Premarket Tobacco Application (PMTA) Technical Project Lead (TPL) Review

Submission Information			
Applicant	Swedish Match North America, Inc.		
Submission Date	March 11, 2015	**FDA Receipt Date**	March 11, 2015
PM0000010: 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)		
Characterizing Flavor	None		
PM0000011: 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)		
Characterizing Flavor	Mint		
PM0000012: General Portion Original Large			
Product Category	Smokeless Tobacco		
Product Sub-Category	Portioned Snus		
Package Type	Plastic Can		
Package Quantity	24.0g		
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)		
Characterizing Flavor	None		

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

PM0000013: General Classic Blend Portion White Large - 12ct	
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
PM0000014: 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
PM0000015: General Nordic Mint Portion White Large - 12ct	
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

PM0000016: 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)
Characterizing Flavor	None

PM0000017: 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)
Characterizing Flavor	Wintergreen

	STN	Submission Date	Solicited Y/N
Amendment(s)	PM0000018	3/31/2015	Y
	PM0000019	3/31/2015	Y
	PM0000020	3/31/2015	Y
	PM0000021	3/31/2015	Y
	PM0000022	3/31/2015	Y
	PM0000023	3/31/2015	Y
	PM0000024	3/31/2015	Y
	PM0000025	3/31/2015	Y
	PM0000026	6/3/2015	Y
	PM0000027	6/23/2015	Y
	PM0000029	7/8/2015	Y

	Cross Referenced Submission	Industry Meetings	Other Related Submission STN(s)
Related Submissions	MR0000020		SE0000140, SE0010524
	MR0000021		SE0000139, SE0010525
	MR0000022		SE0000143, SE0010526
	MR0000024		SE0010528
	MR0000025		SE0000141, SE0010529
	MR0000027		SE0010531
	MR0000028		SE0000144, SE0010532
	MR0000029		SE0000145, SE0010533
Product Use	☒ For Consumer Use ☐ For Further Manufacturing		
Product Type	☒ Complete ☐ Component, Part, or Accessory		

DISCIPLINES REVIEWED	DATE OF REVIEW
Behavioral Pharmacology	October 21, 2015
Chemistry	October 30, 2015
Clinical Pharmacology	October 21, 2015
Engineering	October 2, 2015
Environmental Science	October 8, 2015
Epidemiology	October 6, 2015
Medical	October 20, 2015
Microbiology	October 15, 2015
OCE Review (DEM & DPAL)	October 6, 2015
Social Science	October 2, 2015
Statistics	September 28, 2015
Toxicology	October 16, 2015

Recommended Action(s)

☒ Issue a Marketing Authorization letter; application contains sufficient evidence to demonstrate the product is appropriate for the protection of public health.

☐ Issue a No Marketing Authorization letter; application does not contain sufficient evidence to demonstrate the product is appropriate for the protection of public health.

Technical Project Lead Name:

CTP/OS Ii-Lun Chen, MD
Director, Division of Individual Health Science

Digitally signed by Iilun Chen -S
Date: 2015.11.02 15:44:09 -05'00'

Signatory Decision:

☒ I concur with TPL recommendation and basis of recommendation

☐ I concur with TPL recommendation and am providing additional comments (see separate memo)

☐ I do not concur with TPL recommendation as stated in my separate memo

Signatory: David Ashley, Ph.D.
CTP/OS RADM, U.S. Public Health Service
Director
Office of Science

Digitally signed by David Ashley -S
Date: 2015.11.03 13:25:56 -05'00'

Premarket Tobacco Application Technical Project Leader Review

I. Executive Summary

On March 11, 2015, Swedish Match North America (SMNA) submitted eight General brand snus premarket tobacco product applications (PMTAs) to FDA seeking authorization under Section 910(b) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

Scientific review of these eight applications demonstrates that these eight products have the following qualities:

- Produced with a voluntary, proprietary standard using acceptable manufacturing processes as confirmed by both application review and on-site inspections. The applicant's heat treatment process distinguishes Swedish snus from other types of smokeless tobacco (ST), including snus-like products sold in the US market. The proprietary quality standard for Swedish snus products was developed to ensure product quality. The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products.

  The proposed products contain significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers using ST products. Assuming persons who would have used other US ST products use these product instead, an individual using these products with reduced NNN levels could decrease the excess cancer risk[2] by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of United States (US)-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor.

- Levels of other harmful and potentially harmful constituents (HPHC)(including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels of ST products currently on the US market. Certain HPHCs (such as acrolein, acetaldehyde, cadmium, and nickel) have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products.

- When used as exclusively instead of other smokeless tobacco products or cigarettes on the US market, these products offer potential for reductions in oral cancer risk.

[2]The excess lifetime cancer risk is a toxicological tool to estimate the probability of cancer incidence in a population of individuals for a specific lifetime from projected intakes (and exposures) and dose-response data (i.e., slope factors) for a specific chemical.

- When used as exclusively instead of combusted tobacco products, these products offer lower risk of developing respiratory diseases (i.e., chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis) and cancers (such as oral, esophageal, and lung) than smokers.

- If nonusers were to initiate or users decrease cessation, there would be negative health consequences.

- Use of Swedish snus products is not risk-free and its use is associated with adverse health risks such adverse pregnancy outcomes, oral disease, increased risk of fatal cardiovascular events, pancreatic cancer, diabetes, and all-cause mortality.

- It is anticipated that the marketing of the proposed products, as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

Information from national tobacco use studies and other studies submitted by the applicant indicate that migration of smokers to exclusive use of these proposed snus tobacco products while possible is expected to be limited. It is more likely that uptake of the proposed products occurs among current smokeless tobacco users. Given the above listed justifications based on information gathered from nonclinical and clinical product evaluations as well as substantial epidemiological studies, the totality of evidence provided in the applications support authorization of these products so that current ST product users will have additional options for less toxic tobacco products, thereby potentially decreasing the negative health impact from tobacco product use making the marketing of these proposed products appropriate for the protection of public health.

II. Review of PMTA

1. Background and Regulatory History

A new tobacco product, including a tobacco product modified in any way ("including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient" (section 910(a)(1)(B)), after February 15, 2007 requires premarket review and an order from FDA authorizing the marketing of the product.

A PMTA must be submitted to FDA under section 910(b) of the FD&C Act and a marketing authorization order must be received from FDA under section 910(c)(1)(A)(i) prior to marketing any new tobacco product, unless FDA has found that the product is substantially equivalent to a tobacco product commercially marketed in the US as of February 15, 2007 (see section 910(a)(2)(A)(i)) or is exempt from a substantial equivalence determination pursuant to regulation (see section 910(a)(2)(A)(ii)).

FDA will deny a PMTA and issue a no marketing authorization order that the product may not be introduced or delivered for introduction into interstate commerce under section 910(c)(1)(A)(ii) where FDA finds that:

- there is a lack of a showing that marketing the product is appropriate for the protection of the public health;
- the methods, facilities, or controls used in manufacturing, processing, or packing do not conform to manufacturing regulations issued under section 906(e) (21 U.S.C. 387f(e));
- the proposed labeling is false or misleading; or
- it is not shown that the product complies with any tobacco product standard in effect under section 907 (21 U.S.C. 387g), and there is not adequate information to justify deviation from the standard.

The statute provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the protection of the public health shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account ─

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Regulatory History

On March 11, 2015, Swedish Match North America (SMNA) submitted eight General brand snus PMTAs to FDA seeking authorization under Section 910(b) of the Food, Drug and Cosmetic Act. The PMTAs [PM00000010-PM00000017] were submitted in connection with the June 10, 2014 Modified Risk Tobacco Product Applications (MRTPA) for the same eight snus products. However, the PMTAs are for the eight General brand snus products without any modified risk claims (proposed product labeling submitted March 31, 2015 [PM0000018-PM0000025]).

Significant regulatory interactions include the following:

- March 11, 2015: FDA received PMTAs for eight snus products.
- March 25, 2015: FDA issued eight acknowledgment letters.
- March 26, 2015: FDA held a teleconference with SMNA requesting SMNA submit one label that includes one of the health warnings for each tobacco product because SMNA did not submit specimen labels specific to the PMTAs.
- March 31, 2015: SMNA submitted amendments, PM0000018-PM0000025, in response to a teleconference held on March 26, 2015.
- March-April 2015: FDA conducted on-site clinical and manufacturing inspections of domestic and foreign clinical sites related to the SMNA MRTPAs. FDA inspected clinical study sites (Indianapolis, IN and Serbia), manufacturing sites (Sweden), and a SMNA laboratory facility (Sweden).

- April 2, 2015: FDA conducted a follow-up teleconference with SMNA regarding the status of samples being shipped to Southeastern Regional Laboratory (SRL) for testing.
- April 23, 2015: FDA issued eight Sample Acknowledgement letters acknowledging SRL's receipt of samples on April 15, 2015 from SMNA.
- April 9-10, 2015: A meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) discussed the ten submitted MRTPAs, including the adequacy of the scientific evidence to support proposed health claims of substantially reduced health risk in comparison with cigarettes.
- May 7, 2015: FDA determined that the eight PMTAs met the filing requirements for a PMTA seeking a marketing order under section 910(c)(1)(A)(i) of the FD&C Act. A Filing letter was issued to SMNA.
- May 20, 2015: FDA issued an Advice/Information (A/I) Request letter to SMNA.
- June 3, 2015: SMNA submitted an amendment, PM0000026, in response to FDA's May 20, 2015 A/I letter.
- June 12, 2015: FDA issued an A/I Request letter to SMNA.
- June 23, 2015: SMNA submitted an amendment, PM0000027, in response to FDA's June 12, 2015 A/I letter.
- June 29, 2015: FDA held a teleconference with SMNA to discuss engineering deficiencies for their PMTA and MRTP applications.
- July 8, 2015: SMNA submitted an amendment, PM0000029, in response to a teleconference held on June 29, 2015.

Current Submission Tobacco Product

Swedish Match General brand snus is an oral ST product that is moistened to facilitate use in the oral cavity. The applicant defines "snus" as an ST product that is produced and used in Sweden and manufactured using a heat treatment process according to a proprietary standard. This process distinguishes Swedish snus from other types of ST, including snus-like products sold in the US market. Swedish snus is made mainly from air-dried tobacco varieties, various salts, flavoring, and moisture-preserving substances. SMNA describes the snus products as "moist (% moisture) to semi-moist % moisture) oral smokeless products which are typically placed between the upper lip and the gum and do not require expectoration during use." In contrast, American ST products are typically placed between the lower lip and gum and require expectoration during use (Hatsukami et al., 1988). In Sweden, the product is classified as food, contains only food-approved ingredients, and is manufactured in a way that is consistent for food production.

Swedish Match currently markets other snus products in the US in two packaging formats: loose snus and portioned snus.

- **Loose Snus:** Traditional variant of Swedish snus that is formed by pinching a desired amount upon use.
- **Portioned Snus:** Consists of pre-packed pouches wrapped in a non-woven fabric for discrete and hygienic usage. The pouches are available in different sizes and weights (e.g., from 0.3 g to 1.0 g/pouch). Swedish Match produces two types of pouch products, original and white.

2. Overview of ST Products on the US Market

According to the August 2014 Euromonitor International report, in 2013 the tobacco industry had US sales totaling $112.2 billion (including cigarettes, cigars, ST tobacco, cigarettes including RYO stick equivalent). ST accounted for $7.4 billion. Therefore, ST accounted for 6.6% of tobacco sales in 2013. ST products are marketed in the US in categories such as US-style moist snuff, chewing tobacco, Swedish-style snus, dry and hard snuff. US style moist snuff comprises greater than 82% of the ST market based on sales in the US. ST users purchase moist snuff as pouched products or loose tobacco products. Chewing tobacco, Swedish-style snus, dry snuff, hard snuff products account for approximately 18% of the US ST market. Chewing tobacco consists of products such as plug, twist, and chew. Dry snuff is often inhaled through the nose, or may be a pouched product placed in the mouth. The eight new snus products in this PMTA are categorized as Swedish-style snus, which follows the manufacturing procedures provided by a voluntary industrial quality standard for Swedish snus. This standard aims to reduce selected, undesired constituents in the finished products, such as tobacco-specific nitrosamines (TSNAs), metals, benzo(a)pyrene(BaP), and nitrite, by implementing a series of procedures that includes: tobacco leaf selection, controlled heat treatment that reduces the natural microbial flora, and manufacturing in a closed system to prevent external microflora contamination.

3. Product Science (Chemistry/Engineering/Microbiology)

General Product Description

The eight Swedish snus products are made from (b) (4), and (b) (4) t tobaccos along with various salts, flavorings, and moisture-preserving substances. The applicant indicates that all the products are designed to contain (b) (4) % (weight) nicotine with moisture levels between (b) (4) % and (b) (4) % and pH values between (b) (4) and (b) (4). The total nicotine in the eight snus products ranges from (b) (4) mg/g for PM0000010 and PM0000012-17, and (b) (4) mg/g for PM0000011. These nicotine values are within the reported ranges for other marketed US moist snuff, therefore the abuse potential for these products is similar to other marketed smokeless tobacco products. Other than tobacco, the basic formulations for all the products consist of various salts, flavorings, processing aid, and humectants. The applicant claims that all ingredients other than tobacco are approved for food use. In terms of quantity, water ((b) (4) %), a humectant according to the applicant, is the most abundant ingredient besides tobacco in each product. Except for PM0000011, all of the products also contain (b) (4) or both (b) (4) and (b) (4) as humectants ((b) (4) %). (b) (4) ((b) (4) %) is used as a taste enhancer and preservative. (b) (4) (b) (4) (b) (4) %) are used as pH adjusters. Small quantities of (b) (4) ((b) (4) %) are used as a processing aid. For non-mint and non-wintergreen flavored products (PM0000010, PM0000012-PM0000013, and PM0000016), flavors account for (b) (4) % of the finished products by weight. However, the three mint-flavored products (PM0000011 and PM0000014-PM0000015) and one wintergreen-flavored product (PM0000017) contain higher levels of flavor (b) (4) % by weight). The flavored products also contain an artificial sweetener, (b) (4) ((b) (4) %). For most of the products included in these PMTAs, the vast majority of the ingredients other than tobacco are listed as flavor, which are typically present at very low concentrations (ppm or ppb levels), except for the mint and wintergreen flavor ingredients

as described. Non-portioned snus (PM0000010) is not allocated into a defined serving size; instead, the consumer decides the amount per use. Portioned snus (PM0000011-PM0000017) is allocated into a defined serving size via pouch paper, individual pieces, or other means. In this case, the products utilize pouch paper.

The chemistry evaluation took into consideration product formulation (including HPHCs), chemistry design (nicotine, moisture, pH), tobacco blend, ingredients other than tobacco, manufacturing steps and controls, performance criteria and stability. More specifically, HPHCs evaluated include: acetaldehyde, arsenic, BaP, cadmium, crotonaldehyde, formaldehyde, nicotine (free and total), NNN (N-nitrosonornicotine), NNK ((4-methylnitrosamino)-1-(3-pyridyl)-1-butanone), and pH. Compared to the literature data, we found that the levels of NNK, NNN, B[a]P, and crotonaldehyde in these new snus products are significantly lower than those in the major types of traditional smokeless tobacco products (STPs) on the US market (e.g., moist snuff). These reductions can be mainly attributed to the differences in the types of tobacco (no use of dark-fire cured and fermented tobacco) and manufacturing process (steam heat-treatment versus fermentation). Also, there are no increased levels of formaldehyde, acetaldehyde, arsenic, and cadmium compared to the traditional STPs. Additionally, these new snus products do not contain a wide range of HPHCs that are typically found in mainstream cigarette smoke.

The applicant states that the product for PM0000010 is packed in paraffin-coated cardboard cans with plastic lids and the products for PM0000011-PM0000017 are packed in either round or square plastic cans with plastic lids. The applicant provides the ingredients (e.g., (b) (4) (b) (4)) contained in the packaging materials and states that all ingredients and materials in the new products are food grade, generally recognized as safe (GRAS), or are approved for food contact. The plastic lid, plastic base, cardboard can base, and wax coating used in the new products are the same as other products currently on the market from SMNA. No chemistry or toxicology concerns with the containers were identified based on the information provided. Overall, the chemistry evaluation determined that there was adequate information to characterize the proposed products and that the property parameters, manufacturing and processing were acceptable. Refer to the individual chemistry, engineering and microbiology reviews for a full description of unique properties by product. This review only provides an overview of the products.

Tobacco Blend

PMTA	Product	Quantity (Target with minimum and maximum limits in parenthesis) (mg/g or mg/pouch)*			
		Tobacco Leaf – (b) (4)	Tobacco Leaf – (b) (4)	Tobacco Stem – (b) (4)	Total
PM0000010	General Loose	(b) (4)			
PM0000011	General Dry Mint Portion Original Mini				
PM0000012	General Portion Original Large				
PM0000013	General Classic Blend Portion White Large (12 ct)				
PM0000014	General Mint Portion White Large				
PM0000015	General Nordic Mint Portion White Large (12 ct)				
PM0000016	General Portion White Large				
PM0000017	General Wintergreen Portion White Large				

* mg/g for PM0000010 and mg/pouch for PM0000011-PM0000017.

Overview of Product[3]

Brand	FDA Submission Tracking Number (STN)	Package Type	Can Weight	Can Dimensions	Pouch Size	Pouches per Can	Portion Mass
General Loose	PM0000010	Cardboard Can with Plastic Lid	45.0 g	70.5 x 23 mm			
General Dry Mint Portion Original Mini	PM0000011	Plastic Can	6.0 g	66 x 19 mm	14 x 28 x 5 mm	20	0.3 g
General Portion Original Large	PM0000012	Plastic Can	24.0 g	70 x 24 mm	18 x 33 x 6 mm	24	1.0 g
General Classic Blend Portion White Large	PM0000013	Plastic Can	10.8 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	12	0.9 g
General Nordic Mint Portion White Large	PM0000014	Plastic Can	13.5 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	24	0.9 g
General Nordic Mint Portion White Large	PM0000015	Plastic Can	10.0 g	56.6 x 86 x18 mm	14 x 34 x 5 mm	12	0.9 g
General Portion White Large	PM0000016	Plastic Can	24.0 g	70 x 24 mm	18 x 34 x 5.5 mm	24	1.0 g
General Wintergreen Portion White Large	PM0000017	Plastic Can	24.0 g	70 x 24 mm	18 x 34 x 5.5 mm	24	1.0 g

General Product Design

The applicant identifies the products' components and subcomponents (e.g., tobacco, pouch, can) as well as some of the applicable specifications and a description of the intended function for each. Design parameters are assessed to understand the comprehensive design of the products as each parameter contributes to the overall constituent yields:

- Tobacco cut size is directly related to the particle surface area and the accessibility of saliva to tobacco surfaces, thereby affecting the amount and rate of constituents released from the product.[4]

[3] This table supersedes the tables presented in the clinical pharmacology, behavioral pharmacology, and medical reviews.

[4] Dash S, Murthy PN, Nath L, Chowdhury P (2010). Kinetic modeling on drug release from controlled drug

- Tobacco moisture (tobacco leaf, blend, and final) may affect microbial growth in the product, extraction efficiency, and total exposure to nicotine, NNN, and NNK.[5,6,7]
- Portion mass may affect user exposure to the tobacco product and, in turn, the HPHCs contained in each portion.[8]
- Portion length may affect the constituents in each portion.[8]
- Portion width is directly related to product surface area, which is proportional to the amount and rate of constituents released from the product.[9]
- Portion thickness is directly related to product surface area, which is directly proportional to the amount and rate of constituents released from the product.[9]
- Pouch paper basis weight, the weight of paper per meter area, influences the interactions between the tobacco and oral cavity, thereby affecting the amount and rate of constituents released from the product.[10]
- Pouch paper porosity/permeability influences the interactions between the tobacco and oral cavity, thereby affecting the amount and rate of constituents released from the product.[10]
- Pouch paper wicking allows the transport of tobacco constituents from the tobacco filler to the pouch surface, thereby affecting the amount and rate of constituents released from the product.[11] In this submission, the applicant's nicotine uptake trials demonstrate 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 these new products. Therefore, wicking values are not needed for these products.

Compared to currently-marketed smokeless products, the applicant provided some of the target specifications and upper and lower range limits necessary to evaluate ST products. Industry average ranges are used to compare the design parameters of PM0000010-PM0000017 to typical values that FDA anticipates based on previous submissions. The products chosen for

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delivery systems. Acta Poloniae Pharmaceutica – Drug Research 67(3):217-223.

[5] U.S. Food and Drug Administration (2013). Evaluation and Definition of Potentially Hazardous Foods - Chapter 3: Factors that Influence Microbial Growth. Available at: http://www.fda.gov/Food/FoodScienceResearch/SafePracticesforFoodProcesses/ucm094145.htm (The "tobacco juice" generated when snus is consumed can be ingested similar to foods, thus this reference is relevant here.)

[6] Gale N, Errington G, McAdam K (2013). Effects of product format on nicotine and TSNA extraction from snus pouches. British American Tobacco 67th Tobacco Science Research Conference, Williamsburg, VA, September 15-18, 2013.

[7] Djordjevic MV, Hoffman D, Glynn T, Connolly GN. U.S. commercial brands of moist snuff, 1994. I. Assessment of nicotine, moisture, and pH. Tob Control. 1995;4:62–6.

[8] Stepanov I, Jensen J, Biener L, Bliss R, Hecht SS, Hatsukami DK (2012). Increased pouch sizes and resulting changes in the amounts of nicotine and tobacco-specific N-nitrosamines in single pouches of camel snus and malrboro snus. Nicotine Tob Research 14(10):1241-1245.

[9] Zhang H, Zhang J, Streisand JB (2002). Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications. Drug Deliv Sys 41(9):661-680.

[10] Lewis S, Subramanian G, Pandey S, Udupa N (2006). Design, evaluation and pharmacokinetic study of mucoadhesive buccal tablets of nicotine for smoking cessation. Indian J Pharm Sci 68:829-31.

[11] Morrow NR (1970). Physics and thermodynamics of capillary action in porous media. Ind Eng Chem Res 62(6): 32-56.

comparison are those that are in similar product categories and subcategories as the new products. The table below lists typical smokeless design parameter ranges.

Average Industry Ranges for Smokeless Design Parameters*

Design Parameter	Industry Range	PM0000010-PM0000017 Within Industry Range**
Final Moisture (%)	3.6-57	Yes
Portion Mass (mg)	230-1820	Yes
Portion Length (mm)	10-36	Yes
Portion Width (mm)	6.65-18	Yes
Portion Thickness (mm)	5-5.79	Yes
Pouch Paper Basis Weight (g/m^2)	1-29	Yes
Caliper (µm)	195	Yes

* Data source is FDA database of engineering parameters found in SE Reports submitted to FDA (version 5/9/14); final moisture range determined from portioned and non-portioned smokeless products; portioned parameters determined from portioned smokeless products.
**Due to testing variability, values for the new products that are out of industry range by less than 5% are considered to be within range and acceptable.

The final tobacco moisture level is within the industry range and no other issues are identified. Also, portion mass, length, width, thickness, and caliper are within the industry ranges for all of the new products and no other issues are identified. Furthermore, the tobacco types utilized in the new products are similar to or the same as products currently marketed. Therefore, the new products do not appear to be different from available smokeless products with regard to the tobacco and the design parameters provided. In summary, the results analyzed indicate these products fall in the normal range, and the actual design feature values do not appear to raise concerns related to how these products might adversely impact public health through risk to the user, increased initiation or decreased cessation as compared to the existing ST market.

Sample Testing

The applicant submitted samples of each of its products in support of its PMTAs to FDA's SRL on April 15, 2015. Samples were shipped via UPS from Swedish Match North Europe to the Swedish Match North America Owensboro, Kentucky facility. These samples were then shipped at ambient temperature from the Owensboro facility to SRL.

The CTP Office of Science (OS) requested testing of the PMTA product samples and examples of testing performed:

- Nicotine (filler/SL), pH, TSNA (filler), nicotine (free), NNN, NNK, pouch thickness, pouch width, pouch length, % oven volatiles, portion mass
- Chemistry Tests: Three to four replicates at 1g each; composite from at least two pouches; quantity expressed in units/gram ("as is" [wet] weight)
- Engineering Tests: Three to four replicates; quantity expressed in mm for length, width, thickness; portion mass in g per pouch (including pouch material and filler) and in g per filler
- Micro Tests: Three to four replicates at 1g each (combined with chemistry tests) from at least two pouches

Division of Product Science scientists reviewed the analysis provided by SRL and evaluation of the sample testing did not raise any concerns.

Clinical Microbiology

Product stability (including moisture content, pH, water activity, bacterial counts and validation parameters), heat treatment process, additives, fermentation, storage and microbial concerns were evaluated. The clinical microbiology content of the submission was considered adequate as:

- Descriptions of manufacturing steps and quality control measurements were established and followed.
- A written testing program designed to assess the stability characteristics of the tobacco products was established and followed.
- Sample size and test intervals were determined based on statistical criteria for each attribute examined to assure valid estimates of stability.
- Evaluation of stability was made using the same container-closure systems in which the tobacco products are intended to be marketed.
- Expiration dates were related to storage conditions stated on the labeling, as determined by stability studies.
- Written procedures, designed to prevent the growth of objectionable microorganisms (including the mycotoxin ochratoxin A and aflatoxins B1, B2, G1 and G2) were established and followed.
- Written procedures designed to determine the physical and chemical attributes that affect microbial activity and/or are susceptible to change during product storage were established and followed for pH, moisture content, and water content. Written procedures for sampling and testing parameters were established, described, and followed including method of sampling and the number of batches tested.
- Validation protocols showing the accuracy, sensitivity, specificity, and reproducibility of test methods employed by the applicant were established and documented.
- Statistical quality control criteria including appropriate acceptance levels and/or appropriate rejection levels were established and followed.

Shelf Life

The applicant recommended retail shelf lives of 14 weeks for loose snus, 20 weeks for pouched snus (White and Original) and 30 weeks for "dry" pouched snus. These shelf lives are supported by the provided data.

Manufacturing, Processing, and Controls

The applicant has provided descriptions about tobacco procurement, grading method, countries of origin, curing method for each type of tobacco, tobacco storage conditions, criteria for choosing suppliers, and criteria for acceptance of raw tobacco based on chemical testing results and tolerance levels of certain constituents (see the discussion about the applicant's internal quality standard below). According to the applicant, the tobacco grade is based on the country of origin, curing process, and plant position.

Briefly, manufacture of these products includes grinding, blend processing, and packaging.

During the April 2015 FDA inspection, several issues were observed regarding manufacturing equipment (e.g., the scale for weighing tobacco flour was not calibrated; the calibration of the temperature probes for blenders was outdated). However, these issues are not expected to have a major impact on the quality of the new products because: 1) the applicant will not routinely manufacture the new products unless FDA issues the marketing authorization orders, and 2) the applicant responded that it would take corrective actions in a timely manner and the issues were noted by OCE reviewer to have been corrected on or before May 30, 2015. Furthermore, during the inspection, FDA reviewed the manufacturing processes that would be applied to the new products according to the applicant and found no significant deviations from the process described in the PMTAs.

The applicant states that it uses analytical methods, chemical quality control programs, brands testing programs, and agrochemical management programs according to its proprietary quality standard for snus products to ensure product quality. The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products. Currently, the Swedish Match standard has limits for the following nine constituents:

- NDMA: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Nitrite: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- BaP: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Arsenic: (b) (4) ng/g (dry weight basis); (b) (4) ng/g (as is)
- Lead: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is);
- Cadmium: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- Chromium: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- Nickel: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)
- NNN+NNK: (b) (4) µg/g (dry weight basis); (b) (4) µg/g (as is)

In addition to the Swedish Match standard, the applicant states that the Swedish National Food Agency and the Swedish Medical Product Agency have also set regulatory limits for the following constituents:

- Lead: 3 mg/kg (as is)
- Propylene glycol: 40 g/kg (as is)
- Aflatoxins (sum of B1, B2, G1, and G2): 0.005 mg/kg (as is)
- Ethanol: 2.25% v/v (as is)

The applicant states that all snus products are analyzed three to four times a year in its Chemical Control Program. The applicant has provided the chemical testing data on all the products included in these from the 2011 Chemical Quality Control Program and the 2012 Brands Testing Program. All products have constituent levels below the Swedish Match limits and the Swedish national regulatory limits.

Additionally, the applicant states that their proprietary standard also includes Guidance Residue Limits (GRL) for agrochemical residues in raw tobacco and finished snus products. Testing of raw tobacco is performed and results are reviewed prior to the tobacco's release for

snus manufacturing (if results are acceptable). Testing of the finished products is performed annually. For all the products that are the subjects of these PMTAs, the applicant provided the 2011 testing results, and the levels of the agrochemical residues tested all fell below the applicant's GRL. The reported analyses and use of voluntary standards appear acceptable.

Inspections of Swedish Match Manufacturing Facilities and Laboratory

The Office of Regulatory Affairs (ORA), accompanied by Subject Matter Experts (SMEs) from the Division of Enforcement and Manufacturing (DEM) in the Office of Compliance and Enforcement (OCE) and the Office of Science (OS) within the Center for Tobacco Products (CTP), conducted an inspection of 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). Manufacturing, product analysis, packaging, distribution, recalls and complaints, shipping, laboratory accreditation, validations, raw data, and procedures were evaluated at the different sites. DEM's review of both the application and the manufacturing facilities and laboratory inspection results did not identify any issues of concern for 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.

DEM inspectional review recommends classification as VAI (voluntary action indicated) for facilities inspected other than the Stockholm laboratory facility which was recommended as NAI (no action indicated).

4. Toxicological Risk (Nonclinical Science)

The applicant provided HPHC data for each of the eight snus products in the PMTA based on wet-weight (as is weight). The FDA converted the wet-weight levels into dry-weight levels using the product moisture levels provided by the applicant in the application in order to allow HPHC level comparisons to be made between the eight new snus products and other smokeless tobacco products on the market that reported the HPHC levels as dry-weight levels in the respective publications.

HPHC Levels Calculated on a Dry-weight Basis

Product	NNN	NNK	Acetaldehyde	Arsenic	BaP	Cadmium	Crotonaldehyde	Formaldehyde	Nicotine (total)	Nicotine (free)
	(b) (4)									
PM0000010										
PM0000011										
PM0000012										
PM0000013										
PM0000014										
PM0000015										
PM0000016										
PM0000017										
Average										

HPHCs, Excess Cancer Risk, Relative Risk of Specific Cancers

The PMTA products were compared to other ST products (including moist snuff, chewing tobacco, American snus, and dry snuff) and cigarette products currently on the US market. The eight new Swedish snus products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. NNN and NNK are arguably the most concerning carcinogenic HPHCs in smokeless tobacco products. They showed strong dose response relationships with cancer development, are specific to tobacco products, and biomarkers of exposure are present in minimal to below levels of detection in most nonusers of tobacco products. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers who use these products instead of other US smokeless products. Assuming tobacco product use pattern to be consistent, for an individual the use of PMTA products with low levels of NNN could decrease the excess cancer risk by 90% compared to use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share: 15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff. Even further reductions in excess cancer risk could occur with the corresponding reductions in NNK; however, a quantitative contribution cannot be determined at this time due to the absence of a NNK cancer slope factor. The excess lifetime cancer risk is a toxicological tool to estimate the probability of cancer incidence in a population of individuals for a specific lifetime from projected intakes (and exposures) and dose-response data (i.e., slope factors) for a specific chemical, in this assessment, NNN.

Other HPHCs in these PMTA products, including arsenic, cadmium, acetaldehyde, crotonaldehyde, formaldehyde, and BaP exist at similar or lower levels than in the other types of ST products on US market. The estimated levels of exposure to these HPHCs are typically at or below dietary intake levels or the reference levels set by government agencies, and are therefore not considered to be a significant toxicological concern. Dietary intake levels are used as comparison as the “tobacco juice” generated when snus is consumed can be ingested similar to foods.

Data showed that ST use in general is associated with elevated risks of oral cancer in the US, *but not associated* with oral cancer in Nordic countries where Swedish snus with lower levels of NNN and NNK is used by Swedish ST users (Boffetta, 2008). This suggests that the lower levels of NNN and NNK in the Swedish snus may reduce the risk of oral cancer in US consumers who use a low NNN- and NNK-containing snus product as compared to other ST products.

Comparison to Cigarette Smoke

FDA’s established list of HPHCs includes over 40 more carcinogenic constituents in cigarette smoke than in ST products. Certain HPHCs -- such as acetaldehyde, cadmium, acrolein, and nickel have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products. Direct comparisons of HPHC levels using urinary biomarker information and estimated absolute HPHC levels, which would allow a comparative risk assessment of the proposed Swedish snus products and cigarettes, is difficult. Inherent differences in the products -- such as combusted vs. non-combusted, route of HPHC exposure (oral vs. inhalation), and the complex mechanisms of target organ-specific toxicity

by each individual HPHC, as well as toxicity resulting from the complex mixture of HPHCs, make a direct comparison challenging in terms of nonclinical toxicological assessment. While smokeless tobacco is associated with many health problems, epidemiology studies discussed later in this review, provide evidence that smokeless tobacco users have much lower relative risk of developing oral cancers, respiratory diseases (COPD, emphysema and chronic bronchitis) and lung cancers as compared to smokers. Overall death rate is also lower in smokeless tobacco users as compared to smokers.

5. Abuse Liability, Exposure/Response, and Use Behavior (Clinical Pharmacology/Behavioral Pharmacology)

Abuse Liability

The applicant acknowledges the abuse liability (addictive and reinforcing effects) of its Swedish snus products given their nicotine content. Although the applicant did not submit formal abuse liability studies or predictions about uptake and use specific to the proposed snus products, the reinforcing and addictive effects of the proposed snus products are acknowledged and the abuse potential of the proposed products is understood to be within the range of similar marketed products. Also, the proposed snus products expose individuals to nicotine levels that are broadly similar to traditional combusted tobacco products (e.g., cigarettes). Data provided demonstrate that snus products produce reinforcing effects, as indicated by positive ratings of "liking" and "good effects." The behavioral pharmacology review focuses on the effects of Swedish snus products in general on tobacco use behaviors. This includes consideration of the expected rates of use of snus products by current tobacco users, use of the snus products in conjunction with other tobacco products, the potential for abuse and misuse of the snus products, the potential for experimenters to become addicted, and the impact on cessation rates.

Pharmacokinetics and Exposure/Response

The applicant submitted four clinical pharmacology studies. Three evaluated the nicotine pharmacokinetics after single and multiple administrations of Swedish snus. The nicotine maximum concentration (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 (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 (i.e., loose or pouched) had little influence on the nicotine pharmacokinetic parameters. After overnight abstinence, time to maximum nicotine plasma concentration (Tmax) appeared to be dependent on product use time. Similarly, other studies examining Swedish snus reported Tmax values between 30 and 37 minutes (Holm et al., 1992; Lunell and Curvall, 2011; Lunell and Lunell, 2005). In comparison, after cigarette smoking, nicotine reaches peak venous concentrations within eight minutes and peak arterial plasma concentrations within five minutes (Arcavi and Benowitz, 2004; Benowitz et al., 2009; Gori et al., 1986; Lunell et al., 2000; Lunell and Curvall, 2011; Schaedeli et al., 2002). As used by consumers, the proposed snus products expose individuals to nicotine levels that are broadly similar to cigarettes and traditional ST products. Thus, from

a clinical pharmacology perspective, systemic exposure to nicotine following use of the proposed snus products is expected to produce reinforcing effects and have an abuse liability similar to traditional cigarettes and other ST products.

One study measured the pre- and post-use levels of lead, cadmium, nicotine, and TSNAs in Swedish snus products; however, systemic exposures were not assessed. The systemic exposures to TSNAs and other HPHCs after use of some snus products including Swedish snus are described in peer-reviewed literature (Hatsukami et al., 2004; Sarkar et al., 2012).

Summaries of the four clinical pharmacology studies submitted by the applicant are presented below.

SW WS 02: This study was an open-label, crossover study of nicotine plasma levels after the use of four types of snus and nicotine chewing gum. In the study, male snus users aged 18-23 were administered snus portions [General (8.8±0.4 mg nicotine/portion), Catch Licorice (7.0±0.1 mg nicotine/portion), Catch Mini (4.5±0.3 mg nicotine/portion), Catch Dry Mini (4.8±0.6 mg nicotine/portion)] or nicotine gum (Nicorette, 1.9±0.1 mg nicotine) once an hour for 11 hours (12 doses total). Subjects were instructed to keep the snus between the upper lip and gum for 30 minutes. In the Nicorette gum condition, subjects were administered 2 mg Nicorette chewing gum and instructed to chew each piece for 30 minutes. For each condition, serial venous blood samples, were drawn to assess nicotine levels. After multiple doses (12 doses over 11 hours) of the four types of snus or Nicorette gum, nicotine pharmacokinetic parameters were reported, but only after the last use (Cmax and AUC_{11-12}). The mean±SD nicotine amount extracted per dose was calculated as 2.74±0.80, 1.55±0.68, 2.00±0.56, 1.08±0.94 and 0.84±0.12 mg/portion for General, Catch Licorice, Catch Mini, Catch Dry Mini snus, and Nicorette gum, respectively.

After the multiple dosing regimen, nicotine plasma concentrations reached the following mean±SD Cmax values (ng/mL) for the snus products: General, 29.00± 8.53; Catch Licorice, 23.79± 8.60; Catch Mini 20.95 ±6.90; Catch Dry Mini, 10.85 ±5.65; and nicotine gum, 12.75± 4.67. For the first three snus products, nicotine Cmax values were similar to Cmax values observed in smokers (Benowitz et al., 1982;Benowitz, 2008;Kotlyar et al., 2007). Mean±SD AUC values (ng·h/mL) following the last dosing interval reached the following values for the snus products: General, 26.2 ± 3.4; Catch Licorice, 21.6 ± 8.8; Catch Mini, 19.0 ± 6.7; Catch Dry Mini, 9.8 ± 5.1; and Nicorette, 11.6 ± 4.5. Mean Cmax and AUC_{11-12} values were dose proportional, with R^2 values of 0.82 and 0.81, respectively. Thus, from the comparison of these parameters, the nicotine pharmacokinetics did not differ across all products.

SW WS 06: This study was an open label, single center, three-way cross-over study, designed to examine the nicotine plasma concentrations and subjective effects of a single dose (1 g) of General Onyx and General White portion snus relative to Nicorette chewing gum (4 mg). The study involved male and female subjects aged 18-50 years who smoked more than seven cigarettes per day. After baseline measurements and dosing, plasma nicotine concentrations were monitored for eight hours. Subjective effects assessments were performed using visual analog scale (VAS) assessments. Following the use of Nicorette gum, the extracted dose of nicotine was about 2.56 mg compared to 2.12 and 2.18 mg for Onyx portion snus and General

White snus, respectively. Mean Cmax values for Onyx portion snus and General White snus were 14.76 and 13.72 ng/mL, respectively, both higher than Nicorette gum (12.77 ng/mL). Tmax was reached about 30 minutes after snus use, faster than the 45 min Tmax observed following Nicorette administration. The faster absorption of nicotine following snus administration was reflected in higher VAS ratings of "head rush" following snus use relative to nicotine gum. The applicant concluded that snus provides a higher Cmax in a shorter amount of time (e.g., decreased Tmax) relative to Nicorette, and that the faster onset may account for the increased ratings of "head rush" compared to the gum. However, despite the lower Cmax of Nicorette relative to the snus comparators, Nicorette had a larger AUC, which is consistent with the increased amount of extracted nicotine. This study was limited to single dose administrations, which may not reflect actual use.

SM WS 12: This study compared the nicotine pharmacokinetics and subjective effects of single doses of sublingual nicotine (Nicorette Microtab, 6 mg) to Swedish snus. The study was an open-label, five-way, crossover study involving 18 healthy snus users. The goal of the study was to examine the interaction between nicotine amount and portion size; the study involved four snus products with two nicotine concentrations. Four Swedish snus products with different nicotine concentrations were administered in different portion sizes: 8 mg nicotine in a 1 g portion; 8 mg nicotine in a 0.5 g portion; 16 mg nicotine in a 1 g portion; and 16 mg nicotine in a 2 g portion (composed of two 1 g portions of 8 mg each). Blood plasma samples were taken over a six-hour time period and VAS assessments were performed. For the four snus products, the extracted nicotine doses were 1.56 ±0.95 mg, 1.90±0.82 mg, 3.0 ±1.65 mg, and 3.0 ±1.35 mg, respectively. Nicotine was absorbed more slowly from Nicorette Microtab tablets, but systemic exposure was within the range of the snus products. All products increased "head rush" and reduced craving over the first 30 minutes. The effects were strongest for the portioned snus (i.e., two 1 g portions of 8 mg each), although the effects were not statistically significant from Nicorette Microtab. According to the applicant, the similar nicotine absorption for both 16mg conditions indicates that absorption kinetics were dependent on total nicotine extraction (i.e., dose) rather than mode of administration (i.e., portioned or single dose). Both 16 mg conditions displayed similar pharmacokinetic (e.g., AUC values) and pharmacodynamic effects (e.g., VAS scores) compared to 6 mg Nicorette Microtab sublingual tablets. This study was limited to single dose administration.

SM WS 03: This study examined the in-vivo extraction of cadmium, lead, and TSNAs from four brands of Swedish snus [General Large (1 g), Catch White Licorice Large (1 g), Catch Licorice Mini (0.5 g), and Catch Licorice Dry Mini (0.3 g)] in regular snus users. The study was an open-label, randomized, four-way, single dose study in 32 males. Snus portions were administered once every hour (four administrations/brand) and were kept between the upper lip and the gum for 30 minutes. The received dose of cadmium (Cd), lead (Pb), and TSNAs was calculated by comparing pre- and post-use levels of constituents in used and unused snus products. Systemic exposures to Cd, Pb, and TSNAs were not examined. In this study, the mean±SD extracted amounts of Cd from General Large, Catch White Licorice Large, Catch Licorice Mini, and Catch Licorice Dry Mini were (b) (4), and (b) (4) ng/portion, respectively. The mean extracted amount of Pb was negative for all products and the applicant has not explained this finding, the impact of this to the study as a whole is

unknown. The mean±SD sum of extracted TSNAs from the four brands was calculated as (b) (4) (b) (4), and (b) (4) ng TSNA/portion, respectively.

In summary, the studies focused on nicotine pharmacokinetics and nicotine exposures and found that Swedish snus products were similar to other marketed ST products. None of the submitted studies evaluated exposure-response relationships (i.e., changes in biomarkers and clinical outcomes related to systemic exposures to HPHCs). The health impacts (influence on the disease development and endpoints) of the new tobacco products were not specifically assessed in these sponsored clinical pharmacology studies. Prospectively-designed clinical pharmacology studies that compare systemic toxicant exposures following the use of the proposed Swedish snus products relative to other tobacco products would provide more data to evaluate actual exposure and response differences. However, substantial epidemiological data is submitted by the applicant evaluating health impact of similar Swedish snus products informing anticipated health impact from use of these products.

Use Behavior

ST products are usually chewed, placed in the oral cavity between the cheek and gum, or inhaled or snorted through the nose. The applicant provides a description of data relating to the frequency, amount, duration, and overall use profile of snus products. While the applicant describes general use of the proposed products, the proposed labels do not include a description of "intended use". With traditional ST, topography measures include: self-reported measures of tobacco use such as ST tins used per week, total dips per day, total daily dip duration, and total daily dipping time (time from first to last dip of the day) (Lemmonds et al., 2005). According to the applicant, the most common method of snus use is to place 1-2 grams of product (loose or pouched) in the vestibular area inside the upper lip. Survey data of Swedish snus users suggest that this is the manner of use for 96% of pouched users and 99% of loose snus users, although movement of the product inside the mouth is common (Digard et al., 2009). In a telephone survey of 2,914 Swedish snus users (359 females and 2555 males), pouch snus use was much more common among females (92.8%) than males (42.1%). The survey also indicated that average "loose" snus consumption per day was approximately equal for both genders (29.3 g for men and 29.0 g for women). Similarly, total consumption of portioned/pouched snus was similar for men (32.1 g/day) and women (33.8 g/day). However, men used snus portions for a longer duration (69.6 min vs. 56.1 min for women). These data are broadly similar to values reported in the Norwegian Tobacco report, which found that snus users reported about 9.5 "pinches" of snus per day, with each "pinch" weighing about 2.5 g for a total use of 23.75 g/day.

Snus products are generally placed in the oral cavity but there are some differences in oral placement among users as US studies indicate that American ST users typically place ST between lower lip and gum. Whether the same snus product is placed near upper lip or lower lip, the health impacts from these products are expected to be similar given oral exposures to the product itself. Total snus consumption per day by Swedish users while informative may not be directly transferrable to the US experience.

Acceptability

Receptivity to snus use in Indianapolis, Indiana and Dallas/Fort Worth Texas (two cities with the greatest exposure to the major snus brands) was examined in a telephone and mail survey

conducted in 2011 and 2012 (Biener et al., 2014). More than 5000 adults completed surveys assessing trial, ever use, current use, and reasons for using or quitting snus after the trial. Among male smokers, 29.9% had ever tried snus (95% CI [confidence interval]=22.7-38.1) and 4.2% were current users (CI=1.6-10.7). Among female smokers, 8.5% had tried snus (CI=4.4-15.7) and current use was unknown. Current use was low among former smokers and never smokers. Conventional ST use was a major predictor of any snus use. Those who tried and gave up snus cited curiosity (41.3%) and the fact that it was available at low or no cost (30%). Reasons for not continuing snus use included preferring another form of tobacco (75.1%) and disliking the mouth feel (34.6%). Almost all current snus users indicated that they were trying to cut down on cigarettes, but few (3.9%) were using snus to quit smoking entirely. Low acceptability of snus use has been found elsewhere in the US (Hatsukami et al., 2011; Hatsukami et al., 2013; O'Connor et al., 2011; O'Connor et al., 2014). The low rate of snus adoption suggests that any adverse effects conferred on the population as a whole will be minimal especially given that the proposed snus products have lower NNN, NNK and other HPHC levels compared to other US smokeless tobacco products currently on the market.

Flavors

Of the eight snus products that are the subjects of these PMTAs, one contains mint and the ingredients (b) (4) One product includes (b) (4) (b) (4) is a major chemical component of (b) (4) (World Health Organization, 2002). These ingredients (e.g., (b) (4)) can give the new 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 two products (General Mint Portion White Large 0.9 oz. [24g] and General Nordic Mint Portion White Large .38 oz. [10.8g]) may be sweeter than other Swedish Match Snus products because they contain the artificial sweetener (b) (4) (b. A recent study (Choi et al., 2012) reported that young adults view new ST products (including snus) favorably because these products are available in flavors.

It is possible that introducing the products with new flavor ingredients may make the products more appealing to consumers. It has been suggested that flavored products have a unique and important role with respect to initiation and maintenance of tobacco-use patterns, particularly among young 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 occur (Hatsukami et al., 2007; Oliver et al., 2013b).

Access and utilization of ST remains a public health issue among American middle and high school students, with more than 25 different types of smokeless tobacco (ST) available in the United States (Bromberg et al., 2012). Analyzing data from Legacy's Young Adult Cohort Study, a nationally representative sample collected in January 2012, Villanti et al. (Villanti et al., 2013) sought to determine the prevalence of flavored tobacco use, dual use of flavored and menthol tobacco products, and sociodemographic predictors of flavored tobacco product use in young adults aged 18-34 years (n=4196). Overall, 18.5% of tobacco users report using flavored products, and dual use of menthol and flavored product use ranged from 1% (nicotine products) to 72% (chewing tobacco products). In a multivariable model controlling for menthol use, younger adults were more likely to use flavored tobacco products (OR=1.89,

95% CI=1.14, 3.11), and those with a high school education had decreased use of flavored products (OR=0.56; 95% CI=0.32, 0.97). The authors concluded that individuals most likely to use flavored products are also those most at risk of developing established tobacco-use patterns that may persist through their lifetime.

The proposed products are reported to have flavors such as mint, wintergreen, or tobacco character with citrus. While flavored smokeless tobacco products are a potential concern of youth initiation, these proposed flavors are consistent with traditionally available ST flavors and are not novel flavors that likely increase appeal to youth. Overall uptake of snus products including among youth in the US is low even with such flavors available in currently marketed products and unexpected to dramatically increase with the marketing of the PMTA products at this time. Postmarket data describing sales of these proposed snus products may be informative in better understanding appeal and use of newly marketed flavored products.

6. Health Impact (Medical/Epidemiology/Statistics)

Health Risks of Swedish Snus

The Applicant cites data spanning several decades, derived from numerous cohort, case-control, and cross-sectional studies, to describe the impact of snus use on health risks in Scandinavian countries. In particular, the Applicant discusses the health risks of Swedish snus compared with cigarette smokers and nonusers, and the health risks of dual use and switching from cigarette smoking to Swedish snus use compared with quitting completely and nicotine replacement therapy (NRT) use.

Comparison to Smoking and Nonuse

There is no evidence that snus causes lung cancer and COPD, which together are estimated to account for over 50% of smoking-attributable mortality in the US (CDC, 2008). This alone suggests a difference between cigarette smoking and snus in overall risks to health. Use of snus is not associated with significant 'second-hand' exposure which, in this respect, decreases risk for both users and nonusers. With regards to the risk of oral cancer, the literature[12] indicates that the risk from snus is significantly less than the risk from smoking cigarettes. However, the literature presented does not support use of snus as having no effect on dental health. Gingival recession was noted at increased frequency in several studies, even with younger subjects exposed for shorter periods of time. Snuff-induced lesions (SIL) were found to be almost universal among snuff users in Scandinavia. The long-term health implications of these lesions are unknown. The incidence of oral cancer in Sweden is low and the use of oral snuff is high indicating that malignant transformation of the lesions is uncommon. The prevalence of SIL is lower in the United States but it is not clear whether this is related to the product, patterns of use, differences in diet or dental care, or exposure to other agents. In general, the published literature presented confirms the health risks of snus for the individual user are less, or at least no greater, than those associated with cigarette smoking.

[12] Note that the volume of published literature addressing the risk of oral cancer with snus use is much lower than that for the risk of oral cancer associated with cigarette smoking.

While the available evidence suggests that there are likely to be differences in health risks between snus and cigarettes for some endpoints, the magnitude of these differences appears to vary considerably by endpoint. For example, the available evidence suggests that risks to the fetus due to snus use and cigarette smoking during pregnancy may not be very different. The applicant notes that pregnant or lactating women should not use products containing nicotine, including Swedish snus. Maternal snus use has been reported to be associated with increased rates of stillbirth. The fetal and neonatal effects related to cigarette smoking are well known. NRTs are considered a "safer alternative" but use during pregnancy is discouraged. In addition to adverse pregnancy outcomes, multiple studies have reported associations between Swedish snus use and increased risk of fatal cardiovascular events, pancreatic cancer, diabetes, and all-cause mortality. Finally, the applicant does not address the potentially negative effect of nicotine on the developing brain in youth, however, this is a universal concern of all nicotine containing products. Given that the nitrosamines in snus are still elevated and that there are suggestive associations between snus and a number of diseases, it is unlikely that switching to snus is comparable to quitting tobacco completely with or without using NRTs.

Thus, while the proposed snus products may be a less toxic product compared to cigarettes, the proposed snus products are not risk-free. Nonusers never starting tobacco use and current users quitting tobacco completely are still the optimal outcomes.

Impact on Cessation
Use behavior is described in the above section. Understanding use patterns is important because using the product frequently, using larger portions, or increasing deposition time in the mouth are behaviors known to affect nicotine exposure (Hatsukami et al., 1988; Hatsukami et al., 1991; Hatsukami et al., 2004). Snus appears to increase cigarette smoking cessation rates in some studies (Rutqvist 2012) but 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 US. Swedish Match conducted two clinical trials designed to examine if Swedish snus use could decrease smoking. The subjects recruited for these studies were motivated to quit smoking and the product was provided free of charge; however, the success rate for smoking cessation was low. Of note, the placebo group used a snus product with no nicotine, making the placebo an "active control". Neither study demonstrated that current cigarette smokers are likely to use snus as a smoking cessation aid. Thus, although snus was not associated with certain significant health risks for the users, the studies did not provide evidence that US smokers will use snus to reduce or replace cigarettes. It is unlikely that we can expect to see a large migration of cigarette smokers to switch completely to use of these snus products and decrease individual risk, however, some switching behavior may occur.

SM 07 01: This was a randomized, placebo-controlled, double blind study in Serbia designed to examine whether *ad libitum* snus use could affect smoking relative to placebo. Subjects (n=319) could choose between two pouch sizes (0.5 and 1.0 g) and two flavors of snus. Placebo pouches were identical to the "active" pouches in size and appearance, including flavoring, pH, and other sensory characteristics. Subjects were young adults aged 20-65 who had smoked daily for more than one year and who were motivated to quit. This study involved a smoking reduction stage (weeks 1 to 24 post-randomization) and a smoking cessation stage

(weeks 25 to 48). The primary outcome measure was smoking reduction at week 24. At the week 24 visit, the snus and placebo groups did not differ in the proportion of subjects who achieved the protocol definition of a >50% smoking reduction. However, a higher proportion of participants in the snus group (9.5% vs. 2.5%, $p<0.01$) reported >75% reduction in average number of smoked cigarettes per day compared to baseline, particularly during the first six months of the trial. Fagerström dependence scores were similar in both groups. ST is not available in Serbia; therefore, experience with ST was limited in this population. Because participants were motivated to quit and counseling was offered during the study, the results may not be applicable to the general snus user population; however, the data suggest that some individuals may switch from smoking combusted cigarettes to snus.

SM 08 01: This study was a multi-center, randomized, double-blind, placebo controlled trial in the US comparing snus vs. placebo to examine whether snus use increases quit rates among cigarette smokers aged 25-65 (n=152) who wished to stop smoking. Snus in 0.5 or 1.0 g sachets or matching placebo (without tobacco or nicotine) was used *ad libitum*. The study consisted of four phases: pre-randomization screening (up to two weeks), a study product test period (four weeks), an intervention phase (12 weeks), and a follow-up phase (12 weeks). The primary outcome measure was complete abstention during weeks 6 to 28. This was a smoking cessation trial with participants who were motivated to quit, and study counseling was offered as part of study participation. During the test period, participants were instructed to use the study product when they had an urge to smoke, without requiring complete abstention from cigarettes; instructions were the same during the intervention phase, but participants were encouraged to completely stop smoking. Biologically verified (e.g., expired air carbon monoxide (CO) $\leq$ 8 ppm), continuous abstinence rates during weeks 6 to -28 were 4.0% for snus and 1.6% for placebo. Minnesota Withdrawal Scale scores for craving were not statistically significant between the groups. Nearly two-thirds of the participants had tried other pharmaceutical smoking cessation aids. Given US and Swedish population differences, the results may not be generalizable to the US population.

In the two clinical trials conducted by SMNA, the studies were performed in generally healthy subjects. Reported adverse events (AEs) were generally mild and non-serious and were not unexpected reactions to these products; most reported AEs were either related or possibly related to the study product. In the US study, 616 AEs were reported by 200 subjects (350 in the snus group and 266 in the placebo group). No deaths occurred. Overall, the most common AEs reported were gastrointestinal disorders (45%; gingival pain, dyspepsia, nausea, toothache, diarrhea, dry mouth, gingivitis, salivary hypersecretion, abdominal pain, and sensitivity of teeth), infections and infestations (34%; viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, pharyngitis, bronchitis, otitis media, and viral infection), nervous system disorders (20%; headache, dizziness, and dysgeusia), respiratory, thoracic, and mediastinal disorders (17%; cough, hiccups, oropharyngeal pain, nasal congestion, and rhinorrhea), musculoskeletal and connective tissue disorders (13%; back pain, arthralgia, and myalgia), injury, poisoning, and procedural complications (10%; skin laceration, back injury, and joint sprain), psychiatric disorders (10%; insomnia, anxiety, and mood alterations), general disorders and administration site conditions (6%; irritability), and skin and subcutaneous tissue disorders (6%; 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). A total of five serious AEs were reported in the study, however, none were reported to be related to the study product.

Bioresearch Monitoring (BIMO) Inspection
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). 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 report that while there were some missing and inconsistent data, there was no overt fraud reported. The limited missing and inconsistent data are not considered substantive to prevent product authorization.

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).

7. Population Health (Epidemiology/Social Science/Behavioral Pharmacology)

Initiation
In Sweden and Norway, snus initiation is more prevalent among former cigarette smokers than among nonusers. Generally, in these populations, tobacco initiation is gender-dependent; males are more likely to initiate snus and females are more likely to initiate cigarette smoking. Adolescent males initiate snus use at a median age of 15 while females who used snus usually started by age 18. In the US, tobacco users (male and female) are more likely to initiate with cigarettes, but no specific data compare the likelihood of initiation with snus versus cigarettes.

In 2014 according to the National Survey on Drug Use and Health, 3.3% of the US population aged 12 or older used ST in the past month (SAMHSA, 2015). National estimates of ST use have been reported by a variety of sources and provide relatively consistent results. For example, across several representative surveys, ST use rates were reported as follows: National Adult Tobacco Survey 3.9%; National Health and Nutrition Examination Survey, 2.3%; Tobacco Use Supplement, Current Population Survey, 1.6%; and National Health Information Survey, 2.8% (Agaku et al., 2015). More specifically, overall prevalence of current daily snus use in the US adult population was reported to be 1.8% from National Adult Tobacco Survey data (CDC, 2014). These data indicate that the adoption and initiation of ST product use in the US is relatively low and therefore, overall initiation of the proposed snus products would be expected to be quite low given Swedish snus are a low percentage of the US ST market.

SMNA conducted a US consumer perception study ((b) (4)) in February 2015 and submitted findings (b) (4) on March 6, 2015 (b) (4)
(b) (4)

Due to methodological and data reporting limitations, the data from this study do not offer firm conclusions about consumer perceptions evaluated. However, studies from the US literature indicate low acceptability of snus use has been found, as discussed earlier, and it does not appear there would be significant shift in these snus product use by nonusers or current tobacco users; although current ST users may be more inclined to consider these snus products use. Other General brand snus products are currently available on the market in round and square cans with disposal compartment.

Transition from Snus to Smoking

According to the applicant, there is little evidence that snus use leads to future cigarette smoking and that longitudinal and cross-sectional studies conducted on snus use in Sweden and other Scandinavian countries suggest that snus use is associated with a reduced risk of becoming (or continuing to be) a regular smoker. These longitudinal studies suggest that users will transition from cigarettes to snus, rather than switching from snus to cigarettes. The applicant summarizes studies examining the transitioning of snus users to combusted cigarettes.

Researchers (Tam et al., 2015) conducted a review of published estimates of the proportion of US adults and adolescents transitioning between ST and cigarettes. Six studies of US populations were published since 2000 with longitudinal data on some or all of the transitions between ST and cigarette use. There was considerable heterogeneity across studies in design and tobacco use definitions. Despite these differences, the existing data fairly consistently indicated that switching behaviors from exclusive smoking to exclusive ST use are limited (adults: 0-1.4%, adolescents: 0.8-3.8%) but switching from ST use to smoking may be more common (adults: 0.9-26.6%, adolescents: 16.6-25.5%). Among adults, exclusive cigarette smoking was generally stable and consistent (79.7-87.6%) during follow-up across studies but less stable in adolescents (46.8-78.7%). Exclusive ST use was less stable than exclusive cigarette smoking over time (adults: 59.4-76.6%, adolescents: 26.2-44.8%). A potential limitation of this study is that the data were collected more than a decade ago. Available US data do not address snus specifically and are inconclusive regarding whether prior ST use is associated with or leads to subsequent cigarette smoking in adults. Researchers (Meier et al., 2015) also examined the use of various nicotine-containing products on a tobacco-free college campus and whether the first product tried predicts subsequent tobacco use. The authors

concluded that uptake of emerging tobacco products (including snus) was poor, and does not appear to lead to use of cigarettes and traditional ST products.

In sum, existing data indicate that switching behaviors from exclusive smoking to exclusive smokeless tobacco use are limited. Findings from Tam et al. indicate that in the US, switching from ST use to smoking is more common than switching from smoking to ST use. Nevertheless, limited data suggest overall that the adoption of snus use in the US is low and therefore, unlikely to lead to use of other tobacco products. Thus, it is anticipated that the marketing of these products, as described in the PMTAs, is unlikely to lead to significant increases in initiation of tobacco product use.

Likelihood of Cessation

Cessation is discussed in the Health Impact section above. In addition, the SMNA MRTP Warning Label Evaluation study presented data on the likelihood of quitting or reducing use of different tobacco products. More than 13,000 subjects were enrolled and six warning labels were tested in this online experimental study. Due to study limitations, it is difficult to draw concrete conclusions and implications from the data. Nevertheless, one pattern evident across the different harm measures was that a portion of participants (about 25%) reported not knowing the risks of snus or snus use risks compared to those of other tobacco products. Also, 18% of tobacco users ages 18 to 24 believed that there was little or no risk from using snus. Risk perceptions are often related to use behavior; however, it is unclear from the data presented how risk perceptions will influence use behavior. One caveat is that studies have found that perceptions of relative harm of snus depend on how the question is framed. Preliminary data from the Population Assessment of Tobacco and Health (PATH) Study indicate that nearly 40% of adults and 43% of youth who are current tobacco users use more than one tobacco product. The significant proportion of tobacco users who use multiple products was not accounted for in the MRTP Warning Label Evaluation study. Product labels with appropriate warning labels and educational campaigns to increase awareness of various tobacco product health impacts are important tools to utilize in increasing likelihood of cessation of tobacco products. These proposed product labels do include mandated warnings.

Dual Use

The availability of snus may result in dual use. While relatively uncommon in Sweden, dual use may be more likely in the US. SMNA provided a summary of available scientific evidence addressing snus use and behavior patterns; however, most studies were conducted in Sweden and other Scandinavian countries. Limited data related to US snus use are available, and most relevant studies include the broader category of ST products and are not specific for snus products.

The 2014 NYTS reports that 24.6% of high school students report using tobacco products and more specifically, 1.9% use snus products (prevalence of middle school student snus use is 0.5%). Given the historically low and stable rates of ST use in the US, there is no compelling reason to believe the marketing these products, as described in the PMTAs, that concomitant use of snus and cigarettes will exceed concomitant use of traditional ST products and cigarettes. However, it is possible that a market authorization order may increase dual use due to the perceived favorable profile associated with an “FDA authorization” marketing order which could lead to benefit if tobacco users who use multiple tobacco products then transition

to exclusive use of less toxic tobacco products and then ultimately quit all tobacco products. Conversely, there could be harm if the perceived favorable profile discourages transition to exclusive use of less toxic tobacco products and cessation.

According to the applicant, the Swedish National Tobacco Survey indicates that the prevalence of daily snus and cigarette smoking (i.e., dual use) has remained stable at 2% since 2004. Norway and Sweden have reported roughly similar results with the percentage of dual users ranging from 2-10%. In the MONICA cohort study (representative of Northern Sweden from 1986-1999), dual use was reported to be around 2-5% (Rodu et al., 2002; Stegmayr et al., 2005). In the Norway Tobacco Statistics survey, 7% of individuals reported dual use of snus and cigarettes. In a study of Norwegian youth, dual use was reported to be10%. Overall, the applicant concluded that males and individuals with low educational background were more likely to be dual users of cigarettes and snus. The applicant also notes that data suggests slightly lower overall tobacco use among dual tobacco users.

Concomitant use of two tobacco products may increase the risk of adverse health consequences relative to use of a single tobacco product. Few representative US national data sets on the prevalence of concomitant smoking and ST use exist. The few data sets available suggest that 25% or more of current adult ST users also smoke cigarettes, whereas 2.5-5% of adult smokers also use ST (CDC, 1993; CDC, 2000; SAMHSA, 2001). Using data from the Working Well Trial, a large cancer prevention study that tested the effectiveness of worksite health promotion interventions in reducing cancer risk behavior, researchers (Wetter et al., 2002) examined correlates of concomitant smoking and ST use. The researchers found that the prevalence of concomitant smoking and ST use exists among males (5%) but is nonexistent among females. The characteristics of dual users were relatively distinct from those of exclusive smokers and exclusive ST users (e.g., more likely to live with a smoker, younger, less educated), and indicators of nicotine dependence predicted tobacco cessation for both smokers and ST users but were unrelated to tobacco cessation for dual users. Swedish studies indicate low prevalence of dual use is possible. While this is not the situation in the US, further understanding of factors leading to high rates of multiple tobacco use in the US is important in being able to decrease rates of multiple tobacco use in US with the goal of decreasing risk of adverse health consequences. The most effective way to decrease morbidity and mortality from tobacco use remains to never start or to quit tobacco product use as early in life as possible.

Likelihood Product Used as Designed

The proposed label does not include statement of “intended use”. In particular, as noted in section 2.4, differences in the manner of use between traditional US ST products and Swedish snus include the placement of the product in the mouth and expectoration. Given these differences and the lack of instructions, it is likely that individuals in the US will use the products which are the subject of these applications in a manner that may be different than users of snus in Sweden. It is unknown if and how these different use patterns would impact the health effects associated with these products; however, while discrepancies may be possible, overall, similar health impacts are expected from these snus products given oral exposure whether it is placed near upper lip versus lower lip.

Population Modeling

The applicant describes the implementation of a Dynamic Population Model to track population-based tobacco use and harm and presents results from analyses conducted with the model to assess the hypothetical effects of cigarette and snus use in the US population in a variety of scenarios. (b) (4)

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, it is difficult to determine from these population model results what effect, if any, the marketing and sale of the proposed PMTA products would have on tobacco product use and health effects in the US (b) (4)

In general, it would have been useful if the applicant had provided a clearer description of the 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 the model along with their transition probabilities. It also would have been helpful if the applicant had provided additional information to aid in the interpretation of model analyses and results, including cigarette and snus use prevalence estimates for each model scenario, in order to facilitate an evaluation of the plausibility and relevance of these scenarios for the U.S. population. However, given the particular situation that these PMTAs offer epidemiologic data on Swedish snus use and health impact ("The Swedish Experience"), as well as experience from sales of similar Swedish snus products in the US, CTP reviewers can develop a reasonable understanding of potential impact from marketing of the proposed products as discussed in their reviews.

III. Tobacco Product Science Advisory Committee Meeting

On April 9-10, 2015, the Tobacco Product Scientific Advisory Committee (TPSAC) met to discuss MRTPAs submitted by SMNA for 10 General brand snus tobacco products, of which eight were submitted for PMTA consideration. SMNA submitted MRTPAs seeking risk modification orders under Section 911(g)(1) of the FD&C Act specifically requesting certain modifications to the health warnings currently required by the Comprehensive Smokeless Tobacco Health Education Act for smokeless tobacco products:

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

The FDA identified several topics for discussion for which TPSAC recommendations were sought with respect to the relative health risks to individual users of the snus tobacco products that are subject to the proposed MRTPAs:

1. The relative health risks to individual users of the snus tobacco products that are subject to the proposed MRTPAs, particularly with respect to gum disease, tooth loss, and oral cancer, and a comparison to risks of cigarette smoking

2. The behavioral aspects of snus use, particularly as they relate to:
    - The likelihood that existing users of tobacco products who would otherwise stop using those products will switch to the snus tobacco products that are subject to the proposed MRTPAs
    - The likelihood that persons who do not use tobacco products will start using the snus tobacco products that are subject to the proposed MRTPAs
3. Comprehension of the modified risk information and perception of the product in the context of total health
4. Postmarket surveillance and studies

As per section 911(f)(1), any MRTPAs must be referred to TPSAC for discussion. In the case of PMTAs, the FDA or the applicant may refer applications to TPSAC for discussion but no requirement exists [section 910 (b)(2)(A&B)]. Many of the issues for TPSAC discussion regarding the MRTPAs for the General brand snus products overlap with potential issues related to premarket authorization consideration, such as considerations of health impact from these snus products. FDA determined that there were no issues specific to the PMTAs that would require a second TPSAC meeting to discuss these same products.

TPSAC members generally agreed that Swedish snus products when used exclusively confer lower health risks than cigarettes in terms of respiratory and cardiovascular diseases; however, for other disease end points, the situation is not as definitive that there is lower health risks as compared to cigarette use.

IV. Labeling (DPAL/Social Science)

Labeling for each of the eight snus products without any proposed claims (as compared to those submitted for the respective MRTPAs) were evaluated by reviewers from Social Science Branch and Division of Product Advertising and Labeling (DPAL, Office of Compliance and Enforcement). The MRTP Warning Label Evaluation study included questions about warning claim believability and intention to use based on warning claim; these data have limited applicability to the PMTAs as they focused on the warning label and not the labeling as a whole. This was primarily a test of modified warning labels. While no studies were conducted to evaluate consumer perceptions of the entire labeling, the FDA reviewers concluded that the labeling does not appear to be false or misleading.

Of note, the labeling for General Classic Blend Portion White Large – 12ct (PM0000013) and General Nordic Mint Portion White Large -12 ct (PM0000015) indicates that a disposal compartment is included in the packaging for these two products in particular. The February 2015 (b) (4) Study as discussed earlier in this review (b) (4) Due to methodology and design limitations of the study, no firm conclusions can be drawn from the study. However, other General brand snus products are currently available with disposal compartment. Thus, this feature does not raise new questions that these products may have increased appeal for users or nonusers.

Instructions for Use

Instructions for use are not included with the actual products. The applicant does state in the PMTAs that a pouched snus or a pinch of loose snus is typically placed between the gum and the upper lip at the front of the oral cavity; furthermore, the pouch may be pre-wet on the tongue before being placed in the mouth and is most often worked on orally during use. The applicant states that none of the proposed products "require specific instructions for use or storage to get the proposed reduction in risk… or on how to avoid using the products in a way that could reduce or eliminate the potential benefit or increase the risk of use the products." The applicant refers to the population-based telephone survey of 2,914 randomly selected respondents in Sweden investigating snus use patterns and behaviors (Digard et al., 2009). It found that the typical usage time for one portion snus pouch is 60-70 minutes, and the total usage time is 10-12.5 hours per day. The study further found that the typical usage time is approximately the same among users of loose snus products and users of pouched snus products.

ST products including very similar products to these proposed products have been marketed for many years and the reviewers are unaware of reports of serious adverse experiences from unexpected uses of snus products. Nonetheless, it is recommended that with marketing authorization that the applicant provides with the proposed products any appropriate instructions for use.

V. Conclusions and Recommendation

Section 910(c)(4) of the FD&C Act specifies that FDA deny a PMTA where it finds that, among other things, a new tobacco product is not "appropriate for the protection of public health." One of FDA's goals is to decrease morbidity and mortality from tobacco use and to change the status quo so that nearly half a million Americans no longer die every year from tobacco use. Therefore, the broad overall objective of authorizing new tobacco products to be marketed through the PMTA process is to reduce the morbidity and mortality from tobacco use. In evaluating how marketing authorization for these eight Swedish snus products impact the current market, FDA considered it is possible that a PMTA order may increase use and initiation of snus due to its perceived favorable profile. Given this possibility, the products' impact on health, impact on smoking cessation, impact on snus initiation and uptake, and impact on current ST users must be considered.

Impact on health: SMNA provided a comprehensive review of published literature on the health effects related to Swedish Match snus use and specific disease states. In general, the literature presented confirms that individual snus user health risks are lower, or at least no greater, than those associated with cigarette smoking. The applications provide evidence that use of the products which are the subject of these applications is not likely to be associated with lung cancer, COPD, or chronic respiratory disease. Data are insufficient to support a lack of association between product use of these products and the other disease endpoints specified in the applications (e.g., stomach, pancreatic cancers, CVD, stroke, all-cause mortality). Use of these products is not associated with significant "second-hand" exposure, which decreases disease risks for the general population.

With regard to oral cancer risk, the scientific evidence provided in this application suggests that the *risk from these proposed Swedish snus products* is lower than the risk from smoking cigarettes or use of other smokeless tobacco products. However, the literature presented indicates that Swedish snus use does have a negative effect on dental health. Gingival recession was noted at increased frequency in several studies, even in younger subjects exposed for shorter periods of time. SIL were found to be almost universal among snuff users in Scandinavia. The long-term health implications of these lesions are unknown. Of note, the lesions typically reverse when the user quits using ST. At least one long-term study involving 1,115 individuals with SIL followed for > 25 years (Roosaar et al., 2006) found no cases of oral cancer at the site of snuff placement. The incidence of oral cancer in Sweden is low and the use of oral snuff is high, indicating that malignant transformation of the lesions is uncommon. But, overall the evidence supports that the use of the products which are the subject of these applications has a lower risk of disease for the individual user than the use of other smokeless tobacco products.

Where we may see the greatest impact is among current users of ST products. Given that (1) the full characterization, manufacturing, processing, and labeling of the eight snus products are considered to be acceptable and (2) their toxicological risk is considered to be significantly lower than that of similar products on the market, for current smokeless tobacco users it is likely appropriate to allow access to these tobacco products. Otherwise, available options would be limited to the existing grandfathered products and similar products.

Impact on smoking cessation: SM**NA** provided data from two clinical studies, one of which was conducted in the United States. Both studies were small and subject discontinuation rates were high (~40%). Although study subjects were motivated to quit smoking and the Swedish snus test products were provided free of charge, the success rate for smoking cessation was low. Stated alternatively, neither study demonstrated that current cigarette smokers are likely to use snus as a smoking cessation aid. The studies' analyses of health effects, including AEs and other information related to product use, showed no significant unexpected concerns for individual users.

In contrast, considerable data in the Scandinavian literature support the use of snus to facilitate smoking cessation; this would clearly benefit the individual user as well as the population as a whole due to reduced tobacco smoke exposure. Swedish longitudinal studies indicate that snus use is associated with a reduced risk of becoming or continuing to be a regular cigarette user.

Additionally, studies of Swedish adolescents show that snus use is neither a precursor to exclusive cigarette smoking nor a predictor of future cigarette smoking. Similar data for the US is unavailable. But, given the evidence as described in the PMTAs, it is reasonable to conclude that the marketing of these products which are the subject of these applications will not significantly reduce smoking but some smokers may switch to use of these products and quit smoking.

Impact on snus initiation and uptake: The applicant does not provide U.S. product use data demonstrating that the proposed Swedish Match snus products will be used similarly to traditional American ST products; however, since snus and traditional ST products are broadly similar, use behaviors are not expected to differ. Snus products are a small minority of tobacco products sold in the US and epidemiological data indicate that use rates remain relatively low; thus, there is no compelling reason to consider the marketing of these products, as described in the PMTAs, would result in uptake and initiation of these proposed products will exceed that of traditional ST products. Furthermore, the marketing of snus (including very similar General brand snus) does not appear to have increased overall ST use rates. It is unlikely that a significant portion of US cigarette smokers will switch exclusively to these Swedish Match snus products, given cultural and population differences as discussed in numerous FDA scientific discipline reviews evaluating these PMTAs. It is also expected that uptake of these products by nonusers is also likely to be very low, given that other very similar Swedish snus products currently exist and no increase in these product use has been reported.

In general, the availability of a product with abuse potential might lead to a number of consumers who sustain their addiction to nicotine or individuals who initiate use of the new product; therefore, it is important to understand how different characteristics such as nicotine dose delivered, nicotine delivery pharmacokinetics, and nonpharmacologic factors such as taste and other sensory aspects affect a product's abuse liability (Carter et al., 2009; Fant et al., 1999; Kotlyar et al., 2007). The proposed Swedish snus tobacco products have nicotine content that are considered to have abuse potential. However, several similar Swedish Match snus products are currently marketed in the US, and widespread use of snus has not been reported. A clinical study conducted in five US locations showed no evidence of smokers beginning to use snus along with their cigarettes (i.e., dual use). Several studies have reported low acceptability of snus in the US (Biener et al., 2014; Hatsukami et al., 2011; Hatsukami et al., 2013; O'Connor et al., 2011; O'Connor et al., 2014). Current low snus adoption rates suggest that, any detrimental effects to the US population from marketing these products are likely to be minimal. Overall, it is anticipated that unless use patterns change in unfavorable ways (increased youth initiation, delayed/decreased cessation), the products which are the subject of these applications may decrease the individual risk among current ST user due to their favorable toxicological profile (see below) without posing increased risk to the general population.

Top-line reasons for granting authorization for the proposed eight products include the following:

- Produced with a voluntary, proprietary manufacturing process that distinguishes Swedish snus from other types of ST, including snus-like products sold in the US market. The proprietary standard for Swedish snus products was developed to ensure product quality.

The principal components of this standard include constituent standards, manufacturing standards, manufacturing process requirements, and consumer package labeling with a "best before" date. The constituent standards set maximum levels that must not be exceeded for selected constituents in the finished products.

The proposed products have significantly lower levels of NNN and NNK compared to over 97% the ST products currently on US market. Since NNN and NNK are among the most carcinogenic constituents in tobacco products, reduction of NNN and NNK levels in ST products could reduce the cancer risk for consumers. Assuming that the only users of these products are persons who would have used other ST products currently on the US market, individuals using these products with lower NNN levels could decrease their excess cancer risk by 90% compared use of moist snuff (market share: 82%), 67% compared to use of chewing tobacco (market share:15%), 38% compared to use of US-style snus, and 92% compared to use of dry snuff.

- Levels of other HPHCs (including As, Cd, acetaldehyde, crotonaldehyde, formaldehyde, and BaP) are similar to or lower than levels of ST products currently on the US market. Certain HPHCs (such as acetaldehyde, cadmium, acrolein, and nickel) have been identified as constituents of more toxic concern in the smoke of combusted products as compared to smokeless products.

- When used exclusively instead of other US market smokeless tobacco products or cigarettes, offer potential for reductions in oral cancer.

- When used exclusively instead of cigarettes, offer lower risk of developing respiratory diseases (i.e., COPD, emphysema, chronic bronchitis) and certain cancers (such as oral, esophageal, and lung).

- It is anticipated that the marketing of the proposed products, as described in the PMTAs, there is a low likelihood of nonuser uptake of these products, decreased or delayed cessation, or other significant shifts in user demographics.

The most effective way to decrease morbidity and mortality from tobacco use remains to never start or to quit tobacco product use as early in life as possible. However, given the reasons described above, **authorization of these products is recommended** so that current ST product users who chose to continue using tobacco products will have additional options for less toxic smokeless tobacco products, thereby potentially decreasing the negative health impact from tobacco product use.

Environmental Decision

A finding of no significant impact (FONSI) was signed by Kimberly Benson, Ph.D. on October 8, 2015. The FONSI was supported by an environmental assessment prepared by FDA on October 8, 2015.

Required Postmarketing Reports

1. **Serious and Unexpected Adverse Experience Reporting**

- Report to the FDA all serious and unexpected adverse experiences associated with the tobacco product that have been reported to you **within 15 calendar days** after the report is received by you. These experiences may become known to you through a response to a customer complain, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure reported to you; or identified in the literature/media.

2. **Manufacturing Deviations**

- Promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. For products that have been distributed, if there is a potential for that deviation to impact public health, promptly identify and report to your regional FDA Office of Regulatory Affairs.

3. **Periodic Reporting**

On an annual basis, beginning October 2016, provide the following postmarketing reports:

- A cover letter listing the PMTA submission tracking number, tobacco product name(s), company name, date of report, reporting period, and worldwide marketing authorization status.
- A summary of how the tobacco product continues to be appropriate for the protection of the public health.
- If you have not already submitted specimens of all final printed labeling (actual labeling distributed with the product) including labels, insert/onserts, instructions and other accompanying information or materials for this product as a result of this authorization, include the labeling in your first annual report. Also include descriptions of all labeling changes.
- A description of all changes made to the manufacturing, facilities, or controls during the reporting period, including:
    i. A comparison of each change to what was described in the PMTA
    ii. The rationale for making each change
    iii. A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of the tobacco product;
    iv. The basis for concluding that each change did not result in any modification to the final product
- A summary of all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution and indicate a deviation that may affect the characteristics of the final product.
- An inventory of ongoing and completed studies about the tobacco product conducted by, or on behalf of, the applicant.

- A summary of reports on scientific investigations and full articles from literature about the tobacco product and significant findings from publications not previously reported. Any new scientific data (published or otherwise) should also be reported on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.
- A list of each, and a summary analysis of all, adverse experiences associated with the tobacco product that have been reported to the applicant, accompanied by a statement of any changes to the reference risk information and a summary of important risks, including the nature, frequency, and potential risk factors.
- A summary of sales and distribution of the tobacco product: Total U.S. sales reported in dollars, units, and volume with breakdowns by U.S. census region, major retail markets, and channels in which the product is sold (e.g. convenience stores, food and drug markets, big box retailers, internet/online sales, tobacco specialty shops);
- Data on current product users. Data should be collected about new users, current users, those who have switched tobacco products, and multiple product users. The results should be broken down by key demographic variables including age, gender, and race/ethnicity. Also, any change in the intended target market for the product should be reported. The data described above may include sales data and postmarketing analysis.
- Full-color copies of all advertising for the tobacco product that has not been previously submitted, along with the original date the materials were first disseminated and the date when their dissemination was completely terminated.

Recommended Action

Instructions for use are not included for the proposed products. We recommend that you add consumer instructions for product use and disposal.

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APPENDICES
Full Characterization of Products

1.1. Appendix A

The following information is applicable to PM0000010, 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		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	Ingredient	mg/g		
	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 (b) (4).

Performance Criteria

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

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1.2. Appendix B

The following information is applicable to PM0000011, 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		
	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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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			

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1.3.Appendix C

The following information is applicable to PM0000012, 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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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			

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1.4. Appendix D

The following information is applicable to PM0000013, General Classic Blend Portion White Large – 12 ct:

Chemistry Product Specifications

	Category	Unit of Measure	Target	Range
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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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			

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1.5.Appendix E

The following information is applicable to PM0000014, 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		

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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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			

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1.6. Appendix F

The following information is applicable to PM0000015, 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)	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		

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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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 bottom (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			

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1.7.Appendix G

The following information is applicable to PM0000016, 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)	Ingredient	mg/pouch		
Tobacco (b) (4)	Ingredient	mg/pouch		
(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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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			

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1.8. Appendix H

The following information is applicable to PM0000017, 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)	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		
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	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/m^2)		
Pouch Paper Air Permeability ($L/m^2/s$)		
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's proprietary Quality and Environmental Management System