Swedish Match

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Rationale and Justification for Comparators

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1 Rationale for Choice of Comparators

ZYN is a non-heated, tobacco-free, smoke-free, and spit-free nicotine pouch for oral use and with an appearance similar to Swedish snus products. The product is intended for adult tobacco and nicotine consumers. Use of ZYN does not involve any inhalation of smoke or vapor. ZYN comes in 10 different flavors (Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Citrus, Smooth, Chill, and Fresh) and two nicotine strengths (3 and 6 mg per pouch). ZYN is intended to be used under the upper lip for up to 60 minutes and is then discarded. Therefore, exposure to HPHC's only involves those that are taken up through the oral, mucous membranes or extracted to the saliva that is subsequently swallowed.

In the absence of other relevant Food and Drug Administration (FDA) guidance documents, the *Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS)* Guidance for Industry (June 2019) (FDA PMTA ENDS Guidance 2019) is relied on for this PMTA because the guidance can be applied to a smokeless nicotine product, such as ZYN. In addition, this application is also reflective of the proposed rule for PMTAs (FDA Proposed Rule 2019).

In terms of health effects, a reasonable comparator to ZYN is cigarettes as cigarette smoking accounts for the vast majority of tobacco-related morbidity and pre-term mortality in the US and by far represent the most commonly used tobacco product on the US market.

In the PMTA ENDS Guidance, the FDA recommends that a new product be compared to an existing product within the same category. In this PMTA, comparisons are made with two different smokeless tobacco products: moist snuff and Swedish snus.

1.1 Rationale for Choice Comparator: Moist Snuff ((b) (4))

(b) (4)
(b) (4) Therefore, in this PMTA, ZYN is also compared with existing moist snuff products on the US market. In terms of HPHC levels, the comparison was done using a moist snuff reference product from Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) and available from North Carolina State University Tobacco Analytical Services Laboratory (TASL) (https://strp.wordpress.ncsu.edu). The Smokeless Tobacco Reference Product 2.1 (CRP2.1) that was used is an American style loose moist snuff ST product that was produced without added flavorings, except for those required to produce a product that is characteristic of the style. The composition of CRP2.1 (CORESTA 2019) was judged to be a good representation of a US moist snuff product. It was manufactured in coordination by CORESTA for use in scientific studies as a reference standard product and is packaged in plastic cans that contain 34 g of the product (CORESTA 2019).

1.2 Rationale for Choice Comparator: Swedish Snus (General Snus)

Bridging to Swedish snus products is relevant since the products are similar in terms of use topography. Also, there is an abundance of human health data for snus based on long-term, epidemiological studies. The HPHC content in ZYN is typically much lower than that in snus. In fact, many of the HPHCs that are considered to be the most toxicologically relevant in snus are below the level of detection in ZYN including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene. (b) (4)

As noted in the FDA MRTPA TPL Review 2019, "The applicant has demonstrated that, as actually used by consumers, the eight General Snus products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. The claim 'Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis' is scientifically accurate."

(b) (4)

2 Justification for Choice of Analytes

(b) (4) [redacted]

Various priority lists of toxicants have been proposed for the evaluation of tobacco products, and the lists are mainly based on risk assessments. The FDA established a list of 93 HPHCs in tobacco products and tobacco smoke (FDA Established List of HPHCs 2012) and issued draft guidance on the reporting of an abbreviated list of 18 HPHCs in mainstream cigarette smoke and nine HPHCs in ST products (FDA Reporting HPHCs Draft Guidance 2012). The PMTA ENDS Guidance (FDA PMTA ENDS Guidance 2019) also lists HPHCs. Swedish Match adheres to these guidance documents and other historical documents, such as the 2010 FDA draft list that defines HPHCs for tobacco smoke or ST products (Section H.2.2 Historical List of HPHCs).

The Swedish Match list of analytes contains 45 HPHCs listed by FDA, which Swedish Match considers relevant to test in smokeless products. These HPHCs belong to different chemical classes, such as volatile organic compounds, polycyclic aromatic hydrocarbons, nitrosamines, metals, radionuclides, alkaloids, and mycotoxins. The Swedish Match list of analytes also contains 13 compounds that are product specific and/or required by external authorities or by the internal quality standard on snus products (GOTHIATEK). The reasons for inclusion of each analyte in the battery of testing and Chemical Abstracts Service registry numbers are shown in Table 1.

Table 1 Reasons for Inclusion in the Analytical Battery of Testing

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product Specific	Requirements External/Internal
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	(b) (4)	CA	(b) (4)	
5-Methyl chrysene		CA		
Acetaldehyde		CA, RT, AD		
Acrolein		RT		
Acrylamide		CA		
Aflatoxins (sum of Aflatoxin B1, B2, G1, and G2)		CA (Aflatoxin B1)		
(b) (4)		RT		
Anabasine		AD		
(b) (4)		-		

Table 1 Reasons for Inclusion in the Analytical Battery of Testing

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product Specific	Requirements External/Internal
Arsenic	(b) (4)	CA, CT, RDT	(b) (4)	
(b) (4)		-		
Benzo[a]anthracene		CA, CT		
Benzo[a]pyrene		CA		
Benzo[b]fluoroanthene		CA, CT		
Benzo[c]phenanthrene		CA		
Benzo[k]fluoroanthene		CA, CT		
Benz[j]aceanthrylene		CA		
Beryllium		CA		
Cadmium		CA, RT, RDT		
(b) (4)		-		
Chromium		CA, RT, RDT		
Chrysene		CA, CT		
Coumarin		Banned in food		
Crotonaldehyde		CA		
Cyclopenta[c,d]pyrene		CA		
Dibenzo[a,h]anthracene		CA		
Dibenzo[a,e]pyrene		CA		
Dibenzo[a,h]pyrene		CA		
Dibenzo[a,i]pyrene		CA		
Dibenzo[a,l]pyrene		CA		
(b) (4)		-		
Ethyl carbamate		CA, RDT		
Formaldehyde		CA, RT		
(b) (4)		-		
Indeno[1,2,3-cd]pyrene		CA		
Lead		CA, CT, RDT		
Mercury		CA, RDT		

Table 1 Reasons for Inclusion in the Analytical Battery of Testing

Analyte	CASRN	Reason for Inclusion		
		Health Risk (FDA/HPHCs)	Product Specific	Requirements External/Internal
(b) (4)	(b) (4)	-	(b) (4)	
Naphthalene		CA, RT		
Nickel		CA, RT		
Nicotine		AD, RDT		
(b) (4)		-		
		-		
		-		
		-		
N-Nitrosonornicotine (NNN)		CA		
N-Nitrosodimethylamine (NDMA)		CA		
Nornicotine		AD		
(b) (4)		-		
		-		
Polonium-210		CA		
(b) (4)		-		
(b) (4)		-		
Selenium		RT		
Uranium-235		CA, RT		
Uranium-238		CA, RT		
(b) (4)		-		
		-		

AD=addictive; CA=carcinogen; CASRN=Chemical Abstracts Service Registry Number; CDC=US Centers for Disease Control and Prevention; CT=cardiovascular toxicant; FDA=Food and Drug Administration; HHS=US Department of Health and Human Services; HPHC=harmful and potentially harmful constituent; RDT=reproductive or developmental toxicant; RT=respiratory toxicant; SNFA=Swedish National Food Agency; ST=smokeless tobacco; TSNA=tobacco-specific nitrosamine.

(b) (4)

[a] Not applicable.

[b] Requested by CDC/HHS (DHHS 2009).

3 Justification of Analytical Methods

Analytical methods used for the characterization were selected from protocols published by ISO, CDC or CORESTA where such protocols were available for the specific analyte. All analytical methods used for the characterization were fully validated, for both sample types of the comparators and for ZYN, and found to be fit for purpose for the characterization. All analytical methods used for HPHC analysis were accredited. A summary of all analytical methods is found in H.1.2.3.2 Analytical Procedures.

4 Characterization of Comparators

4.1 Characterization of Comparator: Moist Snuff, CRP2.1

CRP2.1 is an American style loose moist snuff ST product that was produced without added flavorings, except for those required to produce a product that is characteristic of the style. It is manufactured in coordination by CORESTA for use in scientific studies as a reference standard product and is packaged in plastic cans that contain 34 g of the product. The parameters shown in Table 2 were determined at the time of manufacture (CORESTA 2019).

Table 2 Parameters for CRP2.1 Determined at the Time of Manufacture

Parameter	Value
Moisture Content (%)	(b) (4)
pH	
Nicotine (% as is)	

The results from analytical testing of CRP2.1 are found in (b) (4) (b) (4) .

4.2 Characterization of Comparator: General Snus

(b) (4)

Swedish Match hopes to receive a positive ruling by FDA on the current PMTA filing by providing FDA with all the details of production and product characteristics showing that in virtually all aspects relevant to public health, the subject PMTA products have lower levels of undesired HPHCs compared to the selected comparator products.

The manufacture of Swedish snus has in principle remained the same since the early 1800s. Snus became more popular in Sweden in the early 1970s when portion snus was introduced. At that time, production of snus in Sweden was controlled by a state-owned company. The state monopoly was abolished in 1967 and later incorporated in Swedish Match AB in 1992.

With the growing popularity of snus in the late 1960s, several quality problems were noted with the old semi-manual production techniques. In 1971 snus came under the jurisdiction of the Swedish Food Act. Swedish Match modernized the production techniques and introduced several programs for quality assurance and quality control in a modernized manufacturing process at a newly built factory in 1982. Also, compliance with the Swedish Food Act implied stricter hygienic requirements and restrictions of allowed ingredients, additives, and containers, all of which must be food-grade. (b) (4)

Table 3 Target Parameter Values for General Snus Products

FDA Submission Tracking Number (STN)	Product Name	Moisture Content (%) [Range]	pH [Range]	Nicotine (% as is)
PM0000011	General Dry Mint Portion Original Mini	26.0 (24.0-28.0)	7.5 (7.2-7.8)	1.5
PM0000012	General Portion Original Large	51.0 (48.0-54.0)	8.7 (8.4-9.0)	0.85
PM0000014	General Mint Portion White Large	53.5 (51.5-55.5)	8.7 (8.4-9.0)	0.8
PM0000016	General Portion White Large	53.5 (51.5-55.5)	8.7 (8.4-9.0)	0.8
PM0000017	General Wintergreen Portion White Large	53.5 (51.5-55.5)	8.7 (8.4-9.0)	0.8

Swedish Match also has received marketing orders PM0000010, PM0000013 and PM0000015. (b) (4)

(b) (4)

(b) (4)

fully consistent with the standard. Over the following years, the maximum level of TSNA was lowered in steps as improved tobacco growing and curing standards were introduced.

Traditionally, snus was made from a selection of tobacco varieties, typically including a large proportion of fire cured tobacco. This resulted in relatively high levels of polycyclic aromatic hydrocarbons (PAHs) in the finished product. During the 1990s, use of fire-cured tobacco was phased out for General Snus as well as for all other snus brands produced by Swedish Match. Fire-cured tobacco adds a distinct flavor, but the traditional flavor characteristics were preserved using food-approved flavorings. As of May 2002, fire cured tobacco has not been in use in the production of any snus brand by Swedish Match, including General Snus.