



December 14, 2016

RESPONSE

Swedish Match North America, Inc.
Attention: Gerard Roerty, Vice President, General Counsel & Secretary
Two James Center
1021 East Cary Street, Suite 1600
Richmond, VA 23219

FDA Submission Tracking Numbers (STNs): MULTIPLE STNs, see below

Dear Mr. Roerty:

The Food and Drug Administration (FDA) completed review of your Modified Risk Tobacco Product Applications (MRTPAs) submitted under section 911(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) seeking modified risk orders under section 911(g)(1) of the FD&C Act, 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

We have completed the review of your MRTPAs, as amended, and other available information including public comments and recommendations of the Tobacco Products Scientific Advisory Committee, and we are not issuing modified risk orders under § 911(g)(1) of the FD&C Act with respect to your requests to remove the mouth cancer warning and revise the “not a safe alternative” warning. We have determined that in their present form, the applications do not contain sufficient evidence to demonstrate 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. However, we believe your applications could be amended in several ways, for example by changing the proposed claims, supplementing the evidence, and conducting new studies, which could provide sufficient evidence to support issuance of modified risk orders for these tobacco products. We recommend and highly encourage you to meet with the Office of Science in FDA’s Center for Tobacco Products to discuss how your applications could be amended and the steps necessary for issuance of modified risk orders under section 911(g).

Our review of your applications revealed the following deficiencies:

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

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

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

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

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

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

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

presented within a warning or as a standalone claim) affects consumer perception and comprehension.

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

In addition to the deficiencies identified above, we have the following requests and recommendations to assist in our scientific review of any amendment you choose to submit:

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.
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.

Within 45 days from the date of this letter, you should take one of the following actions: (1) request a meeting with us to discuss the evidence needed to support your applications; (2) notify us of your intent to amend the applications; or (3) withdraw the applications.

We have described above our concerns with the applications and, where possible, our recommendations to address these issues. We highly encourage you to meet with us to discuss the steps necessary for issuance of modified risk orders under section 911(g) for **MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029**. As part of the scope of the meeting, we request that you describe the information you plan to develop and submit to specifically address the above deficiencies. In addition, we recommend that you provide the following information:

- Whether you plan to amend the modified risk claim(s) for your tobacco products.
- A proposed schedule for responding to this letter which includes major milestones for developing new information, preparing study reports, etc.

- If you plan to conduct additional studies, include:
 - A detailed outline describing all design features of each study including sample size and justification, eligibility criteria with rationale, duration, assessments to be performed and their timing, and endpoints to be analyzed.
 - A proposed schedule for conducting each study that includes major milestones for the study, e.g., date the protocol is finalized, initiation date of the study, completion date of the study, completion of data analysis.

If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry and Investigators on the Research and Development of Tobacco Products, July 2016 at <http://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM305282.pdf>.

Within 24 months after the date of this letter, we request that you either (1) amend your applications by addressing all deficiencies identified in this letter; or (2) withdraw the applications. If you do not take one of these actions, we may consider your lack of response a request to withdraw the applications.

An amendment to the applications should fully address all the deficiencies listed in this letter and should be clearly marked with "**RESPONSE AMENDMENT for MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this submission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed and will not start a new review. In addition, we request your submission be organized in the following manner so that we can easily identify your responses to each numerated item above:

- List each deficiency number above along with our request as stated above, and provide your response immediately following
 - Your response should address all STNs; if different information/data is being submitted for different STNs in your response, the response should clearly correlate information to the applicable STN(s);
 - If resubmitting information previously submitted (e.g., tables) to correct earlier omissions/errors, clearly identify what information has been revised; and
 - If you have already submitted any of the information requested above, identify the date of the prior submission, page number(s), and line numbers where the requested information is located.
- All pages in your submission should be consecutively numbered.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal¹ (<http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/ucm515047.htm>) using eSubmitter (<http://www.fda.gov/ForIndustry/FDAeSubmitter>). Alternatively, submissions may be mailed to:

¹The FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.

Food and Drug Administration
Center for Tobacco Products
Document Control Center
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The CTP Portal and FDA Electronic Submission Gateway (ESG) are both available 24 hours a day, seven days a week; if the upload is successful, submissions are considered received by DCC on the day of upload. Submissions delivered to DCC by couriers or physical mail will be considered timely if received during delivery hours on or before the due date (see <http://www.fda.gov/tobaccoproducts/aboutctp/contactus/default.htm>); if the due date falls on a weekend or holiday the delivery must be received on the prior business day. We are unable to accept regulatory submissions by electronic mail.

If you have questions regarding these modified risk tobacco product applications, you may contact Shireen Ahmad, M.S., Regulatory Health Project Manager, at (240) 402 – 0435.

Sincerely,

**Benjamin
Apelberg -S**



Digitally signed by Benjamin Apelberg -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
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