario actually occurring. The four data tables from the MRTPA cited below are provided in this response for ease of reference. Posterior intervals presented in the tables summarize the variability in the analytical results and highlight the true uncertainty of the estimates.

- **Base case of smoking quitters switching to MRTP**

  In Table 4, 1%, 5%, or 10% of base case smoking quitters switch to MRTP use in the counterfactual scenario. Switching occurs in the second age category (18 to 22 years) and in all subsequent age categories.

  The effect of reverting to smoking was investigated in sensitivity analyses. In the first set of analyses, none of the base case smoking quitters who switched to MRTP use in the counterfactual scenario revert to smoking. In the second set of analyses, 50% of base case smoking quitters who switched to MRTP use in the counterfactual scenario revert to smoking in each age category following the age category of switching. In the third set of analyses, 100% of base case smoking quitters who switched to MRTP use in the

counterfactual scenario revert to smoking in the next age category following the age category of switching.

If none of the base case smoking quitters who instead switched to the MRTP in the counterfactual scenario revert to smoking, the survival deficit in the counterfactual scenario is small, even in the case of 10% switching (Table 4). Therefore, very small proportions of base case continuing smokers switching to MRTP use in the counterfactual scenario are sufficient to overcome the survival deficits (Table 5). Any survival deficit resulting from base case smoking quitters switching to MRTP use in the counterfactual scenario will be more than overcome by switching to MRTP use among base case continuing smokers.

If 50% of base case smoking quitters who instead switched to the MRTP in the counterfactual scenario revert to smoking in each age category following the age category of switching, survival deficits and tipping points are still fairly low (Table 4 and Table 5). Of particular note, most base case smoking quitters who instead switched to the MRTP in the counterfactual scenario revert to smoking by the end of follow-up. It is unlikely that reverting to smoking will occur after years of MRTP use. Modeling less extreme scenarios where reverting to smoking occurs in the same age category as switching to MRTP use is possible in the current version of the DPM but was not possible when the analyses were conducted for the General Snus MRTPA. Even in the extreme scenarios described in Table 4 and Table 5, tipping points are fairly small (3% or less; Table 5). For example, if 10% of base case smoking quitters switch to MRTP use in the counterfactual scenario and 50% of them revert to smoking in each subsequent age category, then the resulting survival deficit is overcome if just 3% of base case continuing smokers switch to MRTP use (ie, the survival deficit is overcome even if the proportion of base case continuing smokers who switch to MTRP use in the counterfactual scenario is 7 percentage points lower than the proportion of base case smoking quitters who switch to MRTP use in the counterfactual scenario).

If 100% of base case smoking quitters who instead switched to the MRTP in the counterfactual scenario revert to smoking in the next age category, survival deficits and tipping points are still quite low (Table 4 and Table 5). Of particular note in this example, all base case smoking quitters who instead switched to the MRTP in the counterfactual scenario revert to smoking almost immediately. In this extreme scenario, tipping points are still relatively small (6% or less; Table 5). For example, if 10% of base case smoking quitters switch to the next age category, then the resulting survival deficit is overcome if just 6% of base case continuing smokers switch to MRTP use (ie, the survival deficit is overcome even if the proportion of base case continuing smokers who switch to MRTP use is 4 percentage points lower than the proportion of base case smoking quitters who switch to MRTP use).

Table 4: Mean Difference in the Number of Survivors Between the Counterfactual and Base Case Scenario at the End of Follow-up (Age Category 68 to 72 years) and 95% PIs

	% of Base Case Smoking Quitters Switching to MRTP					
	1%		5%		10%	
% MRTP Users Switching to Smoking[1,2]	Mean	95% PI	Mean	95% PI	Mean	95% PI
0%	-38	-43, -32	-188	-217, -158	-376.30	-433, -317
50%	-172	-199, -144	-862	-996, -721	-1724	-1992, -1442
100%	-208	-242, -173	-1041	-1210, -865	-2081	-2419, -1730

Source: MRTPA Table 6-63
MRTP=Modified Risk Tobacco Product; MRTPA=Modified Risk Tobacco Product Application; PI=posterior interval.
Note: Some base case smoking quitters switching to MRTP
1 Remaining subjects continue MRTP use for at least 1 additional age category.
2 No quitting among MRTP users.

Table 5: Tipping Points for Base Case Continuing Smokers Switching to MRTP Versus Base Case Smoking Quitters Switching to MRTP

Base Case Smoking Quitters Switching to MRTP		**1%**			**5%**			**10%**		
%		**Approximate Proportion of Base Case Continuing Smokers Switching to MRTP Needed For**								
Reverting to Smoking	**% Continuing MRTP Use**	**Stat. Sign. Survival Deficit**	**No Survival Deficit or Benefit**	**Stat. Sign. Survival Benefit**	**Stat. Sign. Survival Deficit**	**No Survival Deficit or Benefit**	**Stat. Sign. Survival Benefit**	**Stat. Sign. Survival Deficit**	**No Survival Deficit or Benefit**	**Stat. Sign. Survival Benefit**
0%	100%	<0.01%	0.025%	>0.05%	<0.1%	0.125%	>0.15%	<0.2%	0.25%	>0.275%
50%	50%	<0.25%	0.3%	>0.4%	<1.25%	1.5%	>1.75%	<2.75%	3.0%	>3.5%
100%	0%	<0.5%	0.6%	>0.8%	<2.5%	3.0%	>4.0%	<5.75%	6.0%	>8%

Source: MRTPA Table 6-64
MRTP=Modified Risk Tobacco Product; MRTPA=Modified Risk Tobacco Product Application; stat. sign.=statistically significant.

- **Base case never tobacco users initiating MRTP**

  In Table 6 (included in this response for ease of reference), 1%, 5%, or 10% of base case never tobacco users initiate MRTP use in the counterfactual scenario. MRTP initiation occurs in the first three age categories.

  The effect of switching to smoking was investigated in sensitivity analyses. In the first set of analyses, none of the MRTP initiators switch to smoking. In the second set of analyses, 50% of MRTP initiators switch to smoking in each age category following the age category of MRTP initiation. In the third set of analyses, 100% of MRTP initiators switch to smoking in the next age category after MRTP initiation. Additional sensitivity analyses explored the effect of greater MRTP initiation in the first age category and different proportions of quitters (0%, 25%, and 50%) among MRTP users.

  Even if none of the base case never tobacco users who initiated MRTP use in the counterfactual scenario switch to smoking, the survival deficit in the counterfactual scenario can be considerable. This is especially the case if 5% or 10% of never tobacco users initiate MRTP use in the counterfactual scenario (in each of the first three age categories) and there is no quitting among MRTP users (Table 6). The survival deficit is even larger if there is increased MRTP initiation in the first age category. Tipping points are very large, ie, very large proportions of base case smoking initiators switching to MRTP use in the counterfactual scenario are necessary to overcome the survival deficits (Table 7).

  If 50% of base case never tobacco users who initiated MRTP use in the counterfactual scenario switch to smoking in each age category following MRTP initiation, survival deficits are large (Table 6) and cannot be overcome even if all base case smoking initiators initiate MRTP use in the counterfactual scenario (Table 7).

  If 100% of base case never tobacco users who initiated MRTP use in the counterfactual scenario switch to smoking in the next age category after MRTP initiation, survival deficits are very large (Table 6) and cannot be overcome even if all base case smoking initiators initiate MRTP use in the counterfactual scenario (Table 7).

  To put these results into context, it is important to recognize that these scenarios are extreme. Based on the 2015 National Survey on Drug Use and Health (SAMHSA 2016), the proportion of the US population using smokeless tobacco is 1.5% among persons aged 12 to 17 years, 5.4% among persons aged 18 to 25 years, and 3.2% among persons aged 26 years and older. Therefore, the estimate of 5% and 10% MRTP initiation among base case never tobacco users in each of the first three age categories is considerably higher compared to current tobacco use patterns in the United States.

Table 6: Mean Differences in the Number of Survivors Between the Counterfactual and Base Case Scenario at the End of Follow-up (Age Category 68 to 72 years) and 95% PIs

MRTP Initiation in Age Categories 1-3	% MRTP Users Switching to Smoking[1]	% MRTP Quitters[2] Resuming MRTP	% of Base Case Never Tobacco Users Initiating MRTP					
			1%		5%		10%	
			Mean	95% PI	Mean	95% PI	Mean	95% PI
Constant	0%	No quitters	-641	-757, -528	-3082	-3646, -2541	-5873	-6950, -4838
Doubled in first age category	0%	No quitters	-862	-1022, -708	-4109	-4872, 3375	-7730	-9163, -6347
Constant	0%	25%	-350	-423, -280	-1679	-2026, -1343	-3183	-3839, -2549
Constant	0%	50%	-431	-513, -352	-2071	-2465, -1692	-3936	-4681, -3216
Constant	50%	No quitters	-1927	-2427, -1429	-9282	-11700, -6875	-17700	-22320, -13100
Constant	100%	No quitters	-2041	-2626, -1455	-9833	-12660, -7001	-18760	-24150, -13340

Source: MRTPA Table 6-65
Note: Some base case never tobacco users initiate MRTP
MRTP=Modified Risk Tobacco Product; MRTPA=Modified Risk Tobacco Product Application; PI=posterior interval; US=United States.
[1] Remaining subjects continue MRTP use for at least 1 additional age category.
[2] Same cessation rates as US smoking cessation rates from 2005 to 2008.

Table 7: Tipping Points for Base Case Never Tobacco Users Initiating MRTP Versus Base Case Smoking Initiators Initiating MRTP

Base Case Never Tobacco Users Initiating MRTP		1%			5%			10%		
		Approximate Proportion of Base Case Smoking Initiators Initiating MRTP Needed For								
% Switching to Smoking	% Continuing MRTP Use	Stat. Sign. Survival Deficit	No Survival Deficit or Benefit	Stat. Sign. Survival Benefit	Stat. Sign. Survival Deficit	No Survival Deficit or Benefit	Stat. Sign. Survival Benefit	Stat. Sign. Survival Deficit	No Survival Deficit or Benefit	Stat. Sign. Survival Benefit
0%[1]	100%	<3.0%	4.0%	>7.0%	<14%	20%	>30%	<25%	40%	>60%
0%[2]	100%	<4.0%	5.0%	>9.0%	<20%	25%	>45%	<35%	50%	>80%
0%[1,3]	100%	<1.5%	2.0%	>2.5%	<7%	9%	>12%	<14%	18%	>25%
0%[2,4]	100%	<1.75%	2.5%	>3.5%	<9%	12%	>16%	<18%	24%	>30%
50%[1,5]	50%	<60.0%	-	-	≤100%	-	-	≤100%	-	-
100%[1,5]	0%	<100.0%	-	-	≤100%	-	-	≤100%	-	-

Source: MRTPA Table 6-6
MRTP=Modified Risk Tobacco Product; MRTPA=Modified Risk Tobacco Product Application; stat. sign.=statistically significant.
Note: Table entries are the proportion of base case smoking initiators initiating MRTP necessary to eliminate the survival deficit caused by some base case never tobacco users initiating MRTP instead.

1 Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter; no MRTP quitting.
2 MRTP initiation rate doubled in the first age category; no initiation after age category 3; no MRTP quitting.
3 Some MRTP users subsequently quit (same age-specific smoking cessation rates as were used in the base case [US 2006 estimates] are applied to the MRTP users) and 25% of MRTP quitters resume MRTP.
4 Some MRTP subsequently quit (same age-specific cessation rates as were used in the base case [US 2006 estimates] are applied to the MRTP users) and 50% of MRTP quitters resume MRTP.
5 Too few smoking initiators to reach a tipping point.