Modified Risk Tobacco Product (MRTP) Application – Technical Project Lead (TPL) Review

Submission Information			
Applicant	Swedish Match North America, Inc.		
Submission Date	June 10, 2014	**FDA Receipt Date**	June 10, 2014
MR0000020: General Loose			
Product Category	Smokeless Tobacco		
Product Sub-Category	Loose Snus		
Package Type	Cardboard Can with Plastic Lid		
Package Quantity	45.0 g		
Tobacco Cut Size	(b)(4) [redacted]		
Characterizing Flavor	None		
MR0000021: General Dry Mint Portion Original Mini			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	6.0 g		
Portion Count	20 pouches		
Portion Mass	300 mg		
Portion Length	28 mm		
Portion Width	14 mm		
Portion Thickness	5 mm		
Tobacco Cut Size	(b) (4) [redacted]		
Characterizing Flavor	Mint		
MR0000022: General Portion Original Large			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	24.0 g		
Portion Count	24 pouches		
Portion Mass	1000 mg		
Portion Length	33 mm		
Portion Width	18 mm		
Portion Thickness	6 mm		
Tobacco Cut Size	(b) (4) [redacted]		

[1] SMNA provided (b)(4) [redacted] to characterize the tobacco cut size. Therefore, the tobacco cut size cannot be represented with a single value and corresponding range limit.

Characterizing Flavor	None
MR0000024: General Classic Blend Portion White Large – 12 ct	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Portion Count	12 pouches
Portion Mass	900 mg
Portion Length	34 mm
Portion Width	14 mm
Portion Thickness	5 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	None
MR0000025: General Mint Portion White Large	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	34 mm
Portion Width	18 mm
Portion Thickness	5.5 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Mint
MR0000027: General Nordic Mint Portion White Large – 12 ct	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	10.8 g
Portion Count	12 pouches
Portion Mass	900 mg
Portion Length	34 mm
Portion Width	14 mm
Portion Thickness	5 mm
Tobacco Cut Size	(b) (4)
Characterizing Flavor	Mint
MR0000028: General Portion White Large	
Product Category	Smokeless Tobacco
Product Sub-Category	Portioned Snus
Package Type	Plastic Can
Package Quantity	24.0 g
Portion Count	24 pouches
Portion Mass	1000 mg
Portion Length	34 mm

Portion Width	18 mm		
Portion Thickness	5.5 mm		
Tobacco Cut Size	(b) (4) [redacted]		
Characterizing Flavor	None		
MR0000029: General Wintergreen Portion White Large			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	24.0 g		
Portion Count	24 pouches		
Portion Mass	1000 mg		
Portion Length	34 mm		
Portion Width	18 mm		
Portion Thickness	5.5 mm		
Tobacco Cut Size	(b) (4) [redacted]		
Characterizing Flavor	Wintergreen		
Amendment(s)	**STN**	**Submission Date**	**Solicited Y/N**
	MR0000030	July 31, 2014	**Y**
	MR0000031	August 1, 2014	**Y**
	MR0000032	August 5, 2014	**Y**
	MR0000033	August 15, 2014	**Y**
	MR0000035	December 3,2014	**Y**
	MR0000036	December 9, 2014	**Y**
	MR0000038	January 27, 2015	**Y**
	MR0000039	February 20, 2015	**Y**
	MR0000041	March 11, 2015	**Y**
	MR0000042	May 22, 2015	**Y**
	MR0000044	June 19, 2015	**Y**
	MR0000045	July 8, 2015	**Y**
Related Submissions	**Cross Referenced Submission**		**Other Related Submission STN(s)**
	SE0010524		PM0000010
	SE0010525		PM0000011
	SE0010526		PM0000012
	SE0010527		
	SE0010528		PM0000013
	SE0010529		PM0000014
	SE0010530		
	SE0010531		PM0000015
	SE0010532		PM0000016
	SE0010533		PM0000017
Product Use	☒ For Consumer Use ☐ For Further Manufacturing		
Product Type	☒ Complete ☐ Component, Part, or Accessory		
Proposed Modified	• Remove the mouth cancer warning		

Risk Claims	• Remove the gum disease and tooth loss warning • Revise the "not a safe alternative warning" to "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes"

DISCIPLINES REVIEWED	**DATE OF REVIEW**
Behavioral Pharmacology	October 31, 2016
Chemistry	September 15, 2016
Clinical Pharmacology	October 28, 2016
Engineering	September 15, 2016
Environmental Science	October 13, 2016
Epidemiology	November 2, 2016
Medical	October 26, 2016
Microbiology	September 15, 2016
OCE Review (DEM)	September 20, 2016
OCE Review (DPAL)	September 16, 2016
Regulatory	October 26, 2016
Social Science	October 27, 2016
Statistics	October 24 and 27, 2016
Toxicology	September 19, 2016

Recommended Action(s)
☐ Issue a Modified Risk Order; there is sufficient evidence to demonstrate that, as actually used by consumers, the product 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. ☒Issue a Response; in its present form, the application does not contain sufficient evidence to demonstrate that, as actually used by consumers, the product 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, the application could be amended in several ways, which could provide sufficient evidence to support issuance of a modified risk order. ☒Deny issuance of a Modified Risk Order; based on the available scientific evidence, the applicant has not demonstrated that, as actually used by consumers, the product 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.

Technical Project Lead Name:
CTP/OS

Conrad J. Choiniere -S
Digitally signed by Conrad J. Choiniere -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300218332, cn=Conrad J. Choiniere -S
Date: 2016.11.02 10:14:16 -04'00'

Conrad J. Choiniere, Ph.D.
Former Director
Division of Population Health Science
Office of Science
Center for Tobacco Products

Signatory Decision:

☑ I concur with TPL recommendation and basis of recommendation
☐ I concur with TPL recommendation and am providing additional comments (see separate memorandum)
☐ I do not concur with TPL recommendation as stated in my separate memorandum

Signatory:
CTP/OS

Digitally signed by David Ashley -S
Date: 2016.11.02 10:16:43 -04'00'

David Ashley, Ph.D.
RADM (Ret.), United States Public Health Service
Director
Office of Science
Center for Tobacco Products

Modified Risk Tobacco Product Application Technical Project Lead Review

EXECUTIVE SUMMARY

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

Swedish Match North America, Inc. (SMNA) proposes to manufacture and market eight General Snus products[2] as modified risk tobacco products. The firm asserts that it produces the products in a manner which conforms to Sweden's Gothiatek® standard which, among other criteria, establishes maximum levels on the presence of certain harmful constituents in the products. SMNA provided information about the engineering of the products, as well as their chemical and microbiological properties, for FDA to deduce that the eight General Snus products conform to the Gothiatek® standard and that SMNA has adequate controls in manufacturing to ensure a consistent product from batch-to-batch.

SMNA provided a broad review of the existing literature on the health risks associated with the use of snus products in Sweden and Norway. SMNA asserts that the snus products used in Sweden and Norway over the observation periods for the studies included in the applications conformed to the Gothiatek® standard. Thus, SMNA posits that:

- The eight General Snus products, conforming to the same standards as the products used in Sweden and Norway, pose the same level of exposures of harmful constituents to users as the snus products traditionally marketed in Sweden and Norway; and
- The users of the eight General Snus products will experience the same health outcomes as users of the traditional snus products marketed in Sweden and Norway.

These conclusions about the levels of exposure experienced by users of the General Snus products and ensuing health effects rest on the assumption that users in the United States (U.S.) of the eight General Snus products that are the subject of the applications will use them in a manner similar to users of the snus products in Sweden and Norway. This assumption includes a broad range of potential behaviors related to the use of the products (e.g., frequency or intensity of usage), as well as the use of other tobacco products (e.g., completely switching to the product or use of the product with other tobacco products).

SMNA draws conclusions from the existing scientific evidence that use of the snus products in Sweden and Norway did not result in tooth loss or gum disease and did not result in increased risk of mouth cancer. SMNA also concludes that the health risks from using snus are substantially lower than the risks from smoking cigarettes. Thus, SMNA requests that it be

[2] Although applications for ten products were originally submitted, on October 7, 2015, SMNA submitted a withdrawal request for MR0000023, General Classic Blend Portion White Large-15 count and MR0000026, General Nordic Mint Portion White Large- 15 count. On October 15, 2015, FDA issued withdrawal acknowledgement letters to SMNA for MR0000023, General Classic Blend Portion White Large-15 count and MR0000026, General Nordic Mint Portion White Large- 15 count.

allowed to market the eight General Snus products as modified risk tobacco products by omitting two of the currently required warning statements for smokeless tobacco products,

(1) WARNING: This product can cause gum disease and tooth loss;

(2) WARNING: This product can cause mouth cancer;

and revising a third warning statement from WARNING: This product is not a safe alternative to cigarettes to

(3) WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes.

The eight General Snus products would continue to bear the fourth currently required warning

(4) WARNING: Smokeless tobacco is addictive.

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.

The assessment of whether the products meet the modified risk tobacco product standard begins with an assessment of the scientific substantiation of the proposed modified risk information.[3] To illustrate with an example, if a proposed claim (express or implied) purports reduction or elimination of some specific risk, then the inquiry begins with a determination of whether the products, as actually used by individual tobacco users, will in fact result in the purported reduction or elimination of that risk.

The modified risk inquiry also involves an assessment of whether the proposed modified risk product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users. This assessment includes an evaluation of the relative health risks to individuals, including a broad range of health risks beyond those specifically addressed in the proposed modified risk claim, which the modified risk tobacco products, as actually used, present to individuals.

The modified risk inquiry further includes a determination of the potential benefits and harms to the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. This assessment considers the impact of the product with the proposed modified risk information, on tobacco use behaviors, such as the

[3] Congress found that "[t]he only way to effectively protect the public health from the dangers of unsubstantiated modified risk tobacco products is to empower the Food and Drug Administration to require that products that tobacco manufacturers sold or distributed for risk reduction be reviewed in advance of marketing, and to require that the evidence relied on to support claims be fully verified." Tobacco Control Act (Pub. L. 111-31) § 2(43).

potential for adoption of the product on the part of current tobacco users, dual or poly use of tobacco products by current users, and the ensuing health outcomes resulting from those behaviors in the population. Included in this evaluation are also:

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence.

The modified risk standard also involves an assessment of consumer perception, understanding, and comprehension of the modified risk information, which may be an important precursor to consumer behavior and could affect how consumers actually use the product. Relatedly, section 911(h)(1) of the FD&C Act requires that "any advertising or labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products."

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

In addition to the information contained in the MRTPAs, the assessment considered the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources.

After conducting a thorough scientific review of all of these materials, FDA concludes that:

- With respect to the request to remove the gum disease and tooth loss warning, based on the available scientific evidence, SMNA has 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.
- With respect to the requests to remove the mouth cancer warning and revise the "not a safe alternative" warning, 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.

1. SMNA requests to omit from the label and advertising of the eight General Snus products "WARNING: This product can cause gum disease and tooth loss." 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 gum disease or tooth loss. 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 gum disease or tooth loss.

   After conducting a thorough assessment of the scientific substantiation for the claim that the eight General Snus products cannot cause gum disease or tooth loss, FDA determined that the claim is not substantiated. On the contrary, there is little biologically plausible reason to expect that outcomes related specifically to gum and teeth of users resulting from the use of the eight products would differ from those outcomes resulting from the use of other smokeless tobacco products. Indeed, given that these eight General snus products, like other smokeless tobacco products, cause delayed soft tissue wound healing, these products would not be expected to differ from other smokeless tobacco products with respect to these disease outcomes. Furthermore, the epidemiological evidence indicates that the use of these products, as actually used by consumers in Sweden and Norway, increases the risks of certain outcomes classified as gum disease or tooth loss, or precursors to gum disease and tooth loss. Because the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular "can cause gum disease and tooth loss," the proposed modified risk claim is not substantiated. Additionally, SMNA did not provide evidence regarding how the modified risk information (i.e., the removal of the gum disease and tooth loss warning) would impact consumer behavior or whether consumers would understand the modified risk information in the context of total health. As a result, SMNA has 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. Accordingly, the request to omit the warning related to gum disease and tooth loss should be denied.

2. SMNA requests to omit from the label and advertising of the eight General Snus products "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.

   After conducting a thorough assessment of the scientific substantiation for the claim that the eight General Snus products cannot cause mouth cancer, FDA determined that the claim is not substantiated. 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 nitrosonornicotine (NNN)

and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (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, although many of the epidemiological studies of Swedish snus may not have been statistically powered to detect moderate increases in oral cancer risk, the most recent published epidemiological study found a statistically significant increased risk (Roosaar et al., 2008). Accordingly, because the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular "can cause mouth cancer," the proposed modified risk claim is not substantiated. Additionally, SMNA 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, 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. Accordingly, modified risk orders should not be issued for these products based on the proposed claim in its current form. However, the 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 relating to mouth cancer for these tobacco products.

3. SMNA requests to revise the currently required "WARNING: This product is not a safe alternative to cigarettes" on the label and advertising of the eight General Snus products, 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 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 diseases, particularly in the context of a warning. As a result, 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. Accordingly, modified risk orders should not be issued for these products based on the proposed claim in its current form. However, the 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 relating to health risks compared to cigarettes for these tobacco products.

REGULATORY INFORMATION

Regulatory History

On June 10, 2014, FDA received applications from Swedish Match North America, Inc. requesting modified risk tobacco products orders under section 911(g)(1) of the FD&C Act for the following ten tobacco products listed by the FDA Submission Tracking Numbers:

- MR0000020: General Loose, smokeless tobacco, loose snus, 1.59 oz (45g), cardboard can;
- MR0000021: General Dry Mint Portion Original Mini, smokeless tobacco, snus portions, 0.21 oz (6g), 20 – 0.3g portions, plastic can;
- MR0000022: General Portion Original Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24—1g portions, plastic can;
- MR0000023: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can;
- MR0000024: General Classic Blend Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can;
- MR0000025: General Mint Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can;
- MR0000026: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.48 oz (13.5g), 15 – 0.9g portions, plastic can;
- MR0000027: General Nordic Mint Portion White Large, smokeless tobacco, snus portions, 0.38 oz (10.8g), 12 – 0.9g portions, plastic can;
- MR0000028: General Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can; and
- MR0000029: General Wintergreen Portion White Large, smokeless tobacco, snus portions, 0.9 oz (24g), 24 – 1g portions, plastic can.

These applications were accepted and acknowledged on June 23, 2014. A filing meeting was held on July 23, 2014. The applications were filed on August 25, 2014. 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 these two products are not considered for an order under 911(g)(1).

During the course of review the following types of communication occurred:

Amendments received[4]:

Product Name	MRTPA	Amendment
General Loose	MR0000020	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Dry Mint Portion Original Mini	MR0000021	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Portion Original Large	MR0000022	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038

[4] On October 7, 2015, SMNA submitted a withdrawal request for MR0000023, General Classic Blend Portion White Large-15 count and MR0000026, General Nordic Mint Portion White Large- 15 count (MR0000046). On October 15, 2015, FDA issued withdrawal acknowledgement letters to SMNA for MR0000023, General Classic Blend Portion White Large-15 count and MR0000026, General Nordic Mint Portion White Large- 15 count.

Product Name	MRTPA	Amendment
		MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Classic Blend Portion White Large	MR0000023	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045 MR0000046
General Classic Blend Portion White Large	MR0000024	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Mint Portion White Large	MR0000025	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Nordic Mint Portion White Large	MR0000026	MR0000030 MR0000031 MR0000032

Product Name	MRTPA	Amendment
		MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045 MR0000046
General Nordic Mint Portion White Large	MR0000027	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Portion White Large	MR0000028	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044 MR0000045
General Wintergreen Portion White Large	MR0000029	MR0000030 MR0000031 MR0000032 MR0000033 MR0000035 MR0000036 MR0000038 MR0000039 MR0000041 MR0000042 MR0000044

Product Name	MRTPA	Amendment
		MR0000045

Letters Issued:

- Advice/Information Request letters issued for all ten products submitted. Letters issued on November 12, 2014, March 6, 2015, April 28, 2015, and June 5, 2015.
- Letters related to manufacturing and clinical site inspections issued for all ten products submitted. Letters issued on November 25, 2014, and April 9, 2015.

Teleconferences:

- Calls occurred between representatives of SMNA and FDA on July 24, 2014, July 25, 2014, July 31, 2014, August 6, 2014, August 21, 2014, August 25, 2014, December 1, 2014, December 4, 2014, January 9, 2015, February 6, 2015, March 9, 2015, March 24, 2015, March 26, 2015, April 13, 2015, April 14, 2015, April 24, 2015, May 4, 2015, June 18, 2015, and June 29, 2015.

Other Types of Regulatory Activities related to these MRTPAs:

Public Availability:

Pursuant to Section 911(e) of the FD&C Act, SMNA's MRTPAs, including amendments were made available to the public (except matters in the applications which are personal privacy or trade secrets or otherwise confidential, commercial information). The notice of availability and request for public comment for these applications appeared in the Federal Register of August 27, 2014 for the originally filed applications and July 31, 2015 for the subsequently filed amendments.

Referral to the Tobacco Product Scientific Advisory Panel (TPSAC):

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 modified risk marketing. Information about the meeting, including the complete transcript, is available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm434209.htm.

Inspections:

During March-April 2015, FDA conducted on-site inspections of domestic and foreign clinical and manufacturing sites related to the SMNA MRTPAs. FDA inspected clinical study sites (Indianapolis, IN and Serbia), manufacturing sites (Sweden), and a SMNA laboratory facility (Sweden), including Swedish Match manufacturing and testing facilities from April 13, 2015 – April 17, 2015 (April 13-14 at two Gothenburg sites; April 15-16 at the Kungälv site; and April 17 at the Stockholm site).

SUMMARY OF SCIENTIFIC EVIDENCE

The MRTPAs contain information specific to each of the eight General Snus products, as well as information on the health effects that SMNA posits to be generalizable to all eight of the General Snus products. Given the repetitive nature of the information provided on the health effects, the review below discusses all eight of the products together.

Claim Substantiation and Health Risks to Individuals from Use of the General Snus Products

The eight General Snus products are made from (b)(4) along with various salts, flavorings, and moisture-preserving substances. All of the products contain (b)(4) % nicotine with moisture levels between (b)(4) and pH values between (b)(4) The products adhere to the quality standard GOTHIATEK® (Rutqvist et al., 2011), which includes tolerance limits for certain constituents in the finished products. GOTHIATEK® establishes standards for constituent levels, product construction, the manufacturing process and consumer package labeling, i.e., "best before" date. The constituent standards set maximum levels which must not be exceeded for nine (9) constituents in the finished products[5]:

- NDMA: 10 ng/g (dry weight basis); 5 ng/g (as is)
- Nitrite: 7.0 µg/g (dry weight basis); 3.5 µg/g (as is)
- B[a]P: 5 ng/g (dry weight basis); 2.5 ng/g (as is)
- Arsenic: 0.5 ng/g (dry weight basis); 0.5 ng/g (as is)
- Lead: 2.0 µg/g (dry weight basis); 1.5 µg/g (as is);
- Cadmium: 1.0 µg/g (dry weight basis); 0.5 µg/g (as is)
- Chromium: 3.0 µg/g (dry weight basis); 1.5 µg/g (as is)
- Nickel: 4.5 µg/g (dry weight basis); 2.25 µg/g (as is)
- NNN+NNK: 2.0 µg/g (dry weight basis); 1.0 µg/g (as is)

In addition to GOTHIATEK®, the products also meet limits on constituents established by the Swedish National Food Agency and the Swedish Medical Product Agency for:

[redacted]

[5] These are the levels provided in the applications, which report the 2014 internal tolerance limits.

SMNA has also set tolerance levels (dry weight basis) for certain constituents in the raw tobacco as follows:

(b) (4)

FDA's review of the submitted data confirms that all eight of the General Snus products present constituent levels that fall below the limits specified by the GOTHIATEK® standard and the Swedish national regulatory limits and thus, the eight General Snus products are comparable to the products manufactured and used in Sweden and Norway, as the vast majority of the snus products sold and consumed in those countries conform to the GOTHIATEK® standard and Swedish national regulatory limits. Thus, if one were to assume that U.S. users of the product will behave similarly as those in Sweden and Norway (i.e., use the product in an equivalent manner both within and across occasions of use), it would be reasonable to conclude that U.S. users of these eight General Snus products would likely experience exposures to harmful constituents at levels similar to those experienced by users in Sweden and Norway. However, even with this assumption (an assumption for which Swedish Match did not provide sufficient evidence), the scientific evidence in the applications is not sufficient to conclude that U.S. users would not experience adverse health outcomes with respect to tooth loss, gum disease or mouth cancer.

Tooth loss and gum disease. SMNA proposes to omit from the label and advertising of the eight General Snus products "WARNING: This product can cause gum disease and tooth loss." This warning is currently required for smokeless tobacco products generally, and smokeless tobacco products have been required to bear a warning related to gum disease and tooth loss since 1986. FDA finds it reasonable to believe that the public would conclude that the removal of the warning for particular products indicates that the statement is no longer accurate with respect to these products. Omission of this warning from a subset of smokeless tobacco products therefore indicates that unlike other smokeless tobacco products, the eight General Snus products *cannot* cause gum disease or tooth loss. 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 gum disease or tooth loss. It should be noted that this is not an implied claim that the products pose *lower* risk of gum disease or tooth loss as compared to other smokeless tobacco products.

FDA's understanding and characterization of this claim is consistent with the understanding of this proposed modified risk claim reached by the Tobacco Product Science Advisory Committee (TPSAC). The committee recognized that an existing body of evidence links smokeless tobacco products generally to increased gum disease and tooth loss risk. Accordingly, although initially posed a question about whether the products pose risks of gum disease and tooth loss, after deliberation, the committee asked that the question be changed to: "Does the evidence support that these snus products do not pose risks of gum disease to individual users of these products?" (p. 368 TPSAC). Indeed, it appears that the applicant understood the claim in the same way. (see, e.g., p. 400 of the applications that there is a "lack of convincing scientific evidence linking use of Swedish snus to clinically significant gum disease and tooth loss.")

After conducting a thorough assessment of the scientific substantiation of the claim that the eight General Snus products cannot cause gum disease or tooth loss, FDA determined that the claim is not substantiated. Although the products potentially expose users to lower levels of some harmful constituents than other smokeless products, the data do not support the conclusion that the use of the eight General Snus products would result in different gum or dental health outcomes than traditional U.S. moist snuff and other smokeless tobacco products. SMNA does not present, nor can FDA infer, a biologically plausible rationale for why the use of the eight General Snus products would result in different levels of irritation or inflammation of the tissue within the oral cavity than that which results from the use of other smokeless tobacco products. To the contrary, as explained by Dr. Scott Tomar, DMD, a special government consultant invited to participate at the TPSAC meeting: "One of the properties of tobacco is delayed soft tissue wound healing, so it actually impairs the ability of the periodontal tissues to repair themselves. That, combined with local irritation, is probably what accounts for a good portion of the gingival recession."

The scientific evidence indicates that the use of these products, as actually used by consumers in Sweden and Norway, increases the risks of certain outcomes classified as gum disease or tooth loss, or precursors to gum disease and tooth loss. Studies submitted by SMNA, as well as others reviewed by FDA, indicate that the use of Swedish manufactured snus products decreases periodontal ligament cell growth to a degree comparable to U.S. smokeless products (Andersson et al., 2006) and results in dysplasia of crevicular epithelium (the tooth support structure) (Hirsch et al., 1984; Hirsch et al., 1983), both outcomes which lead to the onset of tooth loss and gum disease. Furthermore, some epidemiological studies demonstrate an association between the use of Swedish snus products and other precursors to tooth loss and gum disease, such as gingivitis and gingival recession. For example, one study found an association between snus use and gingival recession in youth (Monten et al. 2006) and another found an association between snus use and tooth wear in adults (Ekfeldt et al. 1990). Although some studies appear to show no association between the use of the Swedish snus products and gum disease and its precursors, the evidence for the lack of association is based on cross-sectional studies (which cannot establish temporality), studies of youth and young adults (who may not have used the products for sufficient duration to exhibit the symptoms of periodontal disease), and studies with very few users of snus. The overall evidence supports that the eight General Snus products that are the subject of the applications pose risks to users with respect to tooth loss and gum disease. In conclusion, the eight products *can* cause gum disease and tooth loss and therefore, the claim is not substantiated.

Mouth cancer. SMNA proposes to omit from the label and advertising of the eight General Snus products "WARNING: This product can cause mouth cancer." This warning is currently required for smokeless tobacco products generally, and smokeless tobacco products have been required to bear a warning related to mouth cancer since 1986. FDA finds it reasonable to believe that the public would conclude that the removal of the warning for particular products indicates that the statement is no longer accurate with respect to these products. Omission of this warning from a subset of smokeless tobacco products therefore 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. It should be noted

that this is not an implied claim that the products pose *lower* risk of mouth cancer as compared to other smokeless tobacco products.

FDA's understanding and characterization of this claim is consistent with the understanding of this proposed modified risk claim reached by the Tobacco Product Science Advisory Committee (TPSAC). The committee recognized that an existing body of evidence clearly links smokeless tobacco use to increased oral cancer risk. Accordingly, although initially posed a question about whether the products pose risks of oral cancer, after deliberation, the committee asked that the question be changed to: "Does the evidence support that these snus products do not pose risks of oral cancer to individual users of these products?" (p. 380 TPSAC). Indeed, it appears that the applicant understood the same way (see e.g., p. 418 of the applications, stating that: "Overall, relative risks for snus users do not suggest a relationship between snus and oral cancer and further indicate that snus users are at no greater risk of developing oral cancer than non- or never-users of tobacco.")

After conducting a thorough assessment of the scientific substantiation of the claim that the eight General Snus products cannot cause mouth cancer, FDA determined that the claim is not substantiated. SMNA provides information from toxicological studies, clinical studies and long-term epidemiological data from decades of snus use in Sweden. Although the eight General Snus products contain significantly lower levels of certain harmful carcinogens than other smokeless tobacco products currently in the U.S. market, the products contain nitrosamines, including NNN, which have been demonstrated to cause cancer, including cancers of the mouth and therefore still retain increased cancer risk to snus users compared to non-users.

Smokeless tobacco products generally have been demonstrated to cause mouth cancer. In 1986, the Surgeon General released a report concluding that smokeless tobacco use increases the risk for cancers of the oral cavity (USDHHS, 1986). In 2007, the International Agency for Research on Cancer (IARC) classified smokeless tobacco as carcinogenic to humans (Group 1) and concluded that smokeless tobacco causes cancer of the oral cavity, which was reaffirmed in 2012 (IARC, 2007, 2012). In a 2014 report, the National Cancer Institute also concluded that smokeless tobacco products cause cancer of the oral cavity, among other health effects (National Cancer Institute and Centers for Disease Control and Prevention, 2014).

Scientific evidence demonstrates that smokeless tobacco products generally contain tobacco-specific nitrosamines, including NNN and NNK, which IARC has concluded are known human carcinogens (IARC 2007, 2012). Both NNN and NNK are strong carcinogens in laboratory animals. NNN, in particular, is a potent oral carcinogen (Balbo et al., 2013) and induces oral tumors when applied to the oral cavity. Toxicological studies, as well as clinical pharmacokinetic studies, sponsored by SMNA indicate that use of the eight General Snus products, as well as similar snus products manufactured in Sweden, like use of other smokeless tobacco products, exposes users to NNN and NNK. Together, NNN and NNK are the most prevalent carcinogens in Swedish snus.

From a toxicological standpoint, review of available data indicates that use of Swedish snus poses an oral cancer risk. Oral exposure to NNN and NNK from the eight General Snus products [redacted] NNK/g tobacco; [redacted] µg NNN/g tobacco) is considerably less than exposure from cigarette smoke (Hoffman et al., 1979; Hoffman et al., 1974; Benowitz et al., 2012) and

smokeless tobacco not of Swedish origin (0.829 µg NNK/g tobacco; 2.874 µg NNN/g tobacco) (Benowitz et al., 2012). However, no threshold dose has been established for either NNN or NNK carcinogenicity. SMNA did not provide toxicological evidence to the contrary. In the absence of a threshold dose, there is no biological rationale to conclude no increased mouth cancer risk from the use of the eight General Snus products. Specifically, in the absence of data that supports a dose threshold below which the carcinogenicity of a compound can be shown not to occur, it is standard toxicological practice to assume a linear relationship between the dose of a carcinogen and the increased cancer incidence it induces (Crump et al., 1976). This assumption is particularly applicable to carcinogens that directly interact with DNA, such as the TSNAs. Thus, as dose is decreased, cancer incidence is understood to decrease in a linear fashion, but not be eliminated, because no threshold has been established. That is, increased carcinogenicity risk can reasonably be expected at any level of NNN or NNK above zero. Applied here, this leads to the conclusion that the TSNA levels present in the products listed in the MRTPAs carry increased risk of carcinogenicity relative to non-use, even though this risk may be lower than the risk presented by cigarettes and some other smokeless tobacco products. While the applicant did submit several genotoxicity studies of representative snus tobacco in the MRTPAs, the most substantive, relevant genotoxicity study of modern Swedish snus comes from Coggins et al. (2012). Although Coggins et al. (2012) and the genotoxicity studies submitted with these MRTPAs that Coggins et al. (2012) supplements are not sufficiently rigorous to render an unqualified conclusion, both suggest mutagenic potential. Thus, the totality of the evidence from *in vitro* and *in vivo* studies indicates that products listed in the applicant's submission present an increased oral cancer risk to tobacco users compared to non-use.

With respect to the epidemiological evidence, Furthermore, the most recently study published study of Swedish snus and oral cancer[6] reported a three-fold increase in the risk of oral cancer associated with ever daily use of snus compared with never daily use (Roosaar et al., 2008). In this cohort in Uppsala County, Sweden, ever daily Swedish snus use was associated with an increase in the risk of oral cancer (RR=3.1, 95% CI=1.5-6.6), after adjusting for calendar period, area of residence, alcohol consumption, smoking, and an age by smoking interaction. When restricted to never smokers, substantially lowering the number of subjects and thus, the statistical power, the association was still elevated but no longer statistically significant (RR=2.3, 95% CI=0.7-8.3) (Roosaar et al., 2008).

Although the overall body of epidemiological evidence examining the use of Swedish snus and the incidence of mouth cancers among Swedish and Norwegian users has been inconsistent, many of the studies may not have been statistically powered to detect moderate increases in oral cancer risk. One study observed no association among those that currently or ever use Swedish snus (compared with never Swedish snus use), however, an elevated risk, albeit not statistically significant, was observed among former users of Swedish snus, including ever smokers (OR=1.5, 95% CI=0.8-2.9) as well as never smokers (OR=1.8, 95% CI=0.9-3.5) (Schildt et al., 1998). In Lewin et al. 1998, current regular use of at least 1 package per week (compared to never tobacco use) was not associated with oral cancer after adjusting for age, region, alcohol, and smoking (OR=1.0, 95% CI=0.5-2.2) (Table 3.6). However, ever regular Swedish snus use

[6] Due to variability in definitions of mouth cancer in the epidemiological studies, the discussion here generally uses the term "oral" cancer in lieu of "mouth" cancer.

(OR=1.4, 95% CI=0.8-2.4) and former Swedish snus use (OR=1.8, 95% CI=0.9-3.7) were associated with elevated but nonsignificant risks of oral cancer. Evaluated only for head and neck cancer (which includes cancers of the oral cavity), no dose-response was observed for duration and total consumption, but an elevated but non-significant risk was observed for higher intensity of usage (≤50 grams per week, OR=0.8, 95% CI=0.5-1.3; >50 grams per week, OR=1.6, 95% CI=0.9-2.6). In a Norwegian cohort, no elevated risk of oral cancer was observed for regular current Swedish snus use (RR=1.13, 95% CI=0.45-2.83), regular ever use (RR=1.1, 95% CI=0.5-2.41), and regular former use (RR=1.04, 95% CI=0.31-3.5) compared with never or occasional use (Boffetta et al., 2005). In a Swedish Construction Worker cohort analysis restricted to never smokers, no association was observed for oral cancer and current (RR=0.9, 95% CI=0.4-1.8), ever (RR=0.8, 95% CI=0.4-1.7), and former Swedish snus use (RR=0.7, 95% CI=0.1-5.0) compared to never tobacco use (Luo et al., 2007). Other studies did not observe any elevated risk of oral cancer associated with current (OR=1.1, 95% CI=0.5-2.5) and ever Swedish snus use (OR=0.7, 95% CI=0.3-1.3) as compared with never snuff use after adjusting for alcohol and smoking (Rosenquist et al. 2005).

While the six epidemiological studies described above had several important strengths, including the use of population and cancer registries, high participation rates, and adjusted analyses, FDA identified a number of limitations, which limit the ability of these studies to support any conclusions about the association between the use of the eight General Snus products and the incidence of mouth cancer. Indeed, given many of the limitations, study analyses could have underestimated this association.

Study limitations included, for example, variability in the definition of "mouth" cancer across studies - some of which excluded outcomes that could be defined as mouth cancers - and low numbers of observed cases in each study. With respect to the definition of mouth cancer, some case-control studies defined the outcome as squamous cell oral cancer cases, histopathologically verified, and reported to the Regional Cancer Registry (Schildt et al., 1998), whereas others defined the outcome as head and neck cancer consisting of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx, larynx, and esophagus. Among submitted cohort studies, some excluded lip cancers (Boffetta et al., 2008), salivary gland cancer and pharyngeal cancer (Luo et al., 2007), all of which could reasonably be defined as cancers of the mouth.

Additionally, the number of exposed cases tended to be small in most studies, thereby potentially limiting their ability to detect smaller associations. In some studies, there was also a potential for residual confounding with other behaviors such as smoking and drinking alcohol. Some analyses included only never smokers in order to minimize the potential for residual confounding with smoking; however, this restriction reduces the precision of estimates of risk for oral cancers. Furthermore, cohort studies assessed baseline exposure but did not repeat the assessment; thus, if significant numbers of users quit during the duration of the studies, analyses could underestimate the association of current Swedish snus with oral cancer.

The products that are the subject of these applications represent a subset of smokeless tobacco products and, therefore, the available evidence is examined in this context. Smokeless tobacco products, generally, have been demonstrated to cause oral cancer. The most recently published study of Swedish snus products and oral cancer risk observed a large and statistically significant association (Roosaar, 2008). The lack of a consistent association between oral cancer and the

use of Swedish snus observed in other epidemiological studies may be due to the lack of precision in the estimates of risk, the variability in the definition of oral cancer, and other study limitations. Additionally, the products contain known carcinogens and toxicological or other data establishing a threshold dose for those carcinogens does not currently exist. Accordingly, the proposition that these products do not pose an increased risk of oral cancer is not based on biological evidence and lacks any biologically plausible rationale. Taken as a whole, the available scientific evidence supports the statement that smokeless tobacco products in general and these products in particular "can cause mouth cancer" and therefore, the claim is not substantiated.

Health risks as compared to cigarette smoking. SMNA proposes to revise the currently required "WARNING: This product is not a safe alternative to cigarettes" on the label and advertising of the eight General Snus products, 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."

After conducting a thorough assessment of the scientific substantiation of the claim, FDA determined that the claim may be substantiated, but only in part. The scientific information provided by SMNA demonstrates that the eight General Snus products are manufactured in a manner that can expose users of the products to levels of constituents at levels that are lower than smoking and, likely, most other smokeless tobacco products currently being marketed in the U.S. Although resting on certain assumptions about manner of use, including that U.S. users will use the products in a manner similar to users in Sweden or Norway (e.g., frequency or intensity of usage; exclusive snus use versus dual use with cigarettes), 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.

SMNA provided epidemiological evidence to demonstrate that the risks to individual users of these General Snus products exclusively differ from the risks to individuals who smoke cigarettes, but the differences in risk across a broad range of health outcomes varies. For instance, there are differences between the products that are the subject of these applications and cigarettes in terms of risk of lung and respiratory disease, including COPD. However, the evidence indicates that for other outcomes the use of the products does not pose substantially lower risks. For example, the risks to the fetus from using the products during pregnancy are relatively comparable to those from smoking. For other outcomes, such as the risk of fatal cardiovascular events, pancreatic cancer, and diabetes, the magnitude of difference in risks between use of the products and cigarette smoking is unclear. In addition, historical data indicate that nicotine exposures are similar between Swedish snus and cigarettes (Benowitz et al., 1982; Digard et al., 2013). Thus, it is expected that the General Snus products will expose individuals to nicotine levels that are similar to smoking cigarettes, producing reinforcing effects similar to smoking.

The eight General Snus products pose significant risks to health to individual users of the products. However, the data support that the eight General Snus products could potentially reduce the risks of certain tobacco-related disease to current users of tobacco products, particularly smokers. Therefore, the use of the eight General Snus products has the potential to

reduce the risks to individual tobacco users. However, the use of the products may not substantially reduce all of the health risks to individual tobacco users. Furthermore, the reduction in health risks to an individual is dependent on patterns of use of the snus products, i.e., whether individual users switch completely to the use of the eight General Snus products (as observed in male populations in Sweden and Norway). The evidence suggests that reduction in risks would likely accrue to those that switch completely to the General Snus products but we cannot conclude that it would accrue to those users of the eight products that continue to smoke cigarettes.

The following section discusses tobacco use behavior and the potential impact of marketing the product with the proposed modified risk information on current users and non-users of tobacco products. The applicant did not provide evidence regarding how the removal of the mouth cancer and gum disease/tooth loss warnings would impact consumer behavior or whether consumers would understand that modified risk information in the context of total health (*e.g.*, the applicant's Consumer Perception Study did not assess how consumers would understand removal of the warnings or how the removal would impact consumer behavior). Consequently, the following section generally addresses evidence related only to the applicant's express modified risk claim about health risks as compared to cigarettes.

Tobacco Use Behavior and Impacts on the Population as a Whole. As stated earlier, determining whether a proposed modified risk tobacco product meets the section 911(g)(1) standard includes an assessment with respect to the benefit of the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. This assessment considers the impact of the proposed modified risk tobacco products on consumers, including on

- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product (911(g)(4)(B)); and
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product (911(g)(4)(C)).

As concluded in the previous section, while resting on certain assumptions about manner of use, there is evidence to support that use of the eight General Snus products as compared to smoking cigarettes would significantly reduce harm and the risk of certain tobacco-related diseases to individual tobacco users (i.e., lung cancer and COPD). This section assesses the potential impacts of the inclusion of "WARNING: No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes" on the label and advertising of the eight products on tobacco use behavior among non-users and current users of tobacco products.

The applications did not include an actual use study of the eight products to provide information about how U.S. users might use the products, such as whether U.S. tobacco users would adopt the products, switch to exclusive use of the eight products, or use the products while continuing to use other tobacco products, e.g., cigarettes. Instead, to assess the impact of the proposed MRTPs on consumers, including on the increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified

risk tobacco products and the increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco products, the applications provided behavioral epidemiological data from Sweden and Norway as well as some data from a Consumer Perception Study related to interest and intention to use the General Snus products, perceptions of the products, and comprehension of the modified risk information.

Likelihood of Product Use. The information on the behavior of the Swedish and Norwegian populations with respect to snus type products has limited applicability to the U.S. population. Snus products are currently available in the U.S. but there has been very low use of similar types of products by U.S. tobacco users. Snus type products comprise approximately 5% of the U.S. market for smokeless tobacco with General Snus brand products comprising approximately 6% of the market for snus products (Delnevo et al., 2014). Snus products are much more popular among Swedish tobacco users and, as SMNA acknowledges, snus holds status as a traditional Swedish and Norwegian product. Other differences, such as in consumer tastes and preferences, exposure to marketing, and the sociocultural aspects of the product use will also determine whether U.S. consumers, smokers in particular, adopt the General Snus products. SMNA describes a historical shift away from smoking to snus use that occurred in Sweden, particularly among male smokers, but does not provide evidence or information to suggest that a similar process could or would occur in the U.S. population. In contrast, recent research indicates that U.S. cigarette smokers do not find snus to be an appealing alternative to cigarette smoking (Biener et al., 2014; Sami et al., 2012; Hatsukami et al., 2011; O'Connor et al., 2011).

SMNA included a review of the literature on consumer perceptions of snus products and also conducted a Consumer Perception Study to assess the impact of the modified risk information on intentions to use the eight products, as well as attitudes, perceptions and comprehension. FDA identified other research, among U.S. consumers, and included that information in its review. In general, the literature suggests that providing detailed information about the relative harms of tobacco products can affect smokers' reported likelihood of trying smokeless tobacco (Borland et al., 2012) and that smokers who read such information change their perceptions of harm from smokeless tobacco and their beliefs about how cigarette smoking harms health (Borland et al., 2012). Interestingly, in Sweden and Norway, despite the relatively high prevalence of snus use, the majority of people do not perceive snus products to be less harmful than smoking (Wikmans et al., 2010). Labeling and marketing of snus in Sweden has not referred to the product as reduced risk. Thus, it appears likely that one of the primary driving forces for the shift to snus in Sweden was the increasing stigmatization of smoking (e.g., through smoking restrictions) combined with the cultural significance of snus, which, in contrast to cigarettes, would likely carry little stigma to users in Sweden.

The Consumer Perception Study tested the impact of a revised warning statement appearing on labels of the General Snus products. Although the study attempted to assess intentions to use the products, as well as consumer comprehension of modified risk information, the study did not assess the impact of the context – within a warning or as a stand-alone promotional statement, or in the context of an advertisement – of that modified risk information. Furthermore, the stimuli (images of the product package with the label) included in the study did not present the actual proposed revised warning statement verbatim. The warning statement appearing on the label employed the phrase "a substantially lower risk" rather than the proposed "substantially lower

risks" and the statement did not include the signal word "WARNING" preceding the modified risk information.

Putting aside several issues which limit the interpretability and generalizability of the study, including the issues with the stimuli described above, reviewers assessed the results from the study by comparing responses to a question on intention to use the General Snus products between those that viewed the studied revised warning with those that viewed the currently required warnings. Of particular interest is the currently required warning that the applicant requests to revise. Among cigarette users, in general, the presence of a revised warning statement shifted the overall distribution of responses as compared to the presence of the currently required warning, with those viewing the revised warning statement being more likely to state an intention to use the snus products (20.1% vs 7.2%). Similar impacts were observed among smokers that also use other tobacco products (41.4% vs 29.3%) and tobacco users that do not smoke (49.3% vs 36%). Among imminent quitter/reducers, those exposed to the revised warning showed greater interest in the product compared to the current warnings. For non-users, those that saw the revised warning statement were less likely to report that they were not likely to use snus (*i.e.*, they were less discouraged). In general, younger non-users (18 to 24 years old) are more likely to report intentions to use than older non-users, as are non-white non-users as compared to white non-users, and higher income (over $45,000) as compared to lower income.

Conclusion. The data provided in the applications to support that the eight General Snus products would benefit the health of the population as a whole rely heavily on the assumption that U.S. users of the products will use them in a manner similar to users in Sweden and Norway. However, the lack of cultural significance of snus use in the U.S. and the general lack of acceptability of smokeless tobacco products (including snus) among smokers present significant barriers to moving smokers from cigarettes to the General Snus products. SMNA has provided some information (i.e., intentions to use) from a perception study to indicate that the message conveyed in the revised warning statement will resonate more with intended populations (e.g., smokers) than with some non-intended populations (e.g., non-users). As noted above, the message resonated with populations of particular relevance to assessing public health impact, imminent quitters/reducers, as these users may be enticed to continue use when they might otherwise have quit. However, there is a high degree of uncertainty as to whether individual users will adopt the products and switch completely to use of these products. There is also a high degree of uncertainty as to whether non-users will initiate with these products and switch to other tobacco products, including cigarettes. This uncertainty extends to whether the products, as actually used by consumers, will benefit the health of the population as a whole.

Consumer Comprehension. Comprehension of modified risk information provides additional insight on the potential behavioral impacts of the eight proposed modified risk products. For example, the products could have a negative impact if some study participants that state interest in or intentions to use the products comprehend the modified risk information in a manner that could result in unintended consequences, such as having overconfidence in the ability of the products to reduce individual risks or inaccurate beliefs that the products reduce risks of all tobacco-related diseases or do not present any significant risks. In addition, information on consumer comprehension may aid assessment of whether the advertising or labeling concerning the modified risk products enables the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of

total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products. (Section 911(h)(1)). SMNA proposes changes to the currently required warnings (removal of the gum disease/tooth loss and mouth cancer warnings and revision of the warning regarding smokeless tobacco not being a safe alternative to smoking) as opposed to separate stand-alone modified risk information because of concerns that consumers would dismiss, or not believe, the modified risk information when viewing it in the presence of a warning elsewhere on the label. Although such an effect has been demonstrated in one study, SMNA did not test to confirm whether the effect would be present in the context of these eight General Snus products.

The proposed revised warning statement includes information that is not typically used in a warning to consumers, specifically the statement includes language about the relative benefits of using the product as compared to use of another type of product. Thus consumers may not perceive this statement as a warning at all, which could impact consumer behavior as well as consumer comprehension of the modified risk information in the context of total health and in relation to all tobacco-related disease. Smokeless tobacco products are currently required to bear one of four warnings on labels and in advertisements. SMNA states that they do *"not plan to otherwise communicate, highlight, or promote the proposed modified risk claims to consumers using other labeling or advertising,"* and SMNA did not test the impact of the modified risk information in the context of any advertisements. However, if the MRTPAs were to be granted in full, then presumably a significant proportion of advertisements would bear the proposed statement (taking up 20% of the advertisement's area). In addition, the only warnings would be that the proposed MRTPs are addictive and that although no tobacco product is safe, these products pose substantially lower risks to health than cigarettes, which would not fully convey the extent of the risks that the proposed MRTPs pose.

Although SMNA conducted a study to test the impact of including modified risk information on the labels of the eight General Snus products, the Consumer Perception study was not adequately designed to assess consumer comprehension or to adequately demonstrate that consumers' will comprehend the risks of using these products. In addition to some other methodological issues, such as the issues with stimuli employed in the study as noted earlier, the study assessed comprehension by including a set of questions to participants about whether they find the information easy to read or understandable. This approach does not provide insight as to whether and what consumers understand about the risks of using the eight General Snus products after viewing the modified risk information.

Conclusion. The proposed express modified risk claim about health risks as compared to cigarettes broadly asserts a substantial reduction in risks, which may not accurately convey the risks of the use of the eight snus products to consumers. The study conducted by SMNA does not provide sufficient insight as to what consumers understand about the risks of using the eight General Snus products after viewing the modified risk information, especially in the context of a warning.

Quantification of the Impact on the Population as a Whole. Despite the limitations of FDA's ability to review the Dynamic Population Model (DPM), the information provided about the health effects of the General Snus products suggests that current smokers would reduce their risks of certain tobacco related diseases by switching completely to General Snus. However, the

applications provide insufficient information about the impacts of the proposed modified risk marketing on the behavior of current users and non-users of tobacco products, in terms of dual use, cessation and initiation of tobacco use. The uncertainty about the impacts on behavior among these groups precludes the ability to determine, with any degree of certainty, the likely overall impacts on the population. Although the applicant models a number of different scenarios of the impact to users and non-users, some result in population health benefits and some result in population health harms, and the applicant provides inadequate evidence as to which scenarios are more or less likely. Thus, we cannot conclude that the proposed General Snus modified risk tobacco products will benefit the health of the population as a whole.

Tobacco Products Scientific Advisory Committee

FDA's Tobacco Product Scientific Advisory Committee (TPSAC) convened in April 2016 to discuss the applications and provide recommendations to FDA. Meeting materials, transcripts, and summary may be found at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm434209.htm.

In general, 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.

Public Comments

Members of the public submitted comments on the publicly available modified risk tobacco product applications. In addition to comments related to legal or advocacy issues, the comments included several scientific concerns with SMNA's interpretation of the data, the relevance of data on the Swedish population for inferring likely impacts on the U.S. population, and the design of the consumer perception study. FDA identified many of these concerns during the review, and FDA considered all significant comments when making the final determination. The issues raised by those comments are addressed in the individual reviews and in the body of this TPL.

Inspections (Bioresearch Monitoring and Manufacturing)

In March and April 2015, FDA conducted inspections at clinical study sites (Indianapolis, IN and Serbia), manufacturing sites (Sweden) and an SMNA laboratory facility (Sweden), relevant to the applications. Specifically, the Office of Regulatory Affairs (ORA), accompanied by Subject Matter Experts (SMEs) from the Office of Compliance and Enforcement (OCE) and the Office of Science (OS) within the Center for Tobacco Products (CTP), conducted inspections of Swedish Match manufacturing and testing facilities at two Gothenburg sites, one Kungälv site, and one Stockholm site in Sweden and clinical study sites in Indianapolis, IN and Serbia.

The clinical site inspections included the review of paper and electronic source data, electronic case report forms, and administrative files. Documents were reviewed for issues such as: protocol adherence, randomization, informed consent, eligibility, investigational product dispensing, study endpoints, adverse events and subject final status. Overall, the inspection teams reported some missing and inconsistent data; however, they were limited, not substantive, and did not inhibit FDA's ability to make a final determination on the applications.

The manufacturing inspection included evaluation of manufacturing, product analysis, packaging, distribution, recalls and complaints, shipping, laboratory accreditation, validations, raw data, and procedures at the different sites. During one of the manufacturing inspection visits, the inspection team noted that 256 consumer complaints were received by SMNA during the period from January 2013 to April 2015, and only two of these were health-related complaints (burning of mouth/throat and esophagus). The manufacturing facilities and laboratory inspection results did not identify any issues of concern relevant to the methods used in, or the facilities or controls used for, the manufacture, processing, or packing of the tobacco products for which the applications were submitted. All inspections resulted in a VAI classification (voluntary action indicated), except the Stockholm laboratory facility inspection, which was classified as NAI (no action indicated).

SUMMARY OF INDIVIDUAL SCIENTIFIC REVIEWS

What follows is a detailed summary of the scientific reviews of the SMNA MRTPAs. Within those reviews, where appropriate, each of the three requests was assessed individually. To determine whether SMNA demonstrated that the product, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, reviews considered the health risks of the tobacco products to users of the product, including exposures to users, actual use (*e.g.*, frequency or intensity of usage; exclusive snus use versus dual use with cigarettes), and risks as compared to the use of other tobacco products, nicotine replacement therapies, or cessation. To determine whether the products will 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, reviews considered the effects of the product on tobacco use behavior among current users, effects of the product on initiation among non-users, as well as consumer perception and comprehension. This review also integrates the information to evaluate the effect on the population as a whole.

It should be noted that many studies reviewed discuss the use of "snuff" in Sweden. As noted by SMNA in the applications, "snus is and always has been the dominant smokeless tobacco product on the Swedish market, comprising more than 99% of total annual smokeless sales." Thus, the underlying assumption throughout the review is that "snuff" and "snus" refer to the same type of products in Sweden and Norway, and that Swedish and Norwegian epidemiological studies on the effects of smokeless tobacco provide data on the effects of Swedish snus.

(1) Health Risks of the Tobacco Product on Users.

This section assesses the likely health impacts of use of the eight products that are the subject of the MRTPAs on individual users of the product and how those risks compare to risks from other behaviors, such as smoking cigarettes, the use of FDA-approved medications for smoking cessation, cessation, and dual-use with other tobacco products.

(a) Potential exposures to users of the products

The chemical and physical properties of the product, including quantitative levels of constituents under the range of conditions under which the product may be used, provide some information on the potential exposures to users of the products.

Engineering

The eight General Snus products come in both portioned and non-portioned versions. Snus is an oral smokeless tobacco product in a powder form, which is manufactured using a heat treatment process. Since snus is intended to be placed in the oral cavity, specifically between the upper lip and gum, snus is made to be moist to semi-moist in order to aid in tobacco and nicotine release. Non-portioned snus (MR0000020) is not allocated into a defined serving size; instead, the consumer decides the amount per use. Portioned snus (MR0000021-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029) is allocated into a defined serving size via pouch paper.

The applications provided design parameters related to the tobacco and the pouch used in the manufacture of these products which contribute to the overall constituent yields and potential exposures to users of the product. With respect to product engineering, the products have been adequately characterized, and SMNA proposes a well-controlled manufacturing process of the products.

Chemistry

The eight General Snus products are made from (b)(4) along with various salts, flavorings, and moisture-preserving substances. SMNA indicates that all the products are designed to contain (b)(4) nicotine with moisture levels between (b)(4) and pH values between (b)(4). SMNA follows procedures to control the quality of tobacco and follows appropriate procedures for controlling HPHC levels, including storing the raw tobaccos in climate-controlled warehouses.

SMNA demonstrates that the products adhere to the internal quality standard GOTHIATEK®, which includes tolerance limits for the following nine (9) constituents in the finished products: [7]

- NDMA: 10 ng/g (dry weight basis); 5 ng/g (as is)
- Nitrite: 7.0 µg/g (dry weight basis); 3.5 µg/g (as is)
- B[a]P: 5 ng/g (dry weight basis); 2.5 ng/g (as is)
- Arsenic: 0.5 ng/g (dry weight basis); 0.5 ng/g (as is)
- Lead: 2.0 µg/g (dry weight basis); 1.5 µg/g (as is);
- Cadmium: 1.0 µg/g (dry weight basis); 0.5 µg/g (as is)
- Chromium: 3.0 µg/g (dry weight basis); 1.5 µg/g (as is)
- Nickel: 4.5 µg/g (dry weight basis); 2.25 µg/g (as is)
- NNN+NNK: 2.0 µg/g (dry weight basis); 1.0 µg/g (as is)

[7] These are the levels provided in the applications, which report the 2014 internal tolerance limits.

In addition to GOTHIATEK®, the products also meet limits on constituents established by the Swedish National Food Agency and the Swedish Medical Product Agency:

(b) (4)

To meet these standards, SMNA has set tolerance levels (dry weight basis) for certain constituents in the raw tobacco as follows:

(b) (4)

Microbiology

Constituents in tobacco products have been shown to change as a function of storage time (Djordjevic et al., 1993). SMNA submitted results from stability testing of different batches of the products in MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029 and demonstrated product stability in the packaging material intended to be marketed. SMNA also demonstrated that the recommended retail shelf lives of [redacted] for loose snus, [redacted] for pouched snus (White and Original) and [redacted] for "Dry" pouched snus are supported by the provided data.

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

(b) Actual use of the product to assess exposures to individual users of the product

Clinical Pharmacology

Traditionally, use of snus products in Sweden varies from that of American smokeless tobacco (SLT) users in terms of product placement in the mouth and expectoration. As noted above, Swedish snus is typically placed between the upper lip and gum and does not require expectoration while American SLT is usually placed between the lower lip and gum and requires expectoration during use.

SMNA's submission consists largely of data obtained outside the United States. Ideally, the data provided in the submission would be on or generalizable to U.S. SLT users in terms of actual use. However, the Swedish population appears to be more homogenous, have a higher socioeconomic status, and greater access to healthcare services including dental care relative to

individuals in the U.S. Thus, the data obtained from Sweden might not be applicable to U.S. SLT users.

According to the reviewer, the clinical pharmacology studies did not include the actual products that are the subject of the applications. Nor did SMNA provide adequate bridging information to enable the reviewer to infer that the eight products would present similar exposures to nicotine and other compounds as the products included in the studies. The reviewer, however, did not consider information from other reviews, which, as noted earlier, demonstrate that the studies appear to use other Swedish snus products that meet the GOTHIATEK® standard, and therefore are similar in design, construction and constituent levels as the eight General Snus products that are the subject of the applications. Accordingly, if U.S. users of the products behave similarly to those in Sweden and Norway (i.e., use the products in an equivalent manner both within and across occasions of use), then it would be reasonable to conclude that the eight products would present similar exposures to nicotine and other compounds as the products in the studies.

Additionally, none of the studies presents a direct comparison of the pharmacokinetics of nicotine and other harmful compounds (e.g., HPHCs and TSNAs) from the use of the snus products with the use of cigarettes or other smokeless tobacco products. The absence of these comparisons limits our ability to use these particular studies to draw conclusions about user exposures relative to other tobacco product use.

Three of the studies evaluated the nicotine pharmacokinetics after single and multiple administrations of Swedish snus. One study measured the pre and post use levels of lead, cadmium, nicotine and TSNAs from Swedish snus to measure the in vivo extraction and dosing of these compounds. The active moieties (e.g., nicotine) in blood plasma were appropriately identified and measured to assess pharmacokinetic parameters. However, the studies did not include measurements to evaluate exposure-response relationships (e.g., systemic exposures to TSNAs and HPHCS as function of dose or use of the product).

The only physiological response that was assessed in the clinical studies was supine heart rate measured at pre-dose and 10, 20, and 30 minutes post administration of a single dose of two Swedish snus products and Nicorette gum in study SM WS 06. SMNA has not attempted to correlate heart rate and nicotine plasma concentrations. Response endpoints such as exposure to toxicants and disease development have not been measured in the submitted studies. Thus, we are unable to characterize the exposure-response relationship for health impact of the products which are subject of these applications.

Three clinical pharmacology studies evaluated the nicotine pharmacokinetics after single and multiple administrations of Swedish snus. The nicotine Cmax values after use of a single snus portion ranged from about 10.8 – 29 ng/mL, with the highest Cmax values reported after use of “General” and “Catch” brands. Nicotine pharmacokinetics were dose proportional, a finding consistent with previous literature reports (Digard et al., 2013). Estimations of area under the curve (AUC) values are hampered by the use of varied time collection periods across studies and varied product use characteristics (e.g., amount and duration). The format of the products (e.g., loose or pouched) had little influence on PK parameters.

After overnight abstinence, time to maximum nicotine plasma concentration (Tmax) appeared to be dependent on product use time. Similarly, the other studies examining Swedish snus reported Tmax values between 30 and 37 minute (Holm et al., 1992; Lunell et al., 2011; Lunell et al., 2005). By way of comparison, after cigarette smoking, nicotine reaches peak venous concentrations within 8 minutes and peak arterial plasma concentrations within 5 minutes (Arcavi et al., 2004; Benowitz et al., 2009; Gori et al., 1986; Lunell et al., 2000; Lunell et al., 2011; Schaedeli et al., 2002).

Although a direct comparison of nicotine PKs after the use of Swedish snus and cigarettes was not provided in these pharmacokinetic studies, historical data indicate that nicotine exposures are similar between Swedish snus and cigarettes (Benowitz et al., 1982; Digard et al., 2013), although the time to maximum nicotine plasma concentrations likely differs. Thus, as used by consumers, the General Snus products will expose individuals to nicotine levels that are similar to traditional combusted tobacco products (e.g., cigarettes). The systemic exposure to nicotine provided by use of the snus products is expected to produce reinforcing effects and have an abuse potential.

Conclusion. Although more definitive conclusions about user exposures could have been made from actual use studies with the products that are the subject of the applications, the studies submitted to support the snus products provide some insight on the potential exposures from use of the products, particularly nicotine. The historical data indicates that systemic exposure to nicotine provided by use of other Swedish snus products is expected to produce reinforcing effects and have an abuse potential.

(c) The health risks of the tobacco product compared to other tobacco products on the market

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, 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. 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.

Mouth Cancer

Toxicological Studies

As stated above, the omission of the warning related to mouth cancer is an implicit modified risk claim that, compared to other smokeless tobacco products, these products cannot cause mouth cancer. From a toxicological standpoint, review of available data indicates that use of Swedish

snus carries an oral cancer risk. While SMNA did submit several genotoxicity studies in the MRTPAs, the most substantive, relevant genotoxicity study of modern Swedish snus is Coggins et al. (2012). The products that were tested were not adequately evaluated in either Coggins et al. (2012) or in the studies Coggins et al. (2012) supplements (Study Nos. 1138/17, 1138/18, 1138/19 and 1138/20). Coggins et al. (2012) and all four of those genotoxicity studies nevertheless imply that the snus products tested may be mutagenic in some formulations and at some levels of exposure. Another study, Jansson et al. *(*1991), characterizes the carcinogenic potential of Swedish snus as 'low' according to carcinogenicity prediction by battery selection. Further, several studies identified in the research review of Swedish snus-related toxicology literature report potentiation of tobacco-specific nitrosamine (TSNA) tumorigenicity by HSV-1 infection. HSV-1 infection is extremely common, with 65% of the U.S. population having antibodies to HSV-1 (Wald et al., 2007).

The assessment of harmful and potentially harmful tobacco constituents (HPHCs) forms a critical component of the toxicological evaluation of these MRTPAs. Several of these HPHCs, including the tobacco-specific nitrosamines, NNK and NNN, are listed as Group 1 human carcinogens by the International Agency for Research on Cancer (IARC, 2007). The toxicology review team's assessment is that while the products submitted in these MRTPAs do in fact have lower levels of HPHCs, including NNN and NNK, as compared to cigarettes and many other oral tobacco products, the levels present in these products nonetheless still retain increased cancer risk, including mouth cancer, to snus users compared to non-users. While greatly reduced, NNN [redacted] µg/g tobacco) and NNK [redacted] µg/g tobacco) are present in the proposed modified risk products described in MR0000020-MR0000022, MR0000024-MR0000025, MR0000027-MR0000029. NNN and NNK are both mutagenic carcinogens for which a linear dose-response must be inferred for carcinogenesis. Indeed, smokeless tobacco products in which TSNAs were below the limit of detection tested positive for mutagenicity in the Ames assay, albeit to a much less extent than combusted smoke condensates (Rickert et al., 2007).

In the absence of data that supports a dose threshold below which the carcinogenicity of a compound can be shown not to occur, it is standard toxicological practice to assume a linear dose-response relationship between the dose of a carcinogen and the increased cancer incidence it induces (Crump et al., 1976). This assumption is particularly applicable to carcinogens that directly interact with DNA, such as the TSNAs. Thus, as dose is decreased, cancer incidence is predicted to decrease in a linear fashion, but not be eliminated, because no threshold has been demonstrated. Applied here, this principle leads to the conclusion that the TSNA levels present in the eight General Snus products carry increased risk of carcinogenicity relative to non-use, even though this risk may be lower than the risk presented by other tobacco products. Thus, overall, the totality of the evidence from the *in vitro* and *in vivo* studies indicates that eight General snus products present an oral cancer risk to tobacco users.

Epidemiological Studies

Six studies examined the association between Swedish snus and oral cancer, including three prospective cohort and three population-based case-control studies. Five of the six studies were conducted in Sweden, and one cohort study was conducted in Norway. All three cohorts began in the late 1960s or early 1970s and all have 20 to 30 years of follow up through linkages to national cancer and death registries. Boffetta et al. (2005) is based on a cohort of approximately

10,000 Norwegian males and assessed the association between Swedish snus use and risk of incident oral cavity and pharyngeal cancer, as well as esophageal, stomach, pancreatic, lung, kidney, bladder cancer. In Luo et al. (2007) a subset of 126,000 never smoking males within the Swedish Construction Worker cohort (total 280,000 men), was analyzed for associations between Swedish snus and oral, pancreatic, and lung cancers. In Roosaar et al. (2008) a subset of 10,000 men within the Uppsala County cohort from central Sweden (total 20,000) was analyzed for associations between Swedish snus and incident oral, smoking-related cancer, and any cancer, as well as death due to all causes, cardiovascular disease, cancer, and respiratory disease.

In Schildt et al. (1998) 354 cases were identified through the Regional Cancer Registry of Northern Sweden and were individually-matched to 354 controls identified in National Population Registry and National Registry for Causes of Death. In Lewin et al. (1998) 545 cases were primarily identified through weekly conferences among 6 different Ear, Nose and Throat (ENT) departments in southern Sweden, and 641 controls were identified through the population register in Stockholm and southern region. In Rosenquist et al. (2005) 132 cases were identified from weekly meetings between 2 departments, and 320 controls matched to cases 3:1 were selected from the Swedish Population Register.

Definitions of the exposure varied among the studies. Among the cohort studies, exposure to Swedish snus was defined as “ever daily use at entry” in Roosaar et al. (2008) “regular current use” in Boffetta et al. (2005) and “current snuff use” in Luo et al. For all three cohort studies, exposure was assessed at baseline only. Among the case-control studies, active snuff use in Schildt et al. (1998) was defined as use within 1 year of the case’s diagnosis date; ever snuff use in Lewin et al. was defined as ever regular use of "1 package (50 grams) per week” and current users as using oral snuff use within “1 year prior to the time of the interview”; current snuff use in Rosenquist et al. (2005) was use within 6 months of the time of the interview.

Definitions of the outcome also varied among the studies. Among the cohort studies, all of which identified cases through registry linkage, Roosaar et al. (2008) had the broadest definition of oral and pharyngeal cancer, while Boffetta et al. (2005) excluded lip cancers from their definition of oral cavity and pharyngeal cancer, and Luo et al. excluded salivary gland cancer and pharyngeal cancer from their definition of oral cancer. Among the case-control studies, Schildt et al. (1998) defined the outcome as squamous cell oral cancer cases, histopathologically verified, and reported to Regional Cancer Registry of Northern Sweden.; Lewin et al. defined the outcome as head and neck cancer consisting of squamous cell carcinoma of the oral cavity, oro and hypopharynx, larynx, and esophagus (no ICD codes) and identified 90% of the cases at weekly multidisciplinary conferences and the remaining 10% of cases from the regional cancer registry. Rosenquist et al. (2005) identified oral and oropharyngeal squamous cell carcinoma at weekly meetings between 2 hospitals in region.

Although many of the epidemiological studies of Swedish snus may not have been statistically powered to detect moderate increases in oral cancer risk, the most recent published epidemiological study found a statistically significant increased risk (Roosaar et al., 2008). In the Uppsala County cohort, ever daily Swedish snus use was significantly associated with a three-fold increase in the risk of oral cancer (RR=3.1, 95% CI=1.5-6.6) after adjusting for calendar period, area of residence, alcohol consumption, smoking, and the interaction between age and smoking. When restricted to never smokers, substantially lowering the number of

subjects and thus, the statistical power, the association was still elevated but no longer significant (RR=2.3, 95% CI=0.7-8.3). In the Norwegian cohort, based on RR estimates adjusted for age, smoking cigarettes, cigars and pipe, no elevated risk of oral cancer was observed for regular current Swedish snus use (RR=1.13, 95% CI=0.45-2.83), regular ever use (RR=1.1, 95% CI=0.5-2.41), and regular former use (RR=1.04, 95% CI=0.31-3.5) compared with never or occasional use. In the Swedish Construction Worker cohort analysis restricted to never smokers and adjusting for age and BMI, no association was observed for oral cancer and current (RR=0.9, 95% CI=0.4-1.8), ever (RR=0.8, 95% CI=0.4-1.7), and former Swedish snus use (RR=0.7, 95% CI=0.1-5.0) compared to never tobacco use. Additionally, no dose-response relationship was observed for grams per day (p-trend=0.8).

In Schildt et al. (1998), no association was observed for active and ever Swedish snus use (compared with never Swedish snus use) in analyses conditioned on age, sex, county (and date of death for deceased cases) (ORs 0.7 to 0.9). However, ex-Swedish snus use was associated with an elevated but non-significant risk of oral cancer in analyses that included ever smokers (OR=1.5, 95% CI=0.8-2.9) and those restricted to never smokers (OR=1.8, 95% CI=0.9-3.5). Among never smokers, lifetime Swedish snus consumption less than and greater than 156 kg were not statistically significant associated with oral cancer (less than 156 kg, OR=0.8, 95% CI=0.4-1.6; greater than 156 kg, OR=1.3, 95% CI=0.6-2.6). In Lewin et al. 1998, current regular use of at least 1 package per week (compared to never tobacco use) was not associated with oral cancer after adjusting for age, region, alcohol, and smoking (OR=1.0, 95% CI=0.5-2.2). However, ever regular Swedish snus use (OR=1.4, 95% CI=0.8-2.4) and former Swedish snus use (OR=1.8, 95% CI=0.9-3.7) were associated with elevated but nonsignificant risks of oral cancer. Evaluated only for head and neck cancer, no dose-response was observed for duration and total consumption, but an elevated but non-significant risk was observed for higher intensity of usage (≤50 grams per week, OR=0.8, 95% CI=0.5-1.3; >50 grams per week, OR=1.6, 95% CI=0.9-2.6). Rosenquist et al. (2005) did not observe any elevated risk of oral cancer associated with current (OR=1.1, 95% CI=0.5-2.5) and ever Swedish snus use (OR=0.7, 95% CI=0.3-1.3) as compared with never snuff use after adjusting for alcohol and smoking. Former Swedish snus use was associated with a significantly reduced risk of oral cancer (OR=0.3, 95% CI=0.1-0.9), in contrast with the previous two case-control studies. No dose-response was observed for duration or exposure time (hours per day). Although the point estimate was greater at a higher daily consumption, the confidence intervals for these estimates were wide (1 to 14 grams per day, OR=0.9, 95% CI= 0.3-2.5; >14g/day, OR=1.7, 95% CI=0.5-5.7). Finally, in 2001, the Institute of Medicine produced a report titled "Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction", which noted that "the use of snus in Sweden has generally not been associated with oral cavity cancer" (IOM, 2001). However, additional evidence has been published since the release of that report, including the findings from Roosaar et al. (2008), which observed a statistically significant, three-fold increase in the risk of oral cancer associated with the use of Swedish snus, after controlling for smoking, alcohol, and other potential confounders. Therefore, this finding of the 2001 IOM Report does not reflect the most current scientific evidence.

The six epidemiological studies on the use of Swedish snus and risk of oral cancer had several important strengths, including the use of population and cancer registries, high participation rates, and adjusted analyses. However, the studies also had a number of limitations that could result in an underestimation of the association between snus use and mouth cancer. For example,

the number of exposed cases tended to be small in most studies, thereby potentially limiting their ability to detect smaller associations. Some study authors raised the concern about the potential for residual confounding by smoking, even in smoking-adjusted analyses and the potential for changes in behavior over time for cohort studies. If significant numbers of snus users quit over time but only baseline exposure is assessed, any potential associations between snus use and oral cancer risk would be diluted. Analyses restricted to never smokers may minimize residual confounding, but result in less precise estimates. Because only baseline exposure was used in the cohort studies with no reassessment of the exposure, studies of current Swedish snus use could result in underestimates of an association if significant numbers of Swedish snus users quit over time. In addition, heterogeneity in the definitions of snus use and cancer outcomes makes interpretation of the overall body of evidence challenging.

An additional concern was raised about the lack of epidemiological evidence in women, given that most Swedish snus users are, and historically have been male. However, the relative risks associated with smoking do not seem to differ substantially by sex (Thun et al., 2013). Studies of other types of smokeless tobacco, including studies in the U.S., India and Pakistan, have not consistently shown differences in oral cancer risks by sex (IARC, 2007). Finally, we are not aware of a biological rationale for differences in Swedish snus risks between men and women who use the products comparably.

Conclusion with respect to mouth cancer. 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.

Tooth Loss and Gum Disease

Toxicological Studies

There is limited toxicological data on tooth loss related to smokeless tobacco or snus and the mode of tooth loss and causative tobacco constituents are presently unknown. However, two submitted peer-reviewed articles did relate Swedish-source snus to decreased periodontal ligament cell growth to a degree comparable to that of American snuff. Two additional studies of Swedish-source snuff report dysplasia of crevicular epithelium (tooth support structure) which is particularly exaggerated by co-infection with herpes simplex virus-1 (HSV-1). HSV-1 infection is extremely common, with 65% of the U.S. population having antibodies to HSV-1) (Wald et al., 2007).

Epidemiological Studies

The applications included 12 studies on the association between Swedish snus and outcomes related to gum disease and tooth loss (11 cross-sectional-studies and 1 case-control study). FDA completed an independent systematic search for published epidemiologic studies of Swedish

snus use and disease risk and did not identify any additional studies that pertained to gum disease or tooth loss.

The applications group outcomes by dental conditions (e.g., plaque, caries, tooth wear or tooth loss), gingivitis, gingival recession and periodontal disease. Plaque is a potential precursor for dental caries or periodontal disease; dental caries and tooth wear are potential precursors of tooth loss. Both gingivitis and gingival recession are potential precursors of periodontal disease, and bleeding on probing is an indicator of gingivitis (or potential indicator of progressing attachment loss if it occurred over several dental visits).

Dental Conditions

Of the two cross-sectional studies with specific aims to evaluate caries, one found an association between Swedish snus and caries in unadjusted analyses of adolescents (Hirsch et al., 1991), while the other found no association between Swedish snus and caries in analyses of adults adjusted for age, gender, employment status, marital status (Hugoson et al., 2012).[8] The only study with specific aims to evaluate the association between Swedish snus and tooth wear found a positive association in analyses of adults, adjusting for sex, age, bruxism and buffer capacity (Ekfeldt et al., 1990).

None of the studies had primary aims to evaluate the association between Swedish snus and plaque, but five studies found no association between Swedish snus and plaque in unadjusted analyses (Rolandsson et al., 2005; Monten et al., 2006; Bergstrom et al., 2006; Hugoson et al., 2011; Wickholm et al., 2004).

We did not identify any studies that evaluated tooth loss as an outcome. Several studies reported on differences between number of teeth in Swedish snus users and non-users (Hugoson et al., 2012; Rolandsson et al., 2005; Monten et al., 2006; Bergstrom et al., 2006; Hugoson and Rolandsson, 2011). Hirsch et al. (1991) included an outcome called "decayed, filled and missing teeth", but missing teeth were not separated from decayed teeth. Of the studies that examined differences in number of teeth between groups, Bergström et al. (2006) and Monten et al. (2006) found no association between Swedish snus and number of teeth in cross-sectional studies (Monten et al., 2006; Bergstrom et al., 2006), and in the Hugoson et al. (2012) and Rolandsson et al. (2011) population, Swedish snus users had significantly more teeth than non-users in 1983, but the result was not replicated in 1993 or 2003.

Overall, the dental conditions data included no studies that evaluated tooth loss over time, although several studies presented cross-sectional data on number of teeth or evaluated caries and tooth wear, potential precursors of tooth loss. The results on caries were mixed, and the only study to examine the association between Swedish snus and tooth wear found an association. No association was seen between Swedish snus and plaque but all studies of Swedish snus and plaque were unadjusted and 4/5 included less than 50 Swedish snus users per comparison.

[8] also adjusted for plaque in 1993, buffer capacity in 2003

Gingivitis

None of the studies included specific aims to evaluate the association between Swedish snus and gingivitis, although one study with specific aims to evaluate Swedish snus and oral health found gingival index was significantly higher in 12-13 year old Swedish snus users than non-users after adjusting for plaque index and brushing frequency (Modeer et al., 1980). Another study with a specific aim to evaluate periodontal health found no association between Swedish snus and gingivitis after adjusting for age, gender and sociodemographic variables (Hugoson et al., 2011).

Three unadjusted studies with broad aims or specific aims to study factors other than gingivitis found no association between Swedish snus and gingivitis or gingival index (Rolandsson et al., 2005; Monten et al., 2006; Wickholm et al., 2004). In addition, Bergström et al. 2006 found no association between current, former or never users and gingival bleeding on probing (an indication of gingivitis).

Overall the results of the studies on gingivitis were mixed. None of the studies included specific aims to evaluate gingivitis, but one adjusted study with a broad aim to evaluate oral health found an association between Swedish snus and gingival index while another adjusted study did not. Several unadjusted studies found no association between Swedish snus and gingivitis.

Gingival Recession

Only Andersson and Axell (1989) included specific study aims to evaluate the relationship between Swedish snus and gingival recession. The Andersson and Axell (1989) study did not include any non-users of Swedish snus but found that loose Swedish snus users were more than eight times as likely to have more gingival recessions than portioned Swedish snus users in analyses restricted to males and adjusted for age, and exposure (number of sites of placement, hours of use, grams of Swedish snus uses, and years of Swedish snus habit).

In a study with specific aims to evaluate Swedish snus and periodontal conditions, Monten et al. (2006) found a significant association between Swedish snus and gingival recession in 19-year-olds after adjusting for plaque, gingivitis and tooth brushing.

In unadjusted analyses of studies with broad aims or specific aims to study factors other than gingival recession, Hugoson and Rolandsson (2011) found an association between Swedish snus and gingival recession using in 1993 but not 1983 or 2003 (the percentage of sites with gingival recession was less in Swedish snus users in 1993). Wickholm et al. (2004) found significant association between use of Swedish snus and gingival recessions but did not do post hoc comparisons comparing all Swedish snus use groups (however, never users of Swedish snus or cigarettes had the lowest percentage of recessions). In Rolandsson et al. (2005) gingival recessions were seen in seven Swedish snus users and not mentioned in any non- users.

Overall, the only adjusted study of gingival recession to include non-users found a significant positive association between Swedish snus and gingival recession, and several unadjusted studies found significant associations between Swedish snus and gingival recession, although the direction of the association was mixed.

Periodontal Disease

Of the three studies with specific aims to examine periodontal disease or bone loss (periodontal bone loss, incipient alveolar bone loss), none found an association. In adjusted analyses, Bergström et al. (2006) found no association between Swedish snus use and distance from cement enamel junction to periodontal bone crest after adjusting for age. Wickholm et al. (2004) found no association between Swedish snus use and periodontal disease (3 or more teeth with pocket depth >=5mm) after adjusting for age, gender, education, plaque and smoking. Julhin et al. (2008) found no association between Swedish snus use and incipient alveolar bone loss after adjusting for the educational level and occupation of the participant's mother and father.

In adjusted analyses, Hugoson and Rolandsson (2011) found no association between Swedish snus use and severity of periodontal disease in any of the three years examined (after adjusting for smoking, age, gender, education employment, marital status and oral hygiene variables[9] . However, Hugoson and Rolandsson (2011) found a significant association between Swedish snus use and percentage of sites with pocket depth >=4 mm in 1983 (OR 3.98 (p<.001)), after adjusting for age, gender and sociodemographic variables. However, this result was not replicated in 1993 or 2003. Hugoson and Ronaldsson (2011) found no association between Swedish snus and bone level index (BLI).

In unadjusted analyses, Monten et al. (2006) found no association between Swedish snus and mean probing pocket depth (PPD), clinical attachment loss (CAL) and alveolar bone level (ABL). Rolandsson et al. (2005) found no deepened periodontal pockets in either Swedish snus users or non-users.

In a case-control study with specific aims to evaluate the outcome of buccal attachment loss, Kallestal and Uhlin (1992) note that "no differences in the use of smokeless tobacco between the referent and case group were detected in the present study," however, quantitative analyses were not presented and no additional information was provided.

As discussed in the dental conditions section, no association was seen between Swedish snus and plaque (a potential precursor of periodontal disease) in five unadjusted studies (Rolandsson et al., 2005; Monten et al., 2006; Bergstrom et al., 2006; Hugoson and Rolandsson, 2011; Wickholm et al., 2004).

Overall, nearly all of the studies which examine the association between Swedish snus and indicators of periodontal disease (plaque, pocket depth, attachment loss, bone loss) found no association, although Hugoson and Rolandsson (2011) found Swedish snus use was associated with an OR of 3.98 for probing pocket depth in 1983, but not in in 1993 or 2003. Two of the studies included more than 50 Swedish snus users per comparison (Juhlin et al., 2008 and Wickholm et al. 2004), but three did not (Hugoson and Rolandsson, 2011; Monten et al., 2006; Bergström et al., 2006).

[9] subgingival calculus in 1993 and 2003 and plaque index (PLI in 2003)

Overall, the studies on tooth loss and gum disease present a number of limitations. Eleven of the twelve studies included in the applications were cross-sectional, which limits the ability to establish temporality between exposure and outcome and provides limited evidence to infer causality. Six studies included only adolescents or young adults under the age of 25 (Hirsch et al., 1991; Rolandsson et al., 2005; Monten et al., 2006; Modeer et al., 1980; Julihn et al., 2008; Kallestal and Uhlin, 1992). However, many oral health outcomes are not seen until later in life and studies of these outcomes in adolescents may not apply to older adults and/or adults who have been using the product longer. Most of the studies had relatively few Swedish snus users. Small study samples that include few Swedish snus users may limit the ability to detect statistically significant differences. The studies of Swedish snus and gum disease or tooth loss were limited in the extent to which they attempted to control for important potential confounders. Risk factors for periodontal disease include advanced age, male gender, lower socioeconomic status , genetic factors, tobacco smoking, diabetes, stress and microbial factors. One of the major risk factors for gum disease and tooth loss is cigarette smoking, however, only four studies excluded dual users in the design or analysis of the study (Hugoson et al., 2012; Hugoson and Rolandsson, 2011; Monten et al., 2006), and only Wickholm et al. (2004) adjusted for smoking status.

Although well-designed observational studies can provide a strong evidence base, almost all of the twelve gum disease or tooth loss studies presented in the applications were cross-sectional, half included only adolescents and young adults, many had small numbers of snus users, and most did not control for all appropriate potential confounding factors. Despite the limitations mentioned, several of the studies in youth populations found an association between snus use and dental caries (Hirsch et al., 1991), gingival recession (Monten et al., 2006) or gingival index (Modeer et al. 1980). One study found an association between snus and tooth wear in adults (Ekfeldt et al., 1990).

The systematic review by Kallischnigg et al. (2008) found that snuff-induced lesions (SIL) are almost universal among snus users in Scandinavia. The long-term health implications of these lesions are unknown. The prevalence of SIL is lower in the United States though it is not clear whether this is related to the products used, patterns of use, differences in diet or dental care, or exposure to other agents. Given the evidence that SIL develops in almost all regular snus users, we cannot conclude that there is a biologically plausible mechanism by which these products cannot cause gum disease or tooth loss. .

Conclusion on tooth loss and gum disease. There is strong evidence that the use of smokeless tobacco generally and Swedish snus in particular causes gum disease and tooth loss; specifically notwithstanding the limitations in the epidemiological evidence, several studies reported associations between snus use and gum disease and tooth loss (or precursors thereof). There is little biological plausible reason to expect that outcomes related specifically to gum and teeth of users resulting from the use of the eight General snus products would differ from those outcomes for other smokeless tobacco products. Indeed, given that these eight General snus products, like other smokeless tobacco products, cause delayed soft tissue wound healing, these products would not be expected to differ from other smokeless tobacco products with respect to these disease outcomes. Overall, the totality of the evidence demonstrates that the eight General snus products can cause gum disease and tooth loss, and, correspondingly, does not support the removal of the warning that these products can cause gum disease and tooth loss.

Other Health Risks and Comparison with Cigarette Smoking

This section summarizes reviewers' findings with respect to the other health risks posed by the eight General Snus products, including the absolute risks posed to users of the products, as compared to non-users, and the relative risks, as compared to cigarette smoking.

Potential exposures as compared to smoking

Although SMNA proposes to claim that "this product presents substantially lower risks to health than cigarettes," SMNA did not provide a direct side-by-side comparison in HPHC levels with any specific comparator cigarette product. Instead, SMNA provided a document titled "Estimated HPHC Intakes from Snus Consumption – Comparison with Dietary Intakes or Smoking", in which SMNA compared the estimated TSNA intakes from snus consumption with the estimated TSNA exposure from smoking. Based on the analytical data obtained in both the snus products and the reported mainstream cigarette smoke (or the reported mouth level exposure from smoking) and several assumptions (e.g., the amount of products used daily, the extraction rates from the snus products, and the absorption rate from the mainstream cigarette smoke), SMNA concluded that "on average and under worst case conditions, the intakes of NNN and NNK as well as total TSNA from snus consumption and smoking are comparable." SMNA did not make similar comparisons between snus and cigarette smoking for other HPHCs. However, the applicant states that 43 out of the 93 HPHCs currently on the FDA's list [10] are thought to originate from combustion of tobacco or have never been quantified comprehensively in smokeless tobacco products. Therefore, SMNA did not include these HPHCs in its analyses: aromatic amines, volatile hydrocarbons, some carbonyls and carbon monoxide, hydrogen cyanide, hydrazine, certain phenols, heterocyclic aromatic amines, and certain epoxides.

The ranges for cigarette mainstream smoke given below (from the FDA/CDC study referenced in the Chemistry review) represent the mean yields of 50 cigarettes obtained under the ISO and Canadian Intense smoking regimen, respectively, and the ranges for snus represent the lowest and highest levels among the eight snus products.

- Acetaldehyde: 634-1729 µg/cig in mainstream smoke versus (b) (4) µg/portion or pouch in the snus products
- Arsenic: 3.1-8.9 ng/cig in mainstream smoke versus less than (b) (4) ng/g (LOQ) for MR0000020, (b) (4) ng/pouch for MR0000022-MR0000029, and (b)(4) ng/pouch for MR0000021 in the snus products
- B[a]P: 10.1-19.9 ng/cig in mainstream smoke versus (b) (4) ng/g (LOQ) for MR0000020, (b) (4) ng/pouch for MR0000022-MR0000029, (b) (4) ng/pouch for MR0000021 in the snus products

[11] For example, Digard et al. (in "Determination of nicotine absorption from multiple tobacco products and nicotine gum." Nicotine Tob Res 15.1 (2013): 255-61) reported that in 20 subjects, nicotine was absorbed more rapidly from smoking a cigarette with nicotine yield of 0.9 mg/cig under ISO and 2.1 mg/cig under CI; but systemic exposure from smoking such a cigarette (measured as the area under the plasma concentration-time curve AUC and maximum plasma concentration Cmax) was within the range of using a 1 g portion of loose or a pouched snus products containing 10.8 mg to 27.1 mg of nicotine.

- Cadmium: 35.9-117.7 ng/cig in mainstream smoke versus [redacted] ng/portion or pouch in the snus products
- Crotonaldehyde: 10.8-40.2 ug/cig in mainstream smoke versus [redacted] µg/g (LOQ) for MR0000020, and [redacted] µg/pouch for MR0000021-MR0000029 in the snus products
- Nicotine: 0.9-2.3 mg/cig in mainstream smoke versus [redacted] mg/portion or pouch in the snus products
- NNK: 55.0-121.9 ng/cig in mainstream smoke versus [redacted] ng/portion or pouch in the snus products
- NNN: 84.8-188.8 ng/cig in mainstream smoke versus [redacted] ng/portion or pouch in the snus products

For formaldehyde levels in mainstream smoke, we used the data from a market survey study reported by Counts et al. (2005) because the FDA/CDC study does not have such data. Counts et al. (2005) reported that the mainstream smoke yields of formaldehyde were 1.6-52.1 µg/cig under the ISO conditions, and 29.3-130.3 µg/cig under the CI conditions. The formaldehyde levels in the eight snus products are [redacted] µg/portion or pouch.

Therefore, on a per unit of use basis, the eight snus products contain lower levels of acetaldehyde, crotonaldehyde, and B[a]P than mainstream smoke; higher levels of nicotine, NNN, and cadmium than mainstream smoke. The range of NNK levels in the new snus products is wider than those in mainstream smoke. The range of formaldehyde levels in the new snus products is within that in mainstream smoke under the ISO condition, but lower than that in mainstream smoke under the Canadian Intense condition. It is not clear how arsenic levels compare between the two types of products because most of the arsenic concentrations in the new snus products are below the LOQ.

Although there are differences in HPHCs levels between the two product types, those differences may not be sufficient for assessing the potential exposures to users of the two types of products. Snus and cigarettes differ in product design and usage (oral consumption versus inhalation of smoke from combustion). Therefore, the above comparison does not imply that users are exposed to the levels of HPHCs for each type of products as indicated above because the actual exposure levels are influenced by factors such as user behavior (e.g., the amount of product used per day), the route of administration, the rate of absorption, and metabolism.[11]

Toxicological Studies

Studies with laboratory animals suggest that the risk from snus may be less than cigarettes, but not eliminated. For instance, a mouse elastase-IL-1β model of chronic pancreatitis showed that snus produced adverse effects on pancreas (i.e., pancreatic ductal flattening and glandular atrophy, increased proliferative index of ductal epithelial cells and increased COX-2 expression)

[11] For example, Digard et al. (in "Determination of nicotine absorption from multiple tobacco products and nicotine gum." Nicotine Tob Res 15.1 (2013): 255-61) reported that in 20 subjects, nicotine was absorbed more rapidly from smoking a cigarette with nicotine yield of 0.9 mg/cig under ISO and 2.1 mg/cig under CI; but systemic exposure from smoking such a cigarette (measured as the area under the plasma concentration-time curve AUC and maximum plasma concentration Cmax) was within the range of using a 1 g portion of loose or a pouched snus products containing 10.8 mg to 27.1 mg of nicotine.

similar to cigarette smoke extract; albeit to a lesser extent and at later time points (Song et al., 2010).

Although studies in laboratory animals indicate that both Swedish snus and cigarettes can cause cancer, there are no studies that can provide an empirical toxicological comparison of the two tobacco product classes. Rather, a toxicological comparison can proceed based on two basic points: (1) there are many harmful or potentially harmful constituents present in cigarette smoke that are either not present at all or much reduced in snus and (2) the respiratory tract is much more sensitive than the gastrointestinal tract and portal of entry effects from irritating HPHCs can produce respiratory toxicity that has much more severe consequences than the oral irritation caused by the use of snus. With respect to the first point, cigarette combustion and pyrolysis creates many carcinogens, including acetaldehyde, formaldehyde, and polyaromatic hydrocarbons that are either not present or present at low levels in snus. Combustion and pyrolysis also generates smoke irritants, including acrolein and hydrogen sulfide that are present in cigarette smoke, but are either much reduced or not present in snus. Many of the carcinogenic aldehydes, such as acetaldehyde and formaldehyde are also irritants. With respect to the second point, chronic local irritation in the lung from cigarette smoke can lead to serious respiratory disease, including asthma and COPD. COPD is a major source of smoking-related morbidity and mortality. Further, inhaled cigarette smoke creates a situation in which carcinogenic smoke constituents can directly contact the cells that line the respiratory tract putting the lung at risk of neoplasms in a way that oral tobacco use does not.

Thus, when comparing the HPHCs that are present in cigarette smoke and in snus and considering the sites in the body (lungs vs. oral cavity) that are exposed to these HPHCs, then one might expect the health risks related to cancer and lung diseases from snus use to be lower than from smoking.

According to the toxicology review: “The proposed warning label “No tobacco product is safe, but this product presents substantially lower risks to health than cigarettes” is supported by scientific literature. The toxicology review team supports the requested modification to the mandated warning” (p. 90). The reviewer further stated “that available toxicology information is consistent with modified warning that states that snus are [sic] present less risk than cigarettes” (p. 90). The underlying scientific findings by the toxicology review team generally support FDA’s conclusion regarding the lower risks to health presented by the General Snus products. However, that review team was not responsible for considering all of the scientific and regulatory factors that relate to authorizing the requested MRTP claim. Their evaluation was based primarily on the levels of harmful and potentially harmful constituents in these products and an assessment of the toxicological evidence related to the risks associated with lower concentrations of these constituents and sites of exposure (lungs vs. oral cavity). The toxicology review did not take into account, for example whether the magnitude of differences in toxicological risk associated with different constituent levels would apply to each of the disease endpoints shown to be causally related to cigarette smoking. Relatedly, the reviewer did not consider whether the toxicological evidence supported that the products would reduce all, and not just some, disease outcomes. Finally, the reviewer did not consider whether the toxicological data would support the requested modified risk claim for any behavior other than exclusive use.

Clinical Trials

SMNA sponsored two clinical trials to assess the effectiveness of snus as a cessation aid – one in the United States and one in Serbia. These studies were designed to assess the short-term change in cigarette smoking cessation, not the health outcomes in the proposed modified risk claims.

The U.S. clinical trial was a 28-week, multicenter, randomized (1:1), double-blind, placebo-controlled clinical trial conducted in five US clinical sites. The study enrolled 250 healthy adult smokers, ages 25 to 65, who smoked 10 or more cigarettes per day over the month prior to entering the study and who wished to stop smoking. The primary objective of the study was to assess the effect of snus on continued cigarette smoking cessation. The primary endpoint for this objective was sustained cigarette smoking cessation from weeks 6-28, as assessed through self-report and verified by exhaled carbon monoxide (CO) < 8 ppm.

The Serbian clinical trial was a 48 week study where the primary endpoint was assessed at week 24. The study was a multicenter, randomized (1:1), double-blind, placebo-controlled clinical trial of 319 healthy adult smokers, ages 20-65 years old who regularly smoked more than 10 cigarettes per day (CPD) for at least 1 year prior to entering the study, who agreed not to use any non-protocol treatments for smoking cessation (e.g., nicotine replacement therapy) during the study period, and who were motivated to reduce or quit smoking. The primary objective of this study was to assess the efficacy of using snus to aid cigarette smoking reduction. The primary endpoint for this objective was a reduction in average cigarettes smoked per day of ≥ 50% comparing baseline to weeks 20 to 24, as assessed through self-report and verified by a decrease in exhaled CO of at least 1 ppm.

In both studies subjects were assigned to one of two snus products: subjects in the active snus arm received snus that contained nicotine, while subjects in the placebo snus arm received snus which is identical to the active test product without nicotine. In both studies, subjects were given both small (0.5 g) and large (1.0 g) sachets and chose their preferred sachet size. In the Serbian study, subjects were also given two flavors (liquorice and eucalyptus) and chose their preferred flavor.

The two human clinical studies were small; a total of 569 subjects were enrolled in the two studies and 282 withdrew before study completion. Study endpoints focused on use of snus to aid in smoking reduction and cessation. A focused review on short term health effects within these studies indicate the reporting of serious adverse events (AEs) however, the serious AEs were not related to use of the snus products.

Clinical effects related to the use of Swedish snus are the same as other sources of nicotine such as cigarettes. These effects are dose dependent. Common effects of excess nicotine include increased heart rate, elevation of blood pressure, vertigo, headache, nausea, stomach ache, and heart burn. In addition, nicotine is a highly addictive substance regardless of the delivery method.

Study 1 included generally healthy participants. SMNA concluded that snus use was generally well tolerated. However, treatment-related AEs were reported more frequently by participants allocated to snus (19.0%) compared to placebo (11.2%). These AEs were mostly classified as mild, did not result in discontinuation of study treatment, and were mostly symptoms related to nicotine exposure (e.g. tachycardia, nausea, increased salivation, vomiting, and hiccups).

Illnesses first occurring or detected during the study, or a significant deterioration of a pre-existing condition were documented as AEs in the case report form (CRF). Safety assessments were performed by regularly monitoring for AEs, which were classified according to relationship to the study medication. AEs reported during the study were generally mild in severity and non-serious and were not unexpected reactions to these products. Most of the reported AEs were either related or possibly related to the study product.

A total of 88 AEs were reported during the course of the study. Four subjects experienced severe AEs including a right leg fracture, muscular weakness, nausea, and toothache. Of these, only nausea was believed related to the study product. Twenty subjects experienced moderate AEs including four reports of nausea and two reports each of anxiety, erythroplakia, and vomiting.

Commonly reported AEs included nausea, hypertension, gastrointestinal disorders, dizziness, anxiety, and throat irritation; these were generally mild to moderate in severity and non-serious. Gingival erosion, vomiting and gastritis were determined to be probably related to the study product, but also mild to moderate in severity and non-serious.

In study 2, overall, 616 AEs were reported by 200 subjects; 350 in the snus group and 266 in the placebo group. There were no deaths in the study. Overall, highest percentage of distinct subjects reporting an AE were gastrointestinal disorders (44.8%; gingival pain, dyspepsia, nausea, toothache, diarrhea, dry mouth, gingivitis, salivary hypersecretion, abdominal pain, and sensitivity of teeth), infections (33.6%; viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, pharyngitis, bronchitis, otitis media, and viral infection), nervous system disorders (20.0%; headache, dizziness, and dysgeusia), respiratory, thoracic, and mediastinal disorders (16.8%; cough, hiccups, oropharyngeal pain, nasal congestion, and rhinorrhea), musculoskeletal and connective tissue disorders (12.8%; back pain, arthralgia, and myalgia), injury, poisoning, and procedural complications (9.6%; skin laceration, back injury, and joint sprain), psychiatric disorders (9.6%; insomnia, anxiety, and mood altered), general disorders and administration site conditions (6.4%; irritability), and skin and subcutaneous tissue disorders (6.4%; acne). The most frequently reported AEs were gingival pain, headache, dyspepsia, and nausea.

Six subjects discontinued study participation due to AEs (5 from snus group, 1 from placebo group). The AEs leading to discontinuation from the snus group were mild gingival pain (definitely product related), severe vaginal bleeding (unlikely related), glossitis and pharyngitis (probably related), pregnancy (not related), and dyspepsia, diarrhea, and acne vulgaris (unlikely related). The placebo group discontinuation was due to mild dysaesthesia (possibly related). A total of five serious AEs were reported in the study: vaginal bleeding with pregnancy, visual disturbance secondary to cerebrovascular accident, cerebrovascular accident, multiple fractures

right ankle (car accident), and pregnancy. SMNA did not consider these to be related to the study product. All other AEs reported were classified as "non-serious."

SMNA reported that average blood pressure readings for subjects increased from baseline for those in craving levels 1 and 2, and decreased for subjects in higher craving levels. The changes in blood pressures were not statistically significantly different.

Epidemiological Studies

The applications summarize health risks of Swedish snus as compared with cigarettes in forest plots and bullet points for each disease endpoint. Disease endpoints selected for this comparison were based on some, but not all, endpoints with the highest number of deaths attributable to smoking based on the CDC 2008 estimates. The following endpoints selected based on this criterion were ordered from highest to lowest number of smoking-attributable deaths: lung cancer, cardiovascular disease (CVD), stroke, respiratory disease and chronic obstructive pulmonary disease (COPD), esophageal cancer, pancreatic cancer, oral cancer, and stomach cancer, which SMNA noted accounted for 90% of all smoking-related deaths. SMNA also selected "several additional health outcomes" not based on the number of smoking-attributable deaths: diabetes, metabolic syndrome, all-cause mortality, and non-cancer oral effects.

The information provided by the applicant in the description of the literature search for comprehensive review in the ENVIRON snus monograph does not allow for replication. For example, SMNA did not provide a study protocol, information about inclusion or exclusion criteria for studies, or the search terms used, particularly the "targeted outcome terms" that were used "in addition to the basic exposure terms." The applications would have been strengthened if SMNA had followed best practices for the conduct of systematic reviews and meta-analyses when identifying and synthesizing evidence from the open scientific literature (Higgins and Green, 2011; IOM, 2011; Moher et al., 2009)). This includes more detailed reporting of the methodology utilized to complete the literature review, including, but not limited to:

- Literature search protocol
- Specific study/report characteristics used as eligibility criteria with rationale
- Full electronic search strategy, including any limits used, such that the search could be repeated.
- Process for selecting studies (i.e., screening strategy)
- Description of method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators
- Listing and definition of all variables for which data were sought (e.g., participants, exposure, comparators, outcomes, and study design (PICOS), funding sources) and any assumptions and simplifications made
- Numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram
- Database containing citations

The applicant compared health risks between Swedish snus and cigarette smoking based on a visual inspection (via forest plots) of the differences in relative risk estimates for the two

products. The applicant did not provide specifics with respect to what is meant by "substantially lower risks to health" such as identification of particular health outcomes or health risks, identification of a particular level of decrease in risk, or identification of user behavior that affects the risk (e.g., exclusive use versus dual use with other tobacco products). Additionally, there are a wide range of endpoints and substantial variation in the magnitude of the differences by outcome. A qualitative comparison may not be adequate for comparing risks between Swedish snus and cigarettes given the variation in differences across disease endpoints.

The applicant's process for selecting studies to compare the health risks of Swedish snus with those of cigarettes resulted in the presentation of only a subset of the available literature on the health risks of Swedish snus. Including only a subset of the methodologically sound studies in the analysis could bias conclusions about the health risks of Swedish snus.

In general, the data presented indicate that some health risks of use of the products which are the subject of these applications are less, or at least no greater, than those associated with cigarette smoking. However, there are conditions for which the risks of use of these products may not be significantly different from those of smoking, and the proposed modified risk claim would be inaccurate with respect to those risks. Furthermore, reductions in risk presume that users discontinue smoking and switch to the use of the eight products. However, the proposed claim does not specify the conditions under which the risks would be substantially lower; i.e., when the user switches completely to these products or as related to specific medical conditions.

SMNA submitted a review of epidemiological studies on various health outcomes, in addition to oral cancer and tooth loss/gum disease.

Esophageal Cancer

The application contained studies related to the use of Swedish snus products and the risks of esophageal cancers. The General Snus products contain carcinogenic nitrosamines. Because the saliva produced during use of snus may be swallowed instead of expectorated, there is concern the carcinogenic nitrosamines present in the saliva could increase the risk of esophageal (as well as stomach) cancer. SMNA provided two case-control studies (Lagergren et al., 2000; Lewin et al., 1998) and one cohort study (Zendehdel et al., 2008) with risk estimates for both Swedish snus users and smokers. Esophageal cancer risks were nearly universally increased for smokers in these studies, with the applicant reporting relative risks among smokers ranging from "1.6 to 2.9 for adenocarcinoma and 7.6 to 9.3 for squamous cell carcinoma." (p. 414) Boffetta et al. (2008) pooled four studies from Nordic countries and found that risk of esophageal cancer was significantly elevated in the Nordic studies (RR = 1.6, 95% CI = 1.1, 2.4). Lee and Hamling (2009) reviewed 4 studies from Scandinavia, but did not find a significant association (RR = 1.10, 95% CI = 0.92, 1.33). Although the risk of esophageal cancer associated with snus use is less than the risk in cigarette smokers, it is elevated over never-users of snus and nonsmokers.

Stomach Cancer

The applicant identified three case-control studies (Hansson et al., 1994; Lagergren et al., 2000; Ye et al., 1999); and one cohort study (Zendehdel et al., 2008) that reported risk estimates for stomach cancer in both Swedish snus users and smokers. Only the study by Zendehdel et al.

2008 based on the Swedish Construction Worker cohort observed an elevated risk of noncardia stomach cancer among never-smoking Swedish snus users. The association for noncardia stomach cancer was restricted to those 70 and older (RR=1.7, 95% CI= 1.2-2.5), while no significant association was observed in those younger than 70 years (RR=1.2, 95% CI=0.8–1.8) (Zendehdel 2008). The study authors noted that this age effect was "consistent with a very long induction time" and that the oldest "were also most exposed to snus from earlier parts of the 20th century" which "contained higher levels of carcinogenic TSNAs compared to the snus sold today." A systematic review and meta-analysis of cohort studies found that smoking increased the risk of stomach cancer by about 60% in men and 20% in women, compared with never smokers (Ladeiras-Lopes et al., 2008). Based on this evidence, the magnitude of differences in risks of stomach cancer between exclusive Swedish snus users and cigarette smokers is unclear.

Pancreatic Cancer

Findings from two Scandinavian cohort studies suggest an increased risk of pancreatic cancer in snus users (Luo et al., 2007; Boffetta et al., 2005). Although there is a biologically plausible mechanism for the association between Swedish snus use and pancreatic cancer, SMNA cites methodological shortcomings with the analyses which may have led to the finding. Published letters by Nilsson (2006), Ramstrom (2006), and Rodu and Cole (2005) cite concerns with the Boffetta study, specifically:

- confounding by tobacco smoking,
- differences between the Norwegian product and those marketed in Sweden
- the lack of control for alcohol intake

Authoritative reviews by IARC and NCI/CDC have concluded that smokeless tobacco use causes pancreatic cancer (IARC, 2007; National Cancer Institute and Centers for Disease Control and Prevention, 2014). Although SMNA cites a recent pooled analysis of case-control studies that did not observe an association between smokeless tobacco-only use and pancreatic cancer (OR=0.62, 95% CI=0.37-1.04), adjusting for adjusted for center, race, sex, age, education, history of diabetes, body mass index and total alcohol consumption (Bertuccio et al., 2011), these were primarily U.S. studies based on a small number of total exposed cases (N=23 across all studies) and the authors noted that "[i]t is possible that hospital controls include some diagnoses related to tobacco use that would lead to an underestimation of the true association." We found discrepancies between SMNA's assessment of the association between Swedish snus and pancreatic cancer and the full set of study findings on this association. To illustrate, in Section 6.1.1 of the applications, SMNA presents a forest plot comparing the risks of pancreatic cancer for Swedish snus and cigarettes that does not accurately reflect all of the findings for Swedish snus and pancreatic cancer. First, SMNA only presents the smoking-adjusted estimate from the Luo 2007 study, which showed no association between ever Swedish snus use and pancreatic cancer (RR=0.9, 95% CI=0.7-1.2). However, in the never-smoker estimate based on the same cohort, a positive association between ever Swedish snus use and pancreatic cancer was observed (20 exposed cases, RR=2.0, 95% CI=1.2-3.3). The forest plot also excludes findings from 2 other studies, one of which also found a positive association (Boffetta et al., 2005). In the cohort of Norwegian men, Boffetta et al. (2005) observed that current Swedish snus (vs. never use) was associated with pancreatic cancer with borderline significance (27 exposed cases, RR=1.6, 95% CI=1.0-2.55) after adjusting for age, smoking of cigarettes, cigars and pipe. When restricting to

never smokers, there was no longer an association, but it was based only on 3 exposed cases (ever Swedish snus use, RR=0.85, 95% CI=0.24-3.07).

Boffetta et al. (2008) pooled two Nordic studies and found that risk of pancreatic cancer among snus users was elevated in the Nordic studies (RR = 1.8, 95% CI = 1.3-2.5). But Lee and Hamling (2009) pooled the same two studies and found that the smoking-adjusted risk was not statistically significant elevated in the Scandinavian studies (RR = 1.20, 95% CI = 0.66-2.20).

The applicant also stated that the Swedish snus-pancreatic cancer association is not supported by Swedish public health statistics (ecological) in which pancreatic cancer incidence decreased while Swedish snus increased by 50% between 1980 and 2005. However, ecological data, although potentially hypothesis-generating, provides very little evidentiary value in assessing the strength of the association between a risk factor and disease. For example, smoking also decreased at the same time, which is more likely to have driven the trends in pancreatic cancer.

As noted by SMNA, the evidence associating snus use with increased risk of pancreatic cancer has been the topic of scientific debate. The level of risk noted in published literature varies from no increase (RR 0.8) to significant increase (RR 2.0). The studies have inadequacies, particularly with respect to possible confounders (i.e., alcohol use, dietary habits, cigarette smoking). These issues make it difficult to conclusively state that snus use is a risk factor for pancreatic cancer. However, the literature submitted by SMNA does not provide adequate evidence to conclude that use of the products which are the subject of these applications is not a risk factor for the development of pancreatic cancer particularly given that smokeless tobacco products in general have been found to cause pancreatic cancer. Based on the evidence presented, the magnitude of differences in risks of pancreatic cancer between exclusive Swedish snus users and cigarette smokers is unclear.

Lung Cancer

Two Swedish cohort studies and meta-analyses examined the association between Swedish snus use and lung cancer. 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.

Respiratory Disease and Chronic Obstructive Pulmonary Disease (COPD)

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.

Cardiovascular Disease: [ischemic heart disease (IHD), coronary heart disease (CHD), myocardial infarction (MI) and Overall CVD]

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, ischaemic 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.

Stroke (Cerebrovascular Accident/CVA)

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.

Diabetes

Two cross-sectional studies (Wandell et al., 2008), a third cross-sectional study with follow-up (Eliasson et al. 2004), and two cohort studies (Hilding et al., 2005; Ostenson et al., 2012) reported risk estimates for diabetes among snus users and smokers in the same population. Persson et al. (2000) reported a significantly increased prevalence of diabetes among current exclusive snus users, and Ostenson et al. (2012) reported a significant association between high consumption (defined as >5 boxes of snus/week) and type 2 diabetes, but not among consistent snus users adjusted for smoking, or consistent exclusive snus use.

The data are limited, but generally point to an increased risk of type 2 diabetes mellitus in heavy users of snus and in cigarette smokers. The specific level of snus use that leads to increased risk is not clear; generally the level of risk was noted to be elevated when use exceeded 4 boxes per week and it appears to be dose-dependent. The limited data do not provide adequate information to determine the comparative risk of developing diabetes for exclusive snus users compared with cigarette smokers.

All-cause mortality

The applicant identified two cohort studies that reported risk estimates for all-cause mortality for both Swedish snus users and smokers in the same population. Both large cohort studies observed elevated risk of all-cause mortality among never-smoking Swedish snus users. In the Swedish Construction Worker cohort, Bolinder et al. (1994) found that among never smoking men, current Swedish snus use (vs. never tobacco use) was associated with elevated risk of all-cause mortality (among 440 exposed cases, RR=1.4, 95% CI=1.3-1.8), adjusting for age, area of domicile, blood pressure (BP), BP medicines, diabetes, BMI, and previous cardiac symptoms. Since CVD mortality was elevated among Swedish snus users in this population (RR=1.4, 95% CI=1.2-1.6) but not cancer mortality (RR=1.1, 95% CI=0.9-1.4), CVD is likely to have driven the elevated all-cause mortality among Swedish snus users in the Swedish Construction Worker cohort (Bolinder et al., 1994). In the Uppsala County cohort, Roosaar et al. (2008) observed that among never smoking men, ever daily Swedish snus (vs. never daily use) was associated with an elevated risk of all-cause mortality (RR=1.23, 95% CI=1.03-1.4), after adjusting for alcohol, area of residence, calendar time, and interaction terms with age. Both CVD death (never-smoker estimate, HR=1.15, 95% CI=0.97-1.37) and cancer death (never-smoker estimate, HR=1.28, 95% CI=0.96-1.69) are likely to have driven the elevated risk of all-cause mortality in the Uppsala County cohort. Although confounding due to other factors cannot be completely ruled out, we are concerned with the potential implications for the General Snus products that are the subject of the applications of the finding that Swedish snus was associated with a 23% to 40% increased risk of death in these studies. While the risk of all-cause mortality is lower in exclusive Swedish snus use than cigarette smoking, at least in part due to the differences in lung cancer and COPD risk, the precise magnitude of difference in risk is unclear.

Adverse pregnancy outcomes

The applicant reviewed and discussed six cohort studies of Swedish snus use and adverse pregnancy outcomes. FDA identified two additional studies on the use of Swedish snus and adverse pregnancy outcomes. All eight cohort studies are based on the Swedish Medical Birth

Register (MBR). There was significant overlap in both study periods (all of which started in 1999) and outcomes across the studies. The MBR contains "data on 98% of all births in Sweden, including demographic data, information on reproductive history, pregnancy, delivery, and the neonatal period" as well as tobacco use information that "is collected in the MBR at the antenatal booking, which generally occurs at 8 to 12 gestational weeks and before 15 weeks of gestation in 95% of all pregnancies" (Gunnerbeck et al., 2014).

All three cohort studies of preterm birth observed significantly positive associations with Swedish snus use in early pregnancy: England et al. (2003) reported that among pregnant women not currently smoking, snuff use was associated with nearly twice the risk of a preterm delivery as compared with non-users (exposed cases, RR=1.98, 95% CI=1.46-2.68) after adjusting for maternal age, body mass index, height, parity, and infant sex. The association persisted even after the excluding women with preeclampsia. Baba et al. 2012b also reported that among pregnant women not currently smoking, snuff use was significantly associated with preterm birth (RR=1.29, 95% CI=1.17-1.43) after adjusting for early pregnancy, body mass, index, maternal age, parity, education, and cohabitation (Baba et al., 2012). Wikstrom et al. (2010) observed a significant association between exclusive snuff use during pregnancy and subsequent very preterm birth (56 exposed cases, RR=1.38, 95% CI=1.04-1.83), adjusting for maternal age, early-pregnancy BMI, parity and years of education.

Among cohort studies of snuff use and risk of stillbirth, Wikstrom et al. (2010) observed that among pregnant women who were not currently smoking, snuff use was associated with stillbirth (40 exposed cases, RR=1.6, 95% CI=1.13-2.29), adjusting for maternal age, BMI, parity, years of education, chronic hypertension, and pre-gestational diabetes (Wikstrom et al., 2010). Wikstrom et al. (2010) observed that pregnant women who were exclusive snuff users (vs. non-users) had an elevated but not statistically significant risk of stillbirth (40 exposed cases, RR=1.11, 95% CI=0.97-1.28), adjusting for early pregnancy BMI, maternal age, parity, and years of education.

Among other adverse pregnancy outcomes, England et al. (2003) reported that pregnant women who were not current smokers, but used snuff (vs. non-use) had a significantly elevated risk of pre-eclampsia (37 exposed cases, RR=1.58, 95% CI=1.09-2.27), adjusting for maternal age, body mass index, height, and parity. Baba et al. (2012) reported that among pregnant women who were not currently smoking, snuff use (vs. non-use) was associated with an elevated risk of a small for gestational age birth (RR=1.26, 95% CI=1.09-1.46), after adjusting for maternal age, parity, early pregnancy, body mass index, maternal height, cohabitation, education, pre-gestational diabetes and essential hypertension. Gunnerbeck et al. (2011) reported that among pregnant women not currently smoking, snuff use was associated with nearly twice the risk of infant apnea as non-use (26 exposed cases, RR=1.96, 95% CI=1.3-2.96) after adjusting for maternal age, height, parity, education, and tobacco use, was adjusted for cesarean delivery, gender, gestational age, and small for gestational age (SGA).

We identified two additional studies that examined Swedish snus use during pregnancy and oral cleft formations and stillbirth (Gunnerback et al., 2014; Baba et al., 2014). Based on the Swedish Medical Birth Register, using Swedish snus exclusively during early pregnancy was associated with risk of having infants with any oral clefts (RR=1.48, 95% CI=1.00-2.21), adjusting for maternal age, parity, education, living with father-to-be or not, hypertension, diabetes,

preeclampsia, sex of newborn, singleton or multiple birth, variation of diagnosis frequency and mothers' country of birth (Gunnerback et al., 2014). The authors noted that both "nicotine and nitrosamines per se may have teratogenic effects." Another Swedish Medical Birth Register study observed an association between Swedish snus use in early pregnancy and stillbirth (RR=1.43, 95% CI=1.02–1.99), adjusting for maternal age, parity, early pregnancy, body mass index, and education (Baba 2014). This finding is consistent with the Wikstrom et al. (2010) study of snus use and risk of stillbirth. Based on the foregoing evidence, the magnitude of risks of adverse pregnancy outcomes between exclusive Swedish snus users and cigarette smokers are relatively comparable.

Conclusion with respect to the risks of snus use on tobacco users compared to non-use. Several studies suggest that Swedish snus use is associated with pancreatic cancer, all-cause mortality, fatal MI and stroke, diabetes, and adverse pregnancy outcomes (including preterm delivery, stillbirth, pre-eclampsia, small for gestational age, and apnea). To illustrate, Swedish snus was found to increase the risk of dying from any cause by 23% to 40% among never-smokers in two prospective cohort studies (Bolinder et al., 1994; Roosaar et al., 2008). As mentioned above, we identified recently published research reporting significant positive associations between use of Swedish snus and adverse pregnancy outcomes, post-stroke mortality, and mortality following MI (Arefalk et al., 2014; Hansson et al., 2014; Baba et al., 2014; Gunnerbeck et al, 2014). Finally, the applicant does not address the potentially negative effect of nicotine on the developing brain in youth. A recent review that considered the adverse health effects from nicotine itself noted that "Nicotine exposure during periods of developmental vulnerability can impair development of neurons and brain circuits, leading to changes in brain architecture, chemistry, and neurobehavioral function and may impair or dysregulate non-neuronal cellular function" (England et al., 2015).

Conclusion with respect to comparison to cigarette smoking. There are several issues related to the methodology used to identify relevant studies and estimate Swedish snus risks compared to never user and cigarette smokers. SMNA used a qualitative approach for comparing health risks of use of Swedish snus vs. cigarettes with no a priori criteria for determining whether or not the differences would qualify as substantial. The applicant provided what was described as a "comprehensive" literature review of the health risks of Swedish snus in the ENVIRON snus monograph, but it was not a systematic review. Without detailed documentation of the methods such as study identification, screening, and eligibility, the information they provided is not sufficient for others to replicate. For the comparison of health risks between Swedish snus and cigarettes, only a subset of Swedish snus studies and were presented, which may lead to inaccurate conclusions on the risks of the products that are the subject of these applications compared with non-use. Similarly, only a subset of each study's main results were highlighted, which may also affect conclusions. Finally, not all relevant endpoints were assessed in the comparison between cigarettes and Swedish snus.

Despite these limitations, there appears to be some substantial differences between exclusive Swedish snus use and cigarette smoking in terms of lung cancer and COPD. However, for other endpoints, the magnitudes of risk differences are often less clear. Of particular concern are adverse pregnancy outcomes, where risks from exclusive Swedish snus are relatively comparable to cigarette smoking.

Thus, there is partial support for the claim proposed by SMNA, in that exclusive use of the eight products may pose lower risks of certain diseases than cigarettes. However, the scientific evidence is insufficient to support that substantial reductions would be observed across the entire range of risks posed by tobacco products, as implied by a generalized statement about health risks compared to smoking (i.e., "substantially lower risks than cigarettes"). Additionally, the evidence suggests that reduction in risks would likely accrue to those who switch completely to these eight General snus products, but we cannot conclude that they would accrue to those users that also continued to smoke cigarettes, and the claim does not address use and there are no instructions for use.

(d) The health risks of the tobacco product compared to FDA-approved tobacco cessation medication

In assessing whether the eight General snus products, as actually used, will benefit the health of the population as a whole, we took into account the risks and benefits to persons from the use of the products as compared to the use of drug and device products approved as aids for smoking cessation.

Medical

Nicotine replacement therapies (NRTs) are available over-the-counter as patches, gum, and lozenges and via prescription as nasal spray and inhaler. All of these products have been approved as aids to smoking cessation treatments. As approved drugs, the health risks of NRTs are believed to be significantly less than continuing to smoke and, in 2013 FDA noted that published literature indicated that adverse effects of long-term nicotine gum use were minor and transient and that the abuse liability and dependence potential for NRTs was very low. The health risks from use of NRTs are minimal and, thus, likely similar to the health risks experienced by non-users of tobacco products.

Other approved drugs in the U.S., Chantix (varenicline) and Bupropion, are available as prescription medications. Although there is some evidence for an increase in cardiovascular events associated with the use of Chantix use, it is likely that the increase is offset by a corresponding reduction in risk due to smoking cessation. There are no serious safety concerns associated with Bupropion.

Epidemiology

While the levels of nitrosamines in NRTs are trace to non-detectable, there is a measurable presence of nitrosamines in Swedish snus products (Stepanov et al., 2006) and in these products in particular. One study found that among smokeless tobacco users who switched to either Swedish snus or the nicotine patch, the levels of NNAL in users who switched to the nicotine patch were substantially lower than those who switched to Swedish snus. To support their conclusion that the risks of NRT and Swedish snus use are comparable, SMNA refers to a study by Apelberg et al. (2010). However, the aim of the study was to estimate the impact of increased use of NRT in the population, even under circumstances where there might be some harm from long-term use of NRT (Apelberg et al., 2010). Since long-term health risk data for NRTs were

not available, Apelberg et al. used an estimate for Swedish snus as a worst-case scenario for NRT use in the simulation. Thus, SMNA misinterpreted the intention behind the authors' use of the Swedish snus data in the study.

SMNA also claims that, among cigarette smokers switching to Swedish snus, the "risk in switchers appears to be no different from that in smokers who quit smoking" and that "it is reasonable to consider the health effects of Swedish snus as being comparable to that of NRTs." However, SMNA does not provide data that adequately support these claims. Given that the nitrosamines in snus are still elevated and that there are associations between snus and a number of diseases, it is unlikely that switching to the products that are the subject of these applications is comparable to quitting tobacco completely with or without using NRTs. Additionally, none of the studies directly compared switchers with continuing smokers and quitters, taking into account lifetime history of smoking.

Conclusion. Overall, SMNA does not provide adequate data to support their conclusion that the health effects of the products that are the subject of these applications are comparable to that of products approved under Chapter V of the FD&C Act for smoking cessation. And, to the contrary, based on the health risks from use of Swedish snus, we can conclude that the health risks from the use of General Snus products that are the subject of the applications are greater than those posed by FDA-approved cessation therapies.

(e) The health risks of the tobacco product as compared to cessation

Epidemiology

The studies described by SMNA were not designed to specifically examine the health risks of switching from cigarette smoking to Swedish snus use, rather they only compare the risks from smoking against the risk from using snus. SMNA highlighted estimates of current Swedish snus users who were former smokers, but it is possible that some of these users were long-term dual users who then quit smoking or smokers who quit and then took up Swedish snus at a later point in time. Also, the referent group was never users, rather than other groups such as current smokers or former exclusive smokers who never used Swedish snus. As such, lifetime smoking history was not accounted for in the studies presented. An example of a study that more directly estimates the risks of switching from cigarettes to a smokeless tobacco product comes from an analysis of the U.S. cohort, Cancer Prevention Study II (CPS-II) (Henley et al., 2007). In this study, switchers (defined as "currently using spit tobacco and having begun doing so at the time of or after they quit exclusive cigarette smoking") were directly compared with former exclusive smokers (defined as those "who reported having previously used cigarettes but no other tobacco products"). Risks of all-cause and cause-specific death were compared between switchers and those who quit entirely adjusting for smoking history variables including the number of cigarettes formerly smoked per day, number of years smoked cigarettes, and age at which they quit smoking cigarette. The evidence provided by SMNA does not include results from studies comparing switchers and quitters or continuing smokers, while adjusting for cumulative smoking history.

Conclusion. There is insufficient evidence to support SMNA's statement that the risks in switchers are "no different from that in smokers who quit smoking." And, to the contrary, based

on the health risks from use of Swedish snus, we can conclude that the health risks from the use of General Snus products that are the subject of the applications is greater than those posed by cessation.

(f) The health risks associated with using the product in conjunction with other tobacco products

Epidemiology

Although SMNA reports that health risks of dual use of Swedish snus and cigarettes are not higher than that of smoking cigarettes exclusively, the data are limited.

Studying health risks due to dual use of cigarettes and Swedish snus is challenging, given that smoking is already such a strong risk factor for many diseases and the use of a second tobacco product may influence the patterns of cigarette smoking. Because the studies used by SMNA were not specifically designed to examine the health risks of dual use, it is unclear for how long dual users might have used either products concurrently or whether they ever used the products concurrently (since some of the studies presented examined current Swedish snus users who were ever smokers). Also, the referent group in all of the studies was never users, rather than exclusive smokers. Thus, not taken into account are factors such as years smoked and frequency of use that would be important for directly comparing dual users with exclusive smokers.

Furthermore, SMNA presents data on ever use of both products which may not necessarily reflect concurrent use of both products. Finally, the data presented by SMNA is based on studies of dual users in Sweden and does not necessarily reflect the potential differences in the patterns of dual use that might occur in the U.S. given that the patterns of dual use of smokeless tobacco and smoking between Sweden and the U.S. differ.

Conclusion. There is insufficient information to draw any conclusions on the health risks of dual use of these eight General Snus products that are the subject of the applications and smoking cigarettes, thus there is insufficient information to conclude that smokers who use snus in conjunction with smoking will realize any reductions in risk of tobacco-related disease.

(2) Effects on Tobacco Use Behavior among Current Tobacco Users.

Given the information on health risks summarized earlier in this document, one can conclude that any reductions in exposures and health risks to smokers may be reduced foremost from quitting smoking altogether, but there likely would be reductions in certain exposures and certain health risks for those that switch completely from smoking cigarettes to using the eight General Snus products that are the subject of the applications. There is insufficient evidence to conclude that any other behavioral outcome would result in reduced risk in the individual user (e.g., reduced smoking supplemented with use of these eight General Snus products). This section assesses the likely impacts of the modified risk tobacco products that are the subject of the applications on tobacco use behavior.

Clinical studies

Historical data indicate that nicotine exposures are similar between Swedish snus and cigarettes. Thus, as used by consumers, the General Snus products that are the subject of the applications expose individuals to nicotine levels that produce reinforcing effects and have an abuse potential, which could facilitate the transition from cigarette smoking to use of the products.

SMNA believes the data demonstrate that switching from cigarettes to these products reduces individual health risks. SMNA also purports that Swedish snus is preferred over NRTs as a cessation method in Sweden. However, there are no data that support use of snus generally or, more specifically, the products which are the subject of these applications as a means of aiding cigarette smokers in the United States to quit smoking. In fact, the clinical study conducted in the U.S. suggested that U.S. cigarette smokers are not very likely to use these products as an aid to quit smoking cigarettes which may indicate that U.S. smokers may not switch completely to these products.

Behavioral epidemiology

In addressing the impacts on users and non-users, SMNA primarily reviewed the epidemiological evidence from Sweden. These data provide information on patterns of use in Sweden and, SMNA proposes, provide insight into the potential outcomes for the U.S. population upon the marketing of the proposed MRTPs.

An overarching limitation to the evidence provided in the applications is the extent to which the tobacco use experience in Sweden and other Scandinavian countries would be expected to be observed in the U.S. following the issuance of a modified risk order. These snus products are popular among Swedish consumers for reasons unrelated to the provision of SMNA's proposed modified risk information. Snus has been and is marketed with health warnings in Sweden. Labeling and marketing of snus in Sweden has not referred to the product as reduced risk. Based on this information, it cannot be concluded that the rates of adoption of snus in Sweden are related to the presentation of modified risk information. The cited Swedish literature is therefore limited in informing the likely impact that the proposed modified risk tobacco products might have on tobacco use behaviors in the U.S.

Multiple factors may contribute to use of tobacco products, including but not limited to differences in consumer tastes and preferences; exposure to marketing and point of sale advertising; tobacco control policies including health warnings and public education campaigns, taxes, smoke-free and tobacco-free policies and marketing restrictions; diversification of the tobacco market with alternative products competing for market share and the sociocultural context of the product itself. Furthermore, differences in the sociocultural environment and consumer preferences, among other factors, may lead to differences in product uptake between countries. The applicant identifies the cultural significance of snus in Sweden vs. the U.S. as the "most fundamental difference between the U.S. and Scandinavian experiences." The applicant fails to address the similarities and differences of these factors between Scandinavian countries and the United States, and therefore does not make a clear connection as to the likely replicability of the Swedish experience to U.S. consumers.

While SMNA describes gradual population-level shift away from cigarette smoking to snus use in Sweden (particularly among males) and further cites evidence that snus was used both in Norway and Sweden as a popular smoking cessation aid, the epidemiological evidence provided does not enable us to assess the likely adoption of the products that are the subject of these applications among U.S. tobacco users. Specifically, the Applicant did not expressly address potential differences in U.S. and Scandinavian consumers or bridge the Scandinavian consumers experience data to the U.S. consumer experience. Indeed, recent research has indicated that U.S. cigarette smokers may not find snus an appealing alternative to cigarette smoking (Biener et al., 2014; Sami et al., 2012; Hatsukami et al., 2011). Furthermore, Swedish snus is currently available in the U.S., yet uptake of the product is low, with snus as a product class representing approximately 5% of 2014 US smokeless sales (FDA unpublished analysis), and General Snus making up approximately 6% of 2014 snus sales in the U.S. (FDA unpublished analysis).

We further conclude that the cited cross-sectional studies are unable to establish the sequence of product use, and those that retrospectively do so by asking about age at first use are likely vulnerable to recall errors and potential recall bias. Cross-sectional analyses are also unable to account for time-at-risk of smoking initiation among baseline snus users vs. non-users. Among the cohort studies cited, ascertainment of tobacco use (both ever use history as well as current use) is inconsistent across studies, preventing the exclusion of ever or former smokers at baseline from analysis. Lastly, few cited studies adjusted analysis for psychosocial factors associated with a propensity to use tobacco (either smoking or snus). These methodological concerns diminish the strength of SMNA's conclusions. None of the cited studies pertained to tobacco use among US consumers, and so the evidence cited does not inform the likely impact of the proposed MRTPs on the likelihood that tobacco users in the U.S. will adopt the product or switch to or switch back to other tobacco products that present higher levels of individual risk.

With respect to dual use, as SMNA acknowledges, differing definitions of current tobacco use varied across studies, complicating assessment of dual use. Despite this fact, numerous studies of varying design and populations identified factors associated with dual use. What was not immediately clear from the data presented, however, was what proportion of dual use was in fact a transitional state to eventual smoking cessation, versus a chronic dual use scenario where smokers utilized snus to satiate cravings when smoking was not possible. Given high rates of dual use among tobacco users in the U.S. (Benowitz et al., 2012), as well as prior marketing of snus products as an alternative for U.S. smokers to use when smoking is prohibited (Timberlake et al., 2011), dual use patterns of snus and smoking in the U.S. may vastly differ compared to the Swedish and Norwegian experiences. It is further unclear whether the proposed MRTPs may further promote dual use. As indicated above, the evidence does not support that tobacco-related disease risk is reduced as a result of dual use of the eight snus products with cigarettes. Thus, we cannot conclude that dual use will reduce risks to the individual or benefit the health of the population as a whole.

With respect to whether users who would otherwise quit using tobacco products will instead use the proposed MRTPs, the clinical trials and associated meta-analysis were not designed to evaluate the likelihood that tobacco users would initiate the use of snus use rather than quit all tobacco. Instead, they were designed to examine the use of snus as a smoking reduction or smoking cessation aid, by randomly assigning smokers to an active snus use or placebo group and following them over time for the behavioral outcomes of interest. In addition, neither study

evaluated snus use in the context of compete tobacco use cessation. Instead, the primary study endpoints were cigarette smoking reduction for the Serbian clinical trial (Joksic et al., 2011), and continuous smoking cessation for the U.S. clinical trial and the pooled meta-analysis (Fagerstrom et al., 2012). Therefore, the issue of whether those who plan to quit will switch to the products that are the subject of these applications instead could not be addressed using data from studies that evaluated the use of the products to help quit smoking completely.

Perception studies

Indirect behavioral evidence was provided by SMNA via an online Consumer Perception Study (CPS) of 13,203 respondents that included an approximately equal number of tobacco users and non-users. The CPS respondents, who were selected using a quota sample (nonprobability) from multiple online consumer research panels, were exposed to one of six warning labels on SMNA snus packaging (images of the four currently required package labels and two additional labels proposed by SMNA). According to SMNA, the purpose of the study was to measure the impact of these labels on the use of snus, general understanding of the warning label, and also any effect the warning label may have on perceptions of tobacco use related to health risks. Although applicant states this study will assess effects of labels on tobacco use behavior, behavior was not directly measured or observed in this study. Rather, this study assessed behavioral intentions, and a direct assessment of the "effects on behavior," per se is outside the scope of this study.

Overall, tobacco users that viewed the proposed SMNA product labels were more likely to report intentions to use snus than those that viewed the currently required warning labels. The percentage that reported they were likely to intend to use snus was varied by the type of tobacco products that the person was using at the time of completing the CPS. For example, 46% of the non-cigarette daily tobacco users exposed to the proposed SMNA product labels stated they were likely to intend to use snus while no more than 35% of the non-cigarette daily tobacco users exposed to a currently required label reported they were likely to intend to use snus. For cigarette only users, who constitute 48% of all tobacco users, 17% percent exposed to the two SMNA proposed warning labels stated they were likely to intend to use snus while at most 9% of those exposed to the four currently required warning labels stated that they were likely to intend to use snus.

There were several issues with the design and conduct of the consumer perception study. First, as the CPS uses a nonprobability sample, the results therefore may not generalize to a broader population, such as the U.S. population. Secondly, consumers' behavioral intentions to use tobacco products based on only viewing a warning label may not translate into actual behavioral outcomes. Third, questionnaire design issues introduce the potential for respondent error and cause respondent burden. Fourth, the applications do not include the study respondent recruitment and contact protocols.

Fifth, with respect to measurement, the items related to intentions to use the product – i.e., the "likelihood to use" item and "motivation to buy" item – asked participants to speculate about the impact that the warning label would have on their behavior, rather than simply asking them to report their likelihood of buying or using the product. Moreover, the "likelihood to use" item suffered from a flawed "double-barreled" response scale. In other words, they asked about more than one issue, but only allowed participants to choose a single response. For example, with

respect to likelihood of product use, participants were asked about two separate issues in a single question: (1) use likelihood, and (2) how the warning label influenced use likelihood: "…how does the information you saw on the warning label directly influence your likelihood to use snus?" and "Please indicate your likelihood to use this product…" Correspondingly, the response scales were double-barreled: the midpoint of the scale referred to the influence of the warning label ("The warning label has no impact…"), while the endpoints of the scale referred to the likelihood of using snus (e.g., "I would not at all be likely to use snus").

Finally, the stimuli employed in the CPS study (two proposed warning labels) do not match the wording of the proposed modified risk claim in the MRTPAs, so the wording proposed in the MRTPAs is not being assessed. In particular, the modified risk label stimulus does not include the word "WARNING". Moreover, the statement in the applications includes the phrase "substantially lower risks," whereas the statement in the stimulus presents a singular version: "a substantially lower risk". Thus, all of the shortcomings described above were compounded by the fact that the study did not assess participants' reactions to the exact modified label that is proposed in the applications.

Due to study limitations affecting the quality of the data, as well as flaws resulting in discrepancies between study stimuli and the applications' requested modified risk claim, findings from the applicant's consumer perception study do not allow us to draw firm conclusions regarding the effect of the proposed modified risk claim requested in these applications on consumers' perceptions, beliefs, and intentions for using these products, or their understanding of the modified risk claim. Keeping in mind that these limitations compromise the validity of the data, according to the findings, the modified risk label stimulus appeared to increase interest in using the product among users, compared to existing warnings, although descriptively these percent increases were generally not large (single digits); indeed, the effect is described as "modest" by the applicant. The pattern for participants identified as "imminent quitters" (a majority of the sample of current users) was similar. However, based on the information provided, the size of the effect of the information cannot be evaluated. Likewise, it cannot be determined how these individuals would use the product—including whether they would use the MRTP to supplement current tobacco use vs. switch completely.

Valid measures of behavioral intentions can be used as indicators of future behavior. Thus, consumer perception studies, such as those used to assess consumer understanding of modified risk information, may be used to assess behavioral intentions related to product use. Per theories of health behavior, behavioral intentions are considered the proximal predictors of behavior (Ajzen, 1991; Ajzen, 2002; Armitage and Conner, 2001). It is worth noting, however, that the extent to which these self-reported intentions predict future behavior can vary across behavioral domains (Sheeran, Harris, & Epton, 2014), and is sensitive to measurement (Sun & Morwitz, 2010). The predictive utility of self-reported intentions rests on a presumption of their "accuracy". In the current situation, participants were asked to forecast their interest in using a product based on very little information; for some of these participants, who reported they were not aware of snus at the beginning of the study, this was their first exposure to snus. For these participants, it is unclear if they understood what the product is or how it is used. These issues may pose challenges for the predictive utility of self-reported intentions to try a novel product.

In a real-world setting, there are multiple simultaneous influences on behavior, and this is another challenge for the predictive value of intentions to use a novel product. The appeal of the product and consumers' willingness to try the product will be shaped by social context. Lund and Scheffels (2012) describes this issue, noting that culture may affect the link between an individuals' reported willingness to try a product, and the likelihood that they actually will:

> "Thus, the cultural context in Norway and Sweden, where snus has been the most popular quit-smoking method for years (Lund, 2009), will probably facilitate willingness to develop into action. However, the situation might be different in states where experience with snus is low, such as Australia, where snus is banned, or California, where prevalence of snus use is low at the moment. Even if half of the current Australian smokers (Gartner, Jimenez-Soto, Borland, O'Connor, & Hall, 2010) and 13% of the smokers in California (Timberlake, 2009) expressed an interest in trying snus after being briefly informed about its lower harm profile than that of cigarettes, this may differ substantially from what eventually would develop into behavior."

Conclusion. The eight General Snus products expose users to sufficient quantities of nicotine to sustain dependence, thus providing the potential for smokers to adopt and potentially switch to these products. The applicant provided a summary of the Swedish and Norwegian experience, yet failed to demonstrate how the Scandinavian evidence might be applicable to U.S. consumers. Additionally, the body of evidence suggests that U.S. smokers may not be interested in switching to these products and, given the high rates of dual use among tobacco users in the U.S., may be more likely to use them in conjunction with continued smoking. In the absence of behavioral evidence, a well-designed consumer perception study could be used to assess behavioral intentions related to product use. However, the numerous limitations with the study conducted by SMNA in support of the applications preclude that assessment. Thus, there is substantial uncertainty as how current users of tobacco products will respond to the modified risk information proposed by SMNA and whether they will adopt the products and switch completely to the products, and we are unable to conclude that the behavioral response is likely to be one that would result in a reduction in health risks among the population of current tobacco users, overall.

(3) Effects on Tobacco Use Initiation among Non-users.

Given the information on health risks summarized earlier in this document, one can conclude that any use of the General Snus products among non-users, including former users of tobacco products, will increase exposures and health risks among non-users. This section assesses the likely impacts of the eight General Snus products that are the subject of these MRTPAs on tobacco use initiation.

Behavioral pharmacology

Of the eight snus products that are the subject of these MRTPAs, one contains the mint and (b) (4)

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(b) (4)

These ingredients ((b) (4) (b) (4)) can give the products a characterizing mint flavor that is distinct from other Swedish Match Snus products described in the published literature and in the submitted studies. Furthermore, the three products (General Mint Portion White Large 0.9 oz. (24g) General Nordic Mint Portion White Large .48 oz. (13.5g) General Nordic Mint Portion White Large .38 oz. (10.8g) (b) (4) A recent study (Choi et al., 2012) reported that young adults viewed new smokeless tobacco products (including snus) favorably, particularly because these products came in flavors. The same study also reported that study participants believed that these products could be gateways to cigarette smoking.

It has been suggested that flavored products can have a unique and important role with respect to initiation and maintenance of tobacco-use patterns, particularly among young adolescents and adults (Kenny et al., 1996; Lisnerski et al., 1991; Villanti et al., 2012). There is also evidence to suggest smokeless tobacco users typically initiate with a flavored product and that brand switching from a non-flavored to flavored product can often occur (Hatsukami et al., 2007; Oliver et al., 2013). Of note, however, that the aforementioned flavors are present in a variety of marketed ST products. Thus, the addition of these flavored products to the market would not be expected to dramatically or unexpectedly increase initiation rates of snus relative to traditional ST products.

Behavioral epidemiology

SMNA summarizes findings from Scandinavian observational studies regarding the evolving patterns of tobacco use among non-users over time. The applicant states that, in Sweden and Norway, "uptake of snus occurred across all age categories compared to cigarette uptake which appeared to occur more frequently at a younger age. In addition, tobacco initiation was shown to be gender-dependent, as males were more likely to initiate snus while females more likely to initiate cigarette smoking. Studies in Sweden and Norway have shown that snus initiation was more prevalent among former cigarette smokers than among non-tobacco users (Furberg et al., 2005; Furberg et al., 2006; Lund et al., 2010; Lund et al., 2011)." Reviewers noted concerns regarding inconsistent and incomplete ascertainment of tobacco use across studies, which may have underestimated tobacco use initiation among non-users. Similar to research provided for current tobacco users, cited findings of population-level tobacco use behaviors in Scandinavian countries may have limited applicability to assessing the potential impact of the proposed MRTPs on tobacco use initiation among non-users in the US.

In a Swedish Match-funded 2015 article that reviewed the strengths and limitations of many of the Scandinavian studies cited by SMNA, in which the author concluded, "There is currently no good information relating to the question of whether prior snus use might encourage initiation of smoking. All the studies have weaknesses in design or analysis that render their conclusions unreliable, particularly as data on other factors relevant to smoking initiation are not taken into account. Evidence is needed from better designed, better analyzed studies which pay great attention to the problem of confounding." (Lee, 2015) We concur that the cited cross sectional studies are unable to establish the sequence of product use, and those that retrospectively do so

by asking about age at first use are likely vulnerable to recall errors and potential recall bias. Cross-sectional analyses are also unable to account for time-at-risk of smoking initiation among baseline snus users vs. non-users. Among the cohort studies cited, ascertainment of tobacco use (both ever use history as well as current use) is inconsistent across studies, preventing the exclusion of ever or former smokers at baseline from analysis. Lastly, few cited studies adjusted analysis for psychosocial factors associated with a propensity to use tobacco (either smoking or snus). These methodological concerns diminish the strength of SMNA's conclusions. In addition, none of the cited studies pertained to tobacco use among U.S. consumers, and so the evidence cited has limited applicability to assessing the likely impact of the proposed MRTPs on the likelihood that non-users who adopt the tobacco products will switch to other tobacco products that present higher levels of individual health risk.

With respect to former users, SMNA cites data from Scandinavian cohorts "indicates that that being a former smoker is common among snus users (Scientific Committee on Emerging and Newly Identified Health Risks 2008; Scheffels et al. 2012), although there is some suggestion that there are low rates (5%) of relapse among former smoking snus users (Lundqvist et al., 2009)." However, the observational studies from Sweden and Norway, which suggest that snus' role was primarily that of a smoking cessation tool with limited relapse among former smokers who initiated snus, may have limited applicability to assessing the impact of snus marketing among former tobacco users in the U.S.

Perception studies

In the Consumer Perception Study conducted by SMNA, fewer non-users of tobacco who were exposed to the SMNA proposed warning label, *No tobacco product is safe, but this product presents a substantially lower risk to health than cigarettes* reported they were unlikely to use (or discouraged from buying) snus compared to those exposed to the currently required warning labels. Fifty-six percent of tobacco non-users exposed to the proposed label with the *substantially* wording and 60% of those exposed to the other SMNA proposed label stated that would not at all be likely to use snus. The currently required warning label that mentions *mouth cancer* had the highest percentage of tobacco non-users, 71.5%, stating that they would not at all be likely to use snus.

Due to study limitations affecting the quality of the data, as well as flaws resulting in discrepancies between study stimuli and the applications' requested modified risk claim, findings from the applicant's consumer perception study do not allow us to draw firm conclusions regarding the effect of the proposed modified risk claim requested in these applications on consumers' perceptions, beliefs, and intentions for using these products, or their understanding of the modified risk claim. Keeping in mind that these limitations described above that compromise the validity of the data, according to the results, in general, the currently required warning labels discourage non-users from intending to use the products more than the proposed labels in the study. It is unknown how this would translate into actual behavior. Also, it cannot be determined how these individuals would use the product—including whether and how many non-users who initiate would continue using the product, and of those, how many would subsequently transition to other tobacco products.

Conclusion. The application included some behavioral data among Scandinavian populations to shed light on the likely impacts of non-users, however, the data has limited applicability to the U.S. population. In the absence of behavioral evidence, a well-designed consumer perception study could be used to assess behavioral intentions related to product use among non-users. However, the numerous limitations with the study conducted by SMNA in support of the applications preclude that assessment. Thus, there is substantial uncertainty as how current non-users of tobacco products will respond to the modified risk information proposed by SMNA and we are unable to conclude that the behavioral response is not likely to be one that would result in an increase in health risks among the population of current tobacco non-users, overall.

(4) Effect of Marketing on Consumer Understanding and Perception.

Section 911(g)(1) of the FD&C Act requires the agency to determine whether the proposed modified risk tobacco "product, as it is actually used by consumers, will—(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) 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 connection with this determination, the agency assesses the impact of the proposed modified risk tobacco products on tobacco use behavior (including how consumers would use the product and whether consumers will switch to or initiate the product). Consumer comprehension is an important precursor to consumer behavior and can affect how consumers actually use the product. In addition, relatedly, section 911(h)(1) of the FD&C Act also requires that "any advertising or labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the disease and health-related conditions." This section summarizes the information on consumer understanding and perceptions, as both are potential precursors to actual behavior and could affect how consumers actually use the products. This information also provides data on whether consumers are likely to comprehend the modified risk information in the context of total health.

Perception Studies

SMNA provided a literature review focused on knowledge, attitudes, and beliefs related to snus (but also reported studies about smokeless tobacco) among adults and adolescents in Sweden and other Scandinavian populations. The report states that the search was focused on the last 10 years, but the review also includes studies published prior to 2004 (Rolandsson and Hugoson, 2000; Bolinder et al., 2002). Per the report, several search methods were employed, including a search of MEDLINE (search terms provided), a review of the references cited by articles identified in the MEDLINE search, and a separate literature search conducted for a companion ENVIRON report on tobacco use behavior.

Thirteen studies were identified for inclusion in the report. These studies, published between 2000 and 2012, employed a range of methods, including: cross-sectional survey studies (n = 9); prospective longitudinal studies (n = 2); and intervention or experimental studies (n = 2). The studies primarily report data from Sweden and Norway. SMNA's review in section 6.4 of the application is organized by studies pertaining to adults and then studies pertaining to "youth"

(note, this group includes both adolescents and young adults). Some studies are reported in multiple sections. The majority of the studies report findings from cross-sectional surveys examining tobacco users' perceptions of the harms of snus, comparing harms of snus and cigarettes, and relative risk of nicotine addiction. Two studies examined attitudes and knowledge among medical professionals regarding health effects of snus as a cessation aid; and two studies examined the effect of providing information about health risks of tobacco on knowledge and perceptions.

Several findings from this literature review are worth noting. First, the study by Borland et al. (2012) suggests that providing detailed information about the relative harms of tobacco products can affect smokers' reported likelihood of trying smokeless tobacco. Moreover, when smokers read such information, it has the potential to influence their perceptions of harm from smokeless tobacco and to impact their perceptions about the mechanisms through which cigarette smoking harms health (Borland et al., 2012). Second, the findings reported by Wikmans and Ramstrom (2010) shed light on perceptions of harm about snus in Sweden and Norway. Despite the relatively high prevalence of snus use, these findings suggest the majority of people in these countries do not perceive it to be less harmful than smoking. According to SMNA, the situation in the U.S. is similar to that described in the applications, in particular, that most people overestimate the harmfulness of Swedish snus compared to cigarettes. Although SMNA did not include studies from the U.S. in their review of the literature (although one study (Borland et al., 2012) did include a subsample of U.S. participants), to address this gap FDA conducted a complementary literature review. The conclusions of this review are mostly consistent with the characterization by the applicant which is that, in general, individuals in the U.S. do not perceive snus to be less harmful than cigarettes.

A Consumer Perception Study was conducted by SMNA and was intended to address aspects of consumer understanding, among others. However, in addition to the limitations described above, several issues with study design further limit the conclusions that can be drawn. Problems with construct measurement compromise data validity and obscure interpretation of results. For instance, although viewing the modified risk statement appeared to reduce the perceived health risks of snus compared to cigarettes, the survey item assessing this effect explicitly asked participants to consider the influence of the warning label on their perceptions. This may have altered the cognitive processes through which participants would normally have judged the risks of the product. For example, it may have produced a demand characteristic to rate the risk according to the strength of the warning.

Moreover, the study lacked measures for assessing how participants interpreted the modified risk information. The study did not assess perceptions of certain specific risks, such as those from dual use of the products with cigarettes (e.g., use of the products to reduce, rather than totally cease, cigarette consumption) or the risks of using the products while pregnant. Also, the study included an item assessing subjective understanding of the modified risk statement. Whereas the item is face-valid, because it relies on a self-assessment of (subjective) understanding, the data do not provide substantive information about consumers' understanding or comprehension of the modified risk information. And, regardless, participants reported that the modified risk statements evaluated in the CPS were less understandable than the currently required warnings.

Thus, whereas the study can provide information about a related statement, because the modified risk information was not tested verbatim, ultimately, we are unable to use this evidence to draw firm conclusions about consumer understanding of the modified risk information requested in these applications.

These limitations notwithstanding, this study was not designed to address the implications of conveying modified risk information in the context of warning labels. The request of these applications, to provide modified risk information in the context of the warning labels (implicitly by removing two of the currently required warning statements and explicitly by altering another warning statement to convey relative benefit information) itself, may have implications for consumer comprehension of the modified risk information and perceptions of the products.

SMNA proposes to remove two warnings currently required for smokeless tobacco and to modify another warning. Thus, modified risk information about these snus products would be conveyed to consumers in two ways: (1) implicitly, by the removal of warnings (i.e., mouth cancer and gum disease/tooth loss) from product labels, labeling, and advertising; and (2) expressly, through a warning label amended include a statement about a potential benefit of product use (i.e., reduced risk) relative to another class of products (cigarettes). This explicit communication of modified risk information in the context of warnings raises additional questions about consumer understanding of that modified risk information.

SMNA's Consumer Perception Study was not designed to assess the impact of the context of explicit modified risk information on consumer understanding, which could be done, for example, through a comparison of the impact of including modified risk information in the warning label (as SMNA proposes) with including it elsewhere on the product label, separate from and in addition to the warning label. There are no studies that address this question specifically. A related question was addressed in a study conducted by Capella et al. (2012). This study examined the effect of presenting modified risk information alone or in combination with a warning label. However, it did not evaluate the effect of presenting the modified risk information in the warning label itself. The other related study is Popova and Ling (2014). This study examined the same MR claim requested in this application; but their study design did not provide a comparison that would speak to the effect of the context of that information.

The presence of language that conveys a benefit of product use (relative to another product class) included in a place where consumers expect to see information about potential risks could cause confusion. Finally, given that the amended warning includes the communication of (relative) benefits of use (compared to use of another product class)—information that is atypical for inclusion in a product warning (Wogalter, 2006)—it is unclear if consumers still perceive this statement as a warning at all, which could impact consumer behavior as well as consumer comprehension of the modified risk information in the context of total health and in relation to all tobacco-related disease. Without studies specifically designed to test this question, we cannot infer how consumers will perceive and comprehend this type of modified risk information conveyed within the context of a warning label that is authorized by FDA, as a regulatory agency.

Conclusion. SMNA's study findings pertaining to the expressed modified risk statement that was tested (which differs from the one requested in the applications), suggest that compared to the

currently required "not a safe alternative" warning label, participants found the modified risk information labels evaluated in the study less understandable. Relatedly, participants who saw the modified risk labels were more likely to rate snus as somewhat less harmful compared to NRT, compared to the currently required warning labels, which indicates potential for an adverse effect on population health. There is not sufficient information to conclude that participants comprehended the modified risk information in the context of total health. The study was not designed to address the implications of conveying modified risk information in the context of warning labels. The request of this application, which is to include modified risk information in the context of the warning label itself, may have implications for consumer comprehension of the modified risk information and perceptions of the products, leading to a high degree of uncertainty about potential behavioral impacts. We are therefore unable to conclude whether behavioral responses to the modified risk information will result in outcomes that would benefit the health of the population as a whole.

(5) Quantification of the Effect on the Population as a Whole.

This discussion evaluates the quantification of the likely impact on the population as a whole described in the applicant's Dynamic Population Model.

Population Modeling

SMNA describes the implementation of a Dynamic Population Model (DPM) to track tobacco use and harm in a population and presents results from analyses conducted with the model to assess the hypothetical effects of cigarette and snus use in the U.S. population in a variety of scenarios. (b) (4) [redacted].

The DPM is a simulation model to compare all-cause mortality in a base case scenario (individual only exposed to cigarettes) of cigarette use and in a counter-factual scenario (individual exposed to cigarettes and the proposed MRTPs that are the subject of these applications). (b) (4) [redacted]

The information submitted in the applications did not allow for a rigorous scientific review, because it lacked information on the formulation, development, and implementation of the model as well as mathematical details. However, the model and analyses provide for a range of tobacco use behaviors including initiation and cessation of snus and cigarettes, switching between the products, and, to some extent, dual use.

In general, while the DPM may provide some information on possible population health outcomes based on specific assumptions about tobacco use patterns and trends, it is difficult to determine from this population model results what effect, if any, the proposed modified risk tobacco products that are subject of the applications as actually used by consumers would impact

the health of the population as a whole, taking into account both users and non-users. Analyses were conducted to estimate tipping points, i.e. the proportion of a population group that must experience a benefit in survivorship due to a change in tobacco use to offset a specified proportion of the population group experiencing a reduction in survivorship. The provided tipping point analyses present some information on possible trade-offs in health outcomes due to levels of certain tobacco use behaviors, but these analyses consider a limited number of behaviors and the results presented are sensitive to the wide ranges in values that are presented for some behaviors. For example, the applicant presents a tipping point analysis for the proportion of current smokers who otherwise would or would not quit smoking who switch to snus use, but the analyses do not consider the possibility of transition to dual use of both products by current smokers instead of smoking cessation. Similarly, another analysis considers the trade-offs between initiation of snus use among never tobacco users who otherwise would or would not initiate cigarette use, but the presented results are highly sensitive to assumptions about the proportion of never tobacco users who initiate snus use and then switch to smoking, which are presented in a range from 0% to 100%. Although the applicant models a number of different scenarios of the impact to users and non-users, some result in population health benefits and some result in population health harms, and the applicant provides inadequate evidence as to which scenarios are more or less likely.

The applicant also presents results for differences in survivorship for various counterfactual scenarios compared with a base case scenario, but these analyses also present methodological issues. The applicant states that inputs in the base case and counterfactual scenarios are generally based on U.S. and Swedish data, respectively, but it is often unclear how these inputs were specifically derived from the original data. It is also not clear from the applications if certain tobacco use behaviors such as initiation of the proposed MRTP by former cigarette smokers and subsequent relapse to smoking were included in this implementation of the model. Moreover, and perhaps most importantly, the tobacco use patterns in the counterfactual scenarios are said to be based on trends that have been observed previously in Sweden, but SMNA provides little evidence to support the relevance of these transition probabilities to tobacco use patterns that would be expected if the proposed modified risk tobacco products were authorized in the U.S.

Conclusion. SMNA 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. The information provided in the applications is not sufficient for the FDA to conduct an evaluation of the validity of the DPM to provide evidence that could be extrapolated to the population as a whole. We are thus unable to ascertain the direction and magnitude of the effect, if any, the proposed MRTPs would have on health of the population as a whole.

ENVIRONMENTAL IMPACT[12]

[12] This Environmental Impact section only applies to the proposed action to deny issuance of section 911(g)(1) modified risk orders with respect to the request to remove the gum disease and tooth loss warning.

The proposed action is to deny issuance of orders under section 911 of the FD&C Act; therefore, the products that are the subject of these eight applications may not be introduced or delivered for introduction into interstate commerce. This proposed action falls within a class of actions that is categorically excluded under 21 CFR 25.35(b) and, therefore, normally does not require the preparation of an environmental assessment (EA) or an environmental impact statement (EIS). FDA has considered whether this action presents extraordinary circumstances and has determined that none exist. Therefore, this action does not require preparation of an EA or an EIS.

CONCLUSIONS

After conducting a thorough scientific review of all of these materials, FDA concludes that:

- With respect to the request to remove the gum disease and tooth loss warning, based on the available scientific evidence, SMNA has 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.
- With respect to the requests to remove the mouth cancer warning and revise the "not a safe alternative" warning, 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.

1. SMNA requests to omit from the label and advertising of the eight General Snus products "WARNING: This product can cause gum disease and tooth loss." 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 gum disease or tooth loss. 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 gum disease or tooth loss.

   After conducting a thorough assessment of the scientific substantiation for the claim that the eight General Snus products cannot cause gum disease or tooth loss, FDA determined that the claim is not substantiated. On the contrary, there is little biologically plausible reason to expect that outcomes related specifically to gum and teeth of users resulting from the use of the eight products would differ from those outcomes resulting from the use of other smokeless tobacco products. Indeed, given that these eight General snus products, like other smokeless tobacco products, cause delayed soft tissue wound healing, these products would not be expected to differ from other smokeless tobacco products with respect to these disease outcomes. Furthermore, the epidemiological evidence indicates that the use of these products, as actually used by consumers in Sweden and Norway, increases the risks of certain outcomes classified as gum disease or tooth loss, or precursors to gum disease and tooth loss. Because the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in

particular "can cause gum disease and tooth loss," the proposed modified risk claim is not substantiated. Additionally, SMNA did not provide evidence regarding how the modified risk information (i.e., the removal of the gum disease and tooth loss warning) would impact consumer behavior or whether consumers would understand the modified risk information in the context of total health. As a result, SMNA has 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. Accordingly, the request to omit the warning related to gum disease and tooth loss should be denied.

2. SMNA requests to omit from the label and advertising of the eight General Snus products "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.

   After conducting a thorough assessment of the scientific substantiation for the claim that the eight General Snus products cannot cause mouth cancer, FDA determined that the claim is not substantiated. 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 nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (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, although many of the epidemiological studies of Swedish snus may not have been statistically powered to detect moderate increases in oral cancer risk, the most recent published epidemiological study found a statistically significant increased risk (Roosaar et al., 2008). Accordingly, because the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular "can cause mouth cancer," the proposed modified risk claim is not substantiated. Additionally, SMNA 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, 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. Accordingly, modified risk orders should not be issued for these products based on the proposed claim in its current form. However, the 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 relating to mouth cancer for these tobacco products.

3. SMNA requests to revise the currently required "WARNING: This product is not a safe alternative to cigarettes" on the label and advertising of the eight General Snus products, 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 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 diseases, particularly in the context of a warning. As a result, 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. Accordingly, modified risk orders should not be issued for these products based on the proposed claim in its current form. However, the 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 relating to health risks compared to cigarettes for these tobacco products.

RECOMMENDED ACTIONS

With respect to the request to remove the gum disease and tooth loss warning, FDA should deny the issuance of modified risk orders for the eight General Snus products that are the subject of the applications: MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029, as identified on the cover page of this review. Based on the available scientific evidence, SMNA has 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.

Each Denial Letter should cite the following deficiency:

- You request to omit from the label and advertising of the eight General Snus products "WARNING: This product can cause gum disease and tooth loss." 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 gum disease or tooth loss. 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 gum disease or tooth loss.

  After conducting a thorough assessment of the scientific substantiation of the claim that the eight General Snus products cannot cause gum disease or tooth loss, FDA determined that the claim is not substantiated. On the contrary, there is little biologically plausible reason to expect that outcomes related specifically to gum and teeth of users resulting from the use of the eight products would differ from those outcomes resulting from the use of other smokeless tobacco products. Indeed, given that these eight General snus products, like other smokeless tobacco products, cause delayed soft tissue wound healing, these products would not be expected to differ from other smokeless tobacco products with respect to these disease outcomes. Furthermore, the epidemiological evidence indicates that the use of these products, as actually used by consumers in Sweden and Norway, increases the risks of certain outcomes classified as gum disease or tooth loss, or precursors to gum disease and tooth loss. Because the totality of the scientific evidence supports the statement that smokeless tobacco products in general and these products in particular "can cause gum disease and tooth loss," the proposed modified risk claim is not substantiated. Additionally, you did not provide evidence regarding how the modified risk information (i.e., the removal of the gum disease and tooth loss warning) would impact consumer behavior or whether consumers would understand the modified risk information in the context of total health. As a result, you have not demonstrated that, as actually used by consumers, the product 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. Accordingly, the request to omit the warning related to gum disease and tooth loss is denied.

With respect to the requests to remove the mouth cancer warning and revise the "not a safe alternative" warning, FDA should issue a Response Letter for the eight General Snus products that are the subject of the applications: MR0000020-MR0000022, MR0000024-MR0000025, and MR0000027-MR0000029, as identified on the cover page of this review. 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, the applications could be amended in several ways, which could provide sufficient evidence to support issuance of modified risk orders.

The Response letter should cite 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, the Response Letter should include the following requests and recommendations:

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.

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APPENDICES

Appendix A

The following information is applicable to MR0000020, General Loose:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/g		
Tobacco (b) (4)	Ingredient	mg/g		
Tobacco (b) (4)	Ingredient	mg/g		
(b) (4)	Ingredient	mg/g		
	Ingredient	mg/g		
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	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[13]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		

[13] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4).

Performance Criteria

Phase	Test	Method[14]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			

[14] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix B

The following information is applicable to MR0000021, General Dry Mint Portion Original Mint:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[15]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[17]		
Pouch Paper Caliper (µm)		

[15] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b)(4)

[16] The range limits for the portion mass in MR0000021 are what the applicant defines as acceptance criteria. FDA's definition for range limits matches the applicant's definition for acceptance criteria.

[17] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[18]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			

[18] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix C

The following information is applicable to MR0000022, General Portion Original Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[19]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[20]		
Pouch Paper Caliper (µm)		

[19] The applicant provided [(b)(4)] buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: [(b)(4)]

[20] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[21]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			

[21] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix D

The following information is applicable to MR0000024, General Classic Blend Portion White Large – 12 ct:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[22]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[23]		
Pouch Paper Caliper (µm)		

[22] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

[23] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[24]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

[24] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix E

The following information is applicable to MR0000025, General Mint Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[25]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[26]		
Pouch Paper Caliper (µm)		

[25] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

[26] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[27]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

[27] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix F

The following information is applicable to MR0000027, General Nordic Mint Portion White Large – 12 ct:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4) (b) (4))	Ingredient	mg/pouch		
Tobacco (b) (4) (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[28]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[29]		
Pouch Paper Caliper (µm)		

[28] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to (b) (4)

[29] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[30]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

[30] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix G

The following information is applicable to MR0000028, General Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4) (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4) (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[31]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[32]		
Pouch Paper Caliper (µm)		

[31] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

[32] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[33]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

[33] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System

Appendix H
The following information is applicable to MR0000029, General Wintergreen Portion White Large:

Chemistry Product Specifications

	Category	Unit of Measure	Target Value	Range Limit
Nicotine	Design	%	(b) (4)	
Moisture	Design	%		
pH	Design			
Tobacco (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4) (b) (4)	Ingredient	mg/pouch		
Tobacco (b) (4) (b) (4)	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		
	Ingredient	mg/pouch		

Design Parameters

Design Parameter	Target Value	Range Limit
Tobacco Cut Size (%)[34]	(b) (4)	
Final Moisture (%)		
Blend Moisture (%)		
Leaf Tobacco Moisture (%)		
Portion Mass (mg)		
Portion Length (mm)		
Portion Width (mm)		
Portion Thickness (mm)		
Pouch Paper Basis Weight (g/m2)		
Pouch Paper Air Permeability (L/m2/s)		
Pouch Paper Wicking[35]		
Pouch Paper Caliper (µm)		

[34] The applicant provided (b) (4) buckets to characterize tobacco cut size. Therefore, the tobacco blend cannot be represented with a single size value and corresponding range limit. In each cell, the data (given in %) represents the following buckets, from top to bottom: (b) (4)

[35] In this submission, the applicant's nicotine uptake evaluation demonstrates the nicotine extraction rates differ even in the products with the same pouch material, indicating the wicking rates are not affecting the nicotine absorption rates in this new product. Therefore, wicking values are not needed for this product.

Performance Criteria

Phase	Test	Method[36]	Performance Tolerance
Grinding	(b) (4)		
Grinding			
Snus blend processing			
Packaging			
Packaging			
Packaging			
Packaging			

[36] QEMS: Swedish Match North America, Inc.'s proprietary Quality and Environmental Management System