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FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTAs

New Tobacco Products Subject to this Review	
STN.PDs[1]	PM0000593.PD1-PM0000612.PD1; see Appendix A
Common Attributes	
Submit date	March 4, 2020
Receipt date	March 4, 2020
Applicant	Swedish Match USA Inc.
Product manufacturer	Swedish Match USA Inc.
Application type	Standard
Product category	Other[2]
Product subcategory	Other[3]
Cross-Referenced Submissions	
All STN.PDs	(b)(4)
Supporting FDA Memoranda Relied Upon in this Review	
All STN.PDs	"Chemistry Review of In-Vitro Dissolution Study Data for PM0000593-PM0000612 by Swedish Match USA, Inc. (February 3, 2022)"
All STN.PDs	Update to Premarket Tobacco Product Application (PMTA) Review Process: Reviewing Late Amendments (October 30, 2023)
Recommendation	
Issue marketing granted orders for the new products that are subject to this review.	

Technical Project Lead (TPL):

Digitally signed by Mayo J. Wright -S
Date: 2025.01.14 13:42:17 -05'00'

Mayo (Jerry) Wright, Ph.D.
Supervisory Pharmacologist
Division of Nonclinical Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

Digitally signed by Benjamin Apelberg -S
Date: 2025.01.16 06:47:03 -05'00'

Benjamin Apelberg, Ph.D.
Deputy Director
Office of Science

[1]Product details, amendments, and dates provided in the Appendix. STN means submission tracking number including product static identification number (PD) if applicable. PMTA means premarket tobacco application..
[2] Oral pouch products containing nicotine derived from tobacco.

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1. EXECUTIVE SUMMARY

This Technical Project Lead (TPL) review relates to premarket tobacco product application(s) (PMTA(s)) submitted under Section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), as amended by the Family Smoking Prevention and Tobacco Control Act (TCA). Based on the information provided in the applications and other scientific data as described in this TPL review, I find that permitting the marketing of the 20 new products listed in Table 1 below ("new products" or "subject products") is appropriate for the protection of the public health (APPH) (subject to certain marketing restrictions) and that none of the other denial grounds specified in section 910(c)(2) apply. Accordingly, I recommend that marketing granted orders (MGOs) be issued for the new products, subject to the marketing restrictions and post-market requirements.

Table 1. New products subject to this review

STN.PD#	Product Name	STN.PD#	Product Name
PM0000593.PD1	ZYN Cool Mint 3 mg	PM0000603.PD1	ZYN Coffee 3 mg
PM0000594.PD1	ZYN Cool Mint 6 mg	PM0000604.PD1	ZYN Coffee 6 mg
PM0000595.PD1	ZYN Peppermint 3 mg	PM0000605.PD1	ZYN Cinnamon 3 mg
PM0000596.PD1	ZYN Peppermint 6 mg	PM0000606.PD1	ZYN Cinnamon 6 mg
PM0000597.PD1	ZYN Spearmint 3 mg	PM0000607.PD1	ZYN Smooth 3 mg
PM0000598.PD1	ZYN Spearmint 6 mg	PM0000608.PD1	ZYN Smooth 6 mg
PM0000599.PD1	ZYN Wintergreen 3 mg	PM0000609.PD1	ZYN Chill 3 mg
PM0000600.PD1	ZYN Wintergreen 6 mg	PM0000610.PD1	ZYN Chill 6 mg
PM0000601.PD1	ZYN Citrus 3 mg	PM0000611.PD1	ZYN Menthol 3 mg
PM0000602.PD1	ZYN Citrus 6 mg	PM0000612.PD1	ZYN Menthol 6 mg

1.1 APPH STANDARD

Section 910 of the FD&C Act requires that, for a product to receive premarket tobacco product application (PMTA) marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH (Section 910(c)(2)(A)). The statute places the burden on the applicant to make the required showing by providing that FDA "shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health" (Section 910(c)(2)(A)).

The statute further specifies that, in assessing whether permitting the marketing of the new products would be APPH, FDA must consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products (Section 910(c)(4)). The APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. In determining whether permitting the marketing of a new tobacco product would result in a new benefit to public health, FDA weighs the potential negative public

health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching).

Before determining that permitting the marketing of a new tobacco product would be APPH, FDA also considers the potential impact of marketing restrictions and other mitigation efforts that aim to reduce the risk of youth initiation and tobacco use. Marketing restrictions include advertising and promotion restrictions intended to limit youth exposure to and appeal of tobacco product marketing (e.g., measures such as limiting advertising to platforms that are predominantly used by adults and using advertising content and methods that are not known to resonate with youth, or even eliminating advertising in certain media channels altogether) and sales access restrictions intended to restrict youth access to tobacco products (e.g., measures such as selling products only in face-to-face interactions, in adult-only facilities, or via websites that require robust age verification). Restrictions on advertising and promotion and sales access are important to include in MGOs because they can help ensure that the marketing of a new tobacco product remains APPH after authorization. FDA has included such restrictions in MGOs issued to date.

FDA also takes into account whether the applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls (including process controls and quality assurance procedures), toxicology, abuse liability, and other factors that can impact the product's risks and benefits to individual users, including relative to those of other tobacco products on the market. If an applicant does not include information that is needed for FDA to adequately assess the risks and benefits of the product, the applicant has failed to carry its statutory burden of demonstrating that the product's benefits outweigh the risks.

1.2 SUBJECT APPLICATIONS

We have reviewed the subject applications to determine whether they contain sufficient evidence of the type described above to demonstrate that marketing of the products would be APPH. The new products are pouched oral tobacco products that do not contain cut, ground, powdered, or leaf tobacco. The new products come in ten different characterizing flavors[3] and two nicotine levels (3 or 6 mg). The characterizing flavors of the new products include Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Cinnamon, Coffee, Smooth, Chill, and Menthol.[4] FDA's evaluation of these premarket tobacco product applications (PMTAs) determined that these PMTAs contain sufficient information to characterize the product design and that there are adequate process controls and quality assurance procedures to help ensure that they are manufactured consistently.

Based on the information provided in these PMTAs, the overall toxicological risk to the users of the new products is lower compared to both combusted cigarettes and smokeless tobacco products due to significant reductions in measured harmful and potentially harmful constituents (HPHCs) of the new products compared to moist snuff and snus products, including the General Snus products for which FDA has issued marketing orders. Overall, among the 42 HPHCs analyzed in the new products, levels of 36 were too low to be quantified. In fact, the new products do not contain measurable quantities[5] of

[3] The applicant uses the term "flavors" or "varieties" to indicate product flavors.
[4] Due to added ingredients such as sweeteners and cooling agents, FDA has determined that all new products have a non-tobacco characterizing flavor for the purposes of this review.
[5] The chemistry review concluded that all testing methods were validated and fit for purpose. Levels are not above the limit of quantitation (LOQ) of the analytical methods used in these PMTAs, though the applicant did not demonstrate that the new products are free from these chemicals.

carcinogenic tobacco-specific nitrosamines, including NNN[6] and NNK,[7] or the carcinogenic polycyclic aromatic hydrocarbon B[a]P.[8] The available scientific evidence indicates that NNN is the predominant driver of excess oral cancer risk among adults who use smokeless tobacco, so the lack of detectable levels of NNN in these new products has significant clinical relevance, suggesting that these products are among a category of tobacco products likely to pose the lowest risks to health. Also, the new products did not produce genotoxic effects in the applicant's nonclinical toxicology studies (i.e., Ames test, in vitro micronucleus assay), while combusted cigarettes did. The toxicology review concludes that adults who smoke who switch completely to the new products are expected to experience reduced risk of cancer, respiratory toxicity, and cardiovascular toxicity.. The toxicology review also concluded that adults who use smokeless tobacco products who switch to the new products will likely reduce their risk of cancer. Therefore, to the extent that people who currently smoke cigarettes or use most other smokeless tobacco products switch completely to these products instead of continuing to use their current products, we would expect their health risks to decline substantially. In addition, based on evidence suggesting the potential for reduction in lung cancer risk following significant reduction in cigarettes per day (CPD), the new products may also pose a benefit to adults who switch and significantly reduce their cigarette use.

In the applicant's consumer perception and intentions study, adults over age 24 who smoke cigarettes with intentions to quit expressed the highest intentions to purchase the new products and former tobacco product users expressed the lowest. Nearly half of adults who currently smoke cigarettes with intentions to quit found the new products' variety of flavors to be very or extremely appealing. The applicant conducted a 10-week prospective cohort study to observe actual use behavior among current adult tobacco users. This study found that nearly one-quarter of participants who used the new products switched completely from other tobacco products and reported exclusive use of the new products by the end of the 10-week study. The proportion of participants who used the new products in addition to combusted cigarettes at baseline declined from 15.9% to 8.1% over the course of this 10-week study. Similarly, the proportion of study participants who used the new products in addition to moist snuff declined from 15.0% to 7.5%. The Coffee (PM0000603.PD1-PM0000604.PD1), Spearmint (PM0000597.PD1-PM0000598.PD1), and Cinnamon (PM0000605.PD1-PM0000606.PD1) new products were used by study participants most often. By flavor variety, rates of switching ranged from 34.8% (Coffee) to 19.8% (Cool Mint), though these differences were not statistically significant. Given the reduced toxicological risk, the increased interest in purchasing among current tobacco users, and the degree of complete switching observed in the applicant's prospective use study, the applicant has demonstrated that adults that currently smoke and adults that current use smokeless tobacco would benefit from the marketing of these products.

Based on the information provided in these PMTAs, the new products' abuse liability, i.e., the ability to promote continued use, addiction, or dependence – is expected to be lower than that of combusted cigarettes and lower than some smokeless tobacco products. In particular, Behavioral and Clinical Pharmacology (BCP) concluded that the data provided demonstrate that for all flavor varieties of the 3 mg products and for most of the 6 mg new products (Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Chill, and Smooth), the abuse liability is not expected to exceed that of General Snus or the moist snuff comparator product. FDA generally needs product-specific data to draw such conclusions, which was not provided for the 6 mg Menthol new product. However, as TPL, I find

[6] N-nitrosonornicotine
[7] 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
[8] Benzo[a]pyrene

the available information across several lines of evidence showing the new products did not differ based on flavor variety indicating the 6 mg Menthol new product is not likely to differ markedly in its abuse liability when compared to other 6 mg new products, and all products are expected to have an abuse liability lower than cigarettes.

In terms of the risks to nonusers, the applicant's consumer perceptions and intentions study showed that appeal and likelihood to buy the new products was low among former tobacco users and never-users, including those ages 18-24. The new products come in a variety of characterizing flavors, and the literature shows that in general, non-tobacco flavors increase the appeal of tobacco products, particularly for youth, and, as such, increase the risk of youth initiation. However, youth use of nicotine pouches remain relatively low. For example, 1.8% of U.S. middle and high school students reported currently using nicotine pouches in the 2024 National Youth Tobacco Survey (NYTS) including 2.4% of high school students and 1.0% of middle school students. In contrast, 5.9% of U.S. middle and high school students reported current use of electronic nicotine delivery systems (ENDS) in the 2024 NYTS. The evidence related to appeal and intentions to use the new products, combined with observational data on youth use of nicotine pouches, suggest the risk of youth initiation with the new products is relatively low. Nonetheless, given the strong evidence regarding the impact of youth exposure to marketing on youth appeal and initiation of tobacco use, any marketing authorization should include marketing restrictions and post-market requirements to help ensure that youth exposure to marketing of the new products is limited. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adults who currently smoke cigarettes or use smokeless tobacco products who switch completely or significantly reduce their cigarette use would outweigh the risk to youth, provided the applicant follows post-market requirements aimed at reducing youth exposure and access to the products.

Regarding product stability, the applicant stated that the shelf life of the new products is (b)(4) . The applicant provided chemistry and microbial data to support that the new products are stable for at least (b)(4) . As such, the information reported is sufficient to support the applicant-proposed shelf life and does not preclude an APPH finding for the products.

After reviewing the marketing plans submitted by the applicant, the CTP Office of Health Communication and Education (OHCE) concluded that the applicant proposes directing its marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. OHCE supports certain aspects of the applicant's marketing plan, as described in the PMTAs, that are intended to help address the potential for youth exposure and appeal of the new products. For example, the applicant proposes(b)(4)

Based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products, subject to certain marketing restrictions, is APPH. The potential of the new products to benefit adults who smoke or use smokeless tobacco outweighs the risk to youth, provided the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to new product marketing and youth access to the new products. This determination is supported by the information currently available, including the relatively low levels of youth use observed. FDA will continue to monitor youth use of nicotine pouches, as well as the

marketing of these products in particular, because compliance with the MGO alone is not a guarantee that the marketing of these products will remain appropriate for the protection of public health, particularly if, despite these measures, there is a significant uptake in youth initiation, for example.

FDA has examined the environmental effects of finding the new products APPH and made a Finding of No Significant Impact (FONSI).

2. BACKGROUND

2.1. NEW TOBACCO PRODUCTS

The applicant submitted information for the new products listed on the cover page and with more detail in the Appendix. The new products are pouched oral tobacco products containing tobacco-derived nicotine, flavor ingredients, an artificial sweetener, stabilizers, fillers, and pH adjusters. The new products come in two nicotine levels, 3 mg and 6 mg. The new products are not smokeless tobacco products because they do not consist of cut, ground, powdered, or leaf tobacco.

In sections G.1 (Introduction), G.2 (Product Design Summary), G.3 (Product Composition Summary; Table 5), and G.4 (Product Manufacturing and Controls Summary; Table 2) of these PMTAs, the applicant states that the new products come in ten different flavor varieties (i.e., Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Chill, Smooth, and Menthol).

These PMTAs also include documents listing all ingredients for each new product [e.g., H.1.1.1.1 Smooth (8134)], including levels and function for each ingredient. The ingredient lists provided by the applicant state that each new product contains at least one sweetener (i.e., (b)(4) [redacted]). Those ingredient lists also state that each new product except the Smooth new products in PM0000607.PD1-PM0000608.PD1 include at least one additional ingredient that functions as a flavor. The Chill new products in PM0000609.PD1-PM0000610.PD1 also contain (b)(4) a cooling agent that the applicant states functions as a flavor (see Table 2 in "G.4. Product Composition Summary" that was submitted by the applicant). Thus, as discussed in Section 3.2. below, the Smooth and Chill new products contain ingredients that impart a non-tobacco characterizing flavor.

Based on the entirety of the evidence provided by the applicant in PM0000593.PD1-PM0000600.PD1-PM0000612.PD1, as TPL, I have determined that, for the purposes of FDA's evaluation, the new products described as Smooth (PM0000607.PD1-PM0000608.PD1) and Chill (PM0000609.PD1-PM0000610.PD1) have a non-tobacco characterizing flavor.

2.2. REGULATORY ACTIVITY

On March 4, 2020, FDA received 20 PMTAs from Swedish Match USA, Inc (see Appendix A). FDA issued an Acceptance letter to the applicant on March 12, 2020. FDA issued a Filing letter to the applicant on March 19, 2020. FDA issued a Deficiency letter to the applicant on July 24, 2020. On, August 3, 2020, the applicant submitted amendment PM000880 to notify FDA of how much time would be needed for to provide a complete response to all deficiencies. On September 24, 2020, FDA received the applicant's Response to Deficiency letter (PM0003101). On March 7, 2022, the applicant submitted amendment PM0005200 which contained updated labeling and advertising materials. On October 12, 2023, the applicant submitted amendment PM0007480

which contained updated scientific information published since submission of the original applications. On December 21, 2023, the applicant submitted amendment PM0007575 which contained an updated literature search as well as updated labeling and marketing plans for the 2024 program.

As described above, three additional amendments were submitted by the applicant after the Deficiency letter response due date of September 25, 2020 (see Appendix B, Table 6 for amendment details). Although FDA received these amendments after the response due date and after the discipline reviewers had started scientific review, I conducted a review of the amendments to determine their impact on the evaluation and findings from the discipline reviews. The March 7, 2022 amendment contains updated product labeling and marketing materials to (b)(4) The October 12, 2023 amendment notified the Agency of revised study reports, literature search results, organized references, and health risk investigations and summary. The December 21, 2023 amendment notified the Agency of updated literature searches as well as provides the 2024 marketing program. As TPL, I determined that the October 12, 2023 amendment does not impact the discipline reviews because the amendment did not provide any new substantive scientific information, and therefore, I determined that the amendment does not impact the evaluation and findings of the discipline reviews. The March 7, 2022 and December 21, 2023 amendments were reviewed by Social Science to ensure that the updated marketing plan as well as any marketing restrictions and other mitigation efforts aim to reduce the risk of youth initiation and tobacco use.

Refer to Appendix B (Table 6) for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the new products that are subject to this review.

Table 2. Disciplines reviewed

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Regulatory	Not Assigned	N/A	Taylor Worsley	7/18/2023
Engineering	Jimin (Peter) Kim	7/24/2020	Jimin (Peter) Kim	1/2/2025
Chemistry	Selvin Edwards	7/23/2020	Not Assigned[9]	N/A
Microbiology	Wen Lin	7/23/2020	Not Assigned[9]	N/A
Toxicology	Ana DePina	7/23/2020	Not Assigned[9]	N/A
Behavioral and Clinical Pharmacology	Sean Dolan	7/23/2020	Sean Dolan	1/3/2025
Medical	Vy Nguyen	7/24/2020	Vy Nguyen[9]	12/18/2024
Epidemiology	Baoguang Wang	7/24/2020	Terrence Lee/ Nicole Tashakkori	1/6/2025
Social Science	Jennifer Alexander	7/23/2020	Catherine (Kemp) Villavaso	1/6/2025

[9] Second cycle review was not necessary because there was no new information or data to review for this discipline as they do not have deficiencies nor do later amendments have data related to that discipline.

Discipline	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Environmental Science	Dilip Venguopal	7/23/2020	Christy Leppanen/Dilip Venguopal	1/2/2025
OCE – BIMO	Rachel Dailey	4/7/2020	Not Assigned[9]	N/A
OCE – Manufacturing/Lab	Basabi Roy	4/14/2020	Not Assigned[9]	N/A

Table 3. Consultations

Discipline or Office	Cycle 1		Cycle 2	
	Reviewer(s)	Review Date	Reviewer(s)	Review Date
Chemistry	Selvin Edwards	2/3/2022	Not Assigned[9]	N/A
OHCE	Emily Talbert	8/16/2021	Emily Talbert	8/1/2024
OCE – DPAL	Nneka Adibe	6/4/2020	Caroline Strotman	1/2/2025

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCTS

3.1.1. Discipline key findings

The following discussion is based on the key findings regarding comparison products that were provided in discipline reviews:

- The chemistry and engineering reviews concluded that the new products contain (b)(4), flavor ingredients, an artificial sweetener, stabilizers, fillers, and pH adjusters.
    - Detailed lists of ingredients in the new products are discussed in section 2 of the chemistry and engineering reviews.
    - The ingredients listed above are contained in sealed pouches that have a similar appearance to Swedish snus and are composed of (b)(4)
    - The new products are not smokeless tobacco products because they do not consist of cut, ground, powdered, or leaf tobacco.
    - The characterizing flavors of the new products are presented in Table 5 of Appendix A and include Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Cinnamon, Coffee, Smooth, Chill, and Menthol (see footnote 4 on page 5 of this review for more information).
- The comparison products used in analytical, nonclinical, clinical, and observational studies evaluated in these PMTAs include:
    - Swedish Match General Snus (Portioned Snus White Large or PSWL), a Swedish-style, tobacco-based snus.

        - Swedish Match General Snus products used in these studies have both PMTA and modified risk tobacco product (MRTP) authorizations from FDA.
        - The characterizing flavors of the General Snus products used in these studies (i.e., Mint, Wintergreen) appear similar to the characterizing flavors of several of the new products (e.g., Cool Mint, Wintergreen).
    - Comparison data from the new products in PM0000607.PD1 (Smooth 3 mg) and PM0000608.PD1 (Smooth 6 mg) are included in the nicotine pharmacokinetics (PK) study discussed in Section 3.3.1.1.
    - CORESTA Smokeless Tobacco Reference Product (CRP 2.1), an American-style loose moist snuff that includes few flavor ingredients.
    - Longhorn Pouch Natural, an American-style loose moist snuff.
    - Longhorn Pouch Wintergreen, an American-style loose moist snuff.
    - Kentucky Reference Cigarette (1R6F), a combusted cigarette.
    - Tobacco products used by participants in observational studies included cigarettes, ENDS, moist snuff, chewing tobacco, snus, nicotine pouches, cigars/cigarillos/filtered cigars filled with tobacco, pipe tobacco, or waterpipe/water pipe tobacco.
- Comparison product evaluation
    - The chemistry, engineering, medical, toxicology, and behavioral and clinical pharmacology (BCP) reviews noted that the new products are intended to be used in the same manner as smokeless tobacco products.
        - The HPHCs reported in these PMTAs include those commonly found in smokeless tobacco products, which also supports comparisons of the new products with currently available smokeless tobacco products.
    - The applicant did not provide engineering design parameters for any of the tobacco products to which the new products were compared, but the engineering review concluded it was appropriate to compare the new products to portioned smokeless tobacco products because use topography for General Snus and the new products is similar and moist snuff was the most commonly used tobacco product by study participants in the weeks before starting to use the new products.
    - The toxicology review of these PMTAs concluded that comparisons between the new products and General Snus are appropriate given similarities in manufacturing (e.g., similar quality management systems), structural materials, ingredients, flavors, HPHCs that are present, and methods of use.
        - The toxicology review also evaluated changes in risk of cancer and noncancer hazards (e.g., respiratory and cardiovascular toxicity) in adults who smoke that switch completely to the new products, indicating such a comparison was appropriate.
    - The chemistry review concluded that comparisons between General Snus and the new products are appropriate given similarities in frequency of use (i.e, user topography), nicotine content, pH, and units of use.
    - The epidemiology and BCP reviews noted that 66% of participants in the applicant's patterns of use study used moist snuff before they began using

the new products while 42% used combusted cigarettes, indicating that comparisons of these products are appropriate.

- The social science review concluded that consumer populations for the new products, moist snus, and combusted cigarettes overlap, indicating that comparisons between these products are appropriate.
  - The social science review also noted that adults who currently smoke expressed higher intentions to buy the new products when compared to users of other tobacco product types, former tobacco product users, and those that never used tobacco products, indicating that comparisons between the new products and combusted cigarettes are appropriate.
- The medical review concluded that comparing the health effects of the new products to Swedish snus, moist snuff, and cigarettes is appropriate in part because of similarities noted in the chemistry and toxicology reviews (e.g., manufacturing, structural materials, ingredients, flavors, nicotine content, pH, HPHCs that are present, methods of use).

3.1.2. Synthesis

Though the new products do not consist of cut, ground, powdered, or leaf tobacco, as TPL, I find that comparisons against moist snuff and snus are appropriate because the stated and intended user populations of the new products, as described by the applicant, overlap with those of moist snuff and snus; the products are used in the same manner and similar amounts; nicotine content, pH, route of exposure, and exposure levels are comparable; and the characterizing flavors are similar. For example, data submitted by the applicant indicate users of the new products are more likely to be current users of moist snuff or snus than other tobacco products. Also, moist snuff, snus, and the new products are all intended to be placed in the oral cavity where nicotine dissolves in saliva and is absorbed through the mucous membrane of the mouth. Clinical data submitted by the applicant indicate that the moist snuff and snus products tested produced similar levels of nicotine exposure and pharmacokinetics when compared to the new products, even though there are differences in nicotine chemistry between the products (i.e., nicotine salt in the new products vs. fermented tobacco in snus). As mentioned above, the characterizing flavors of most of the new products are consistent with flavors commonly found in moist snuff and snus (e.g., mint).

The applicant also compared health effects of the new products to those of combusted cigarettes. As TPL, I agree with findings from the BCP review indicating that current users of combusted tobacco products or ENDS are less likely to use the new products when compared to moist snuff or snus users. However, I find it is appropriate to compare health effects of the new products and combusted cigarettes because of the previously discussed similarities in user populations and the HPHCs that are present, as well as the fact that combusted cigarettes are the most commonly used tobacco product on the U.S. market.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

The following discussion is based on key findings regarding product characterization provided in discipline reviews:

3.2.1.1. Product design and composition

- From an engineering perspective, the information regarding design and principles of operation adequately characterize the new products.
    - The applicant provides adequate details on product description and principles of operation from an engineering perspective.
    - The applicant provides the target specifications and upper and lower range limits for all of the necessary design parameters.
    - The new products have high solubility and dispersibility, which may increase burst release rate of all constituents, as well as overall nicotine release rates.
        - As discussed in Section 3.3., nicotine extraction and subjective ratings of the new products in PM0000595.PD1-PM0000600.PD1 are comparable to the General Snus comparison product.
    - The new products include a perforated side label that is broken when the product is opened along with printed instructions to "break perforation on side label".
        - This type of side label is used commonly on smokeless tobacco products.
        - Together, the perforated side label and the instructions demonstrate tamper resistance sufficiently from an engineering perspective.
- From a chemistry perspective, the information, applicable specifications, and description of the intended function regarding nicotine source, components, ingredients, additives, and structural materials in each new tobacco product are sufficient to characterize the new products.
- While the new products contain humectants ((b)(4) [redacted]) that may impact microbial activity during the applicant-proposed product shelf life, the applicant provided adequate microbial shelf life data to demonstrate the stability of the products during the applicant-proposed product shelf life (see Section 3.2.1.3.).

3.2.1.2. Manufacturing

- From a chemistry perspective, the information on manufacturing steps and quality control measures in place are adequate to demonstrate that the new products consistently meet manufacturing specifications.
    - However, in a nicotine PK study submitted by the applicant (SM 18-01), product characterization data of the new products used in the study revealed that nicotine quantity in half of the samples of the new products was lower than the target quantity of nicotine (approximately 4.5 mg rather than the 6.0 mg target specification).

        - The chemistry review recommended FDA independently verify nicotine content and pH of the new products due to this discrepancy.
        - However, the chemistry review also noted that this lower nicotine content was only observed in the test materials used for the nicotine PK study.
        - After evaluating product release specifications for 18 batches of the new product (3 replicates of each measurement), the chemistry review also concluded that:
            - The information in these PMTAs below does not indicate the occurrence of any other nicotine measurements that are outside of the target specifications.
            - Overall, the applicant's HPHC and stability test data for nicotine content in selected batches of the tobacco products met the manufacturing target specifications.
            - The applicant has demonstrated that it can manufacture the new products consistently within the established manufacturing specifications.
    - The new products do not include processed tobacco; therefore, manufacturing practices such as fermentation or heat treatment to process tobacco are not applicable to the new products.
- From an engineering perspective, the PMTAs provide evidence demonstrating that the new products are manufactured in a consistent manner to minimize variability in product quality.
    - The applicant provides a description of product manufacturing and packaging processes for the new products, and provides adequate details such as process controls, process control parameters, performance criteria tolerance limits, and test data related to semi-finished and finished products for the manufacturing facility in Owensboro, KY.
        - Additionally, the applicant states that the manufacturing facilities in Owensboro, KY and in Kungälv, Sweden produce the new products via the same manufacturing steps with the same quality control measures.
        - Therefore, the general findings and evaluations of the manufacturing and controls information for the manufacturing facility in Owensboro are applicable to the facility in Kungälv, Sweden.
    - Inspection findings: None of the site facilities were selected for inspection at this time.
    - An Adverse Experience Database Search conducted by the medical reviewer on December 18, 2024 identifed a report of "nicotine poisoning" in a 20-month-old child exposed to a different nicotine pouch brand.
        - As noted in the engineering review and discussed below in Section 3.6.1.2, the new products subject to this review are packaged in certified child-resistant polypropylene cans and safety lids, which reduce the risk of accidental exposure in children.
        - No other engineering-related adverse experiences from product design were reported to FDA.

3.2.1.3. Product stability

- From a chemistry perspective, the data on chemical endpoints demonstrated that the applicant-proposed shelf life of (b)(4) is supported by the data submitted.
    - Information related to test methods, number of replicates, testing laboratories, and product storage conditions is acceptable from a chemistry perspective.
    - All moisture data for the time points within the applicant-proposed shelf life are within the associated range limits for the new products. The applicant has adequately characterized moisture stability for the new products.
- The microbiology review evaluated moisture content and stability data submitted by the applicant.
    - The average percentage of oven volatiles (OV%), an index of moisture content, of all new products is substantially lower (↓ 94%) when compared to CRP2.1 and General Snus tobacco products.
        - The engineering review noted that product moisture target specifications for the new products ((b)(4)) are also lower when compared to pouched smokeless tobacco products (30%-57%).
        - The lower moisture content of the new products is less conducive to microbial growth compared to pouched smokeless tobacco products or General Snus.
- The stability data measured over (b)(4) of storage adequately supports the applicant-proposed shelf life of (b)(4) for these new products and is acceptable from a microbiology perspective.
    - All measured stability testing parameters (pH, moisture, nitrate, nitrite, TAMC[10], TYMC[11], microbial toxins, NNN, NNK, and TSNAs[12]) are within the shelf life acceptance criteria established by the applicant.
    - The new products have at or below LOQ[13] levels of TAMC ((b)(4) CFU/g), TYMC (b)(4) CFU/g), microbial toxins (aflatoxins (b)(4) ng/g] and ochratoxin (b)(4) ng/g]), and measured levels of nitrate ((b)(4)); nitrite ((b)(4) µg/g), NNN and NNK ((b)(4) µg/g), and total TSNAs ((b)(4) µg/g).

3.2.1.4. Product test data

- From the chemistry perspective, with the exception of nicotine dissolution (discussed further below), the test methods, number of replicates, testing laboratories and accreditation, and storage conditions reported in these PMTAs are adequate to demonstrate the reliability of the stability and HPHC data provided.
    - The test data demonstrates that the new products contain reliably lower levels of the majority of HPHCs, including nicotine, free nicotine, NNN, and NNK than Swedish Match General Snus products, including General Dry Mint Portion Original Mini (6 g), General Portion Original Large (24 g), General Mint Portion White Large (24 g), General Portion White Large (24 g), and General Wintergreen Portion White Large (24 g).

[10] Total aerobic microbial count
[11] Total yeast/mold count
[12] Total tobacco-specific nitrosamines
[13] In this review, limit of quantitation (LOQ) is defined as the minimum amount or concentration that can be quantified with acceptable precision.

- Comparison of HPHC levels in the new products and Swedish Match General Snus is informative because General Snus is used in the same manner as the new products, is manufactured by the applicant under similar quality management systems as the new products, likely would have overlapping consumer populations, shares characterizing flavors, and has received both PMTA and MRTP authorizations from FDA.
- Levels of 36 of the 42 HPHCs reported for the new products are too low to be quantified.
    - The chemistry review concluded that all testing methods used to measure HPHCs were validated and fit for purpose.
    - The HPHCs that are quantifiable in at least one of the new products are acetaldehyde, coumarin, formaldehyde, naphthalene, nicotine, and nornicotine.
    - HPHC exposure is discussed further in Section 3.5.1.1 below.
- Acetaldehyde is quantifiable in the new products in all PMTAs and levels are 78%-89% lower when compared to General Snus.
- Nicotine is quantifiable in the new products in all PMTAs and levels are 14%-61% lower when compared to General Snus.
- Nornicotine is quantifiable in the new products and levels are 98%-100% lower when compared to General Snus.
- Formaldehyde is quantifiable in the new products in all PMTAs and levels are 24%-52% higher when compared to General Snus.
- Coumarin is quantifiable in the new products in PM0000605.PD1 and PM0000606.PD1, but not in the General Snus products listed above.
- Naphthalene is quantifiable in the Citrus new products (PM0000601.PD1-PM0000602.PD1) and levels are 55%-93% higher when compared to General Snus.
- As discussed in Section 3.5.1.2, the estimated exposure to formaldehyde, coumarin, and naphthelene from these new products is acceptable from a toxicology perspective because levels are below amounts that can be consumed orally by humans each day over a lifetime without appreciable health risk.

- The chemistry consult for the PMTAs dated February 3, 2022 raised issues about nicotine dissolution data reported by the applicant.
    - The nicotine dissolution study submitted by the applicant was intended to determine whether differences in the flavor ingredients of the new products affect nicotine release.
    - The chemistry consult concluded that it is unclear whether the nicotine dissolution method used by the applicant can precisely measure nicotine release from the new products.
    - Despite this concern about the method of determining nicotine release used by the applicant, other data indicate that differences in flavor ingredients used do not significantly affect nicotine release from the new products.
        - As discussed in Section 3.3.1.1, nicotine exposure from the new product PM0000607.PD1 (Smooth 3 mg) and from the

mint-flavored new products in PM0000595.PD1 (Peppermint 3 mg), PM0000597.PD1 (Spearmint 3 mg), and PM0000599.PD1 (Wintergreen 3 mg) are bioequivalent even though these new products have different flavor ingredients.

- Published data show that flavor ingredients do not significantly affect nicotine release from commercially available nicotine pouches (Aldeek et al., 2021) or moist snuff products (Miller et al., 2020).
  - While tobacco products reported in these papers are not the new products, the findings are consistent with nicotine exposure data discussed in Section 3.3.1.1 of this review.
- While the method used to determine nicotine dissolution was not optimized for the new products, the chemistry consult noted that the nicotine dissolution data in the applications indicate that flavor ingredients do not impact nicotine release from the new products during dissolution.
  - As discussed in Section 3.3.1.1 below, the BCP review did not rely on the applicant's nicotine dissolution study to determine nicotine exposure, which is an important component of abuse liability.

- From an engineering perspective, the applicant provides adequate test data for all necessary design parameters.
- The applicant provided adequate stability testing to support the applicant-proposed shelf life of these new products and comparisons to currently marketed smokeless tobacco products (e.g., moist snuff, dry snuff, snus, chewing tobacco, dissolvables).

3.2.1.5. Other microbial issues

- None noted

3.2.1.6. Other issues

- Characterizing flavor of the Smooth and Chill new products.
  - The applicant refers to the Smooth and Chill new products as flavored in some parts of the applications but refers to them as unflavored in other parts:
    - In their response to the Deficiency letter for PM0000593.PD1-PM0000612.PD1, the applicant refers to the Smooth and Chill new products as a "flavor variety" on pages 323, 325, and 326.
      - The applicant also refers to the Cool Mint, Spearmint, and Citrus new products, which they identify as flavored products, as "flavor varieties."
    - However, the applicant also refers to the Smooth new products as unflavored in their response to the Deficiency letter for PM0000593.PD1-PM0000612.PD1 (see pgs. 18, 23-24, and 405).
    - The applicant refers to the Chill new products as unflavored on page 18 of their response to this Deficiency letter.
- Use of sweeteners

- The chemistry review notes that all new products contain (b)(4) mg/pouch of (b)(4) an artificial sweetener that has nearly identical sweetness intensity as (b)(4)
    - At these levels, the concentration of (b)(4) in the new products is (b)(4) mg/L (or (b)(4) millimolar) or (b)(4) mg/L (or (b)(4) millimolar).
    - The applicant repeatedly states that (b)(4) functions as a sweetener in the new products (e.g., Tables 5-14 in "c-descript-prdt-info-zyn.pdf")
    - The chemistry review states that (b)(4) have nearly identical sweetness intensity.
    - FDA notes that both (b)(4) are about 200 times sweeter than sugar (US Food and Drug Administration, 2018).
        - Given the difference in sweetness intensity, the new products would need to contain 20% sugar by weight (or 102 mg) to have the sweet taste produced by (b)(4)
    - The Smooth new products (PM0000607.PD1-PM0000608.PD1) contain the same level of (b)(4) as the Cool Mint new products in PM0000593.PD1-PM0000594.PD1 (i.e., (b)(4) mg/pouch), which are identified as flavored by the applicant.
    - The Chill new products (PM0000609.PD1-PM0000610.PD1) contain the same level of (b)(4) as most other new products, including the Spearmint (PM0000597.PD1-PM0000598.PD1) and Citrus (PM0000601.PD1-PM0000602.PD1) new products, which are identified as flavored by the applicant.
- The concentration of (b)(4) in the Smooth new products PM0000607.PD1-PM0000608.PD1 is (b)(4) mg/L (or (b)(4) millimolar).
    - Currently available literature shows that humans detect (b)(4) concentrations as low as (b)(4) mg/L (or (b)(4) millimolar; Deitrich, et al. 2021, Wiriyawattana, et al., 2018).
    - Currently available literature also shows that humans recognize a sweet taste from (b)(4) at (b)(4) mg/L (or (b)(4) millimolar; Schiffman, et al, 1981) or higher.
- Thus, the levels of (b)(4) in the Smooth new products is high enough to produce a sweet taste for consumers.The concentration of (b)(4) in the Chill new products (PM0000609.PD1-PM0000610.PD1) is (b)(4) mg/L (or (b)(4) millimolar).
    - For the reasons discussed in the preceding bullets, the levels of (b)(4) in the Chill new products is high enough to produce a sweet taste for consumers.

- Use of cooling ingredients
    - The BCP and chemistry reviews note that the Chill new products in PM0000609.PD1-PM0000610.PD1 contain (b)(4) a synthetic cooling agent (b)(4) mg/0.4 g pouch).
    - The applicant repeatedly states that (b)(4) functions as a flavor in the Chill new products (e.g., Tables 6, 7, and 13 in "c-descript-prdt-info-zyn.pdf")
    - The BCP review concludes that (b)(4) may impart a cooling sensation to the new products in PM0000609.PD1-PM0000610.PD1 because (b)(4) is known to elicit a

cooling sensation in humans (Johnson et al., 2018) and has been added to tobacco products as a cooling agent.

3.2.2. Synthesis

The chemistry, engineering, and microbiology reviews state that, with the exception of high variability in the method used to determine nicotine dissolution, these PMTAs characterize product design, composition, manufacturing, stability, and test data sufficiently. Specifically, these discipline reviews note that product design, packaging, stability, applicant-proposed shelf life, and use life are acceptable from the perspective of these disciplines, and the new products contain lower levels of most measured HPHCs than the comparison products. As TPL, I note that HPHC levels in one of those comparison products (i.e., Swedish Match General Snus) are themselves lower than many other smokeless tobacco products (US Food and Drug Administration Center for Tobacco Products, 2019).

The engineering review concludes that the new products have high solubility and dispersibility, which could increase burst release rate of all constituents, as well as overall nicotine release rates. However, as discussed in Section 3.3., nicotine extraction and subjective ratings of the new products in PM0000595.PD1-PM0000600.PD1 are comparable to the General Snus comparison product. Thus, as TPL, I conclude that overall nicotine release rates of the new products are similar to General Snus.

The chemistry review for these PMTAs includes several findings that are noteworthy. First, the product samples used in a nicotine PK study contained less nicotine than the stated target specification of these products (i.e., 4.5 mg instead of the (b)(4) mg target specification). Thus, the chemistry review recommended that FDA verify the nicotine content and pH of the new products. As discussed in Section 3.2.1.2 above, the chemistry review also concluded that the applicant can consistently manufacture the new products within the established manufacturing specifications, the discrepancy in nicotine content occurred in a limited number of test pouches prepared for research purposes and used in a single research study, the discrepancy was not apparent in nicotine release specifications for 18 other batches of the new products, and the data are acceptable from a chemistry perspective. Thus, as TPL, I conclude that this discrepancy in nicotine content does not warrant FDA verification testing of nicotine content and pH of the new products.

While the method used by the applicant was not precise enough to reliably measure nicotine release from the new products, the available evidence indicates that flavor ingredients do not significantly affect nicotine release. For example, published data show that flavor ingredients do not significantly affect nicotine release from commercially available oral tobacco products. Also, clinical evidence submitted by the applicant shows that nicotine exposure from the mint-flavored new products in PM0000595.PD1 (Peppermint 3mg), PM0000597.PD1 (Spearmint 3 mg), PM0000599.PD1 (Wintergreen 3 mg), PM0000600.PD1 (Wintergreen 6 mg), and PM0000607.PD1 (Smooth 3 mg) are bioequivalent. As TPL, I believe the similarity of nicotine exposure from these products, which have different flavor ingredients, further supports the conclusion that flavor ingredients do not significantly affect nicotine release from the new products in these PMTAs. As discussed in Section 3.3.1.1 below, the BCP reviewer did not rely on the nicotine

dissolution data to estimate nicotine exposure, an important component of abuse liability, because the applicant's method was unable to measure nicotine release repeatably and reliably. As TPL, I also note that these findings from the chemistry review do not affect my overall conclusions about product manufacturing or other test data, largely because the chemistry review concluded that that the applicant can consistently manufacture the new products within the established manufacturing specifications. Finally, the chemistry review concluded that all the new products contain higher levels of formaldehyde, and the new products in PM0000605.PD1 and PM0000606.PD1 have higher coumarin levels, compared to Swedish Match General Snus. As discussed in Section 3.5.1.2, the estimated exposure to formaldehyde and coumarin from these new products is acceptable from a toxicology perspective because levels are below amounts that can be consumed orally by humans each day over a lifetime without appreciable health risk.

As TPL, I agree with the conclusions from the engineering, chemistry, and microbiology reviews that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the products meet the manufacturer's specifications.

As TPL, I note that the applicant refers to the Smooth and Chill new products as flavored in some parts of the applications but refers to them as unflavored in other parts. In its response to the Deficiency letter for PM0000593.PD1-PM0000612.PD1, the applicant refers to the Smooth and Chill new products as a "flavor variety" on pages 323, 325, and 326. The applicant also repeatedly states that (b)(4) functions as a sweetener in the Smooth and Chill new products. However, the applicant also refers to the Smooth and Chill products as unflavored in its response to the Deficiency letter for PM0000593.PD1-PM0000612.PD1 (see pgs. 18, 23, and 405). As discussed below, the data provided within the applications support the conclusion that the Smooth and Chill new products have a characterizing flavor for the purposes of this review.

The chemistry review states that the Smooth and Chill new products contain (b)(4) an artificial sweetener that has nearly identical sweetness intensity as (b)(4) FDA notes that both (b)(4) are about 200 times sweeter than sugar (US Food and Drug Administration, 2018). As TPL, I note that the level of (b)(4) in the Smooth new products is (b)(4) mg/L (or (b)(4) millimolar) and the level of (b)(4) in the Chill new products is (b)(4) mg/L (or (b)(4) millimolar). Currently available literature shows that humans detect (b)(4) at concentrations as low as (b)(4) mg/L (or (b)(4) millimolar; Deitrich, et al. 2021, Wiriyawattana, et al., 2018). The currently available literature also shows that humans recognize a sweet taste from (b)(4) mg/L (or 0.161 millimolar; Schiffman, et al, 1981) or higher. Since the levels of (b)(4) in the Smooth and Chill new products are 39-77 times higher than the levels reported in the literature as being recognized by humans to produce a sweet taste from (b)(4) as TPL, I conclude that presence and amount of (b)(4) in the Smooth and Chill new products are high enough to produce a characterizing flavor for consumers.

The Chill new products (PM0000609.PD1-PM0000610.PD1) also contain (b)(4), a synthetic cooling agent ((b)(4) mg/0.4 g pouch). The BCP review concludes that (b)(4) may impart a cooling sensation to the new products because (b)(4) is known to elicit a cooling sensation in

humans (Johnson, et al., 2018) and has been added to tobacco products as a cooling agent. As TPL, I note that the concentrations of (b)(4) in the Chill new products (i.e., (b)(4) mg/0.4 g or (b)(4) ppm) are at least 5 times higher than than those reported in the literature as eliciting a cooling sensation in humans (i.e., 100 ppm; Johnson, et al., 2018). As TPL, I conclude that the presence and amount of (b)(4) contributes to the characterizing flavor in the Chill new products.

Thus, as TPL, I conclude that the Smooth new products (PM0000607.PD1-PM0000608.PD1) and the Chill new products (PM0000609.PD1-PM0000610.PD1) have a non-tobacco characterizing flavor for the purposes of this review.

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

The following discussion is based on key findings regarding abuse liability provided in the BCP reviews:

3.3.1.1. Current tobacco users

- "Abuse liability" refers to the ability of the product to promote continued use and the development of addiction and dependence. This can be relevant to determining the likelihood that addicted users of one nicotine product would switch to another. For example, if a new tobacco product has a low abuse liability, current addicted tobacco users may find it to be an inadequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted.
- Abuse liability of a tobacco product is a multifaceted construct that can be influenced by a number of factors, including subjective effects, relative reinforcing properties, and nicotine exposure.
- The BCP review concludes that:
    - The abuse liability of the new products in PM0000593.PD1-PM0000611.PD1 is expected to be comparable or lower than that of General Snus and the moist snuff comparison products (i.e., Longhorn Pouch Natural).
    - However, the applicant did not demonstrate the abuse liability of the 6 mg Menthol new product (PM0000612.PD1) will not exceed the abuse liability of the moist snuff comparison products.
        - The BCP review specifically noted insufficient abuse liability data and bridging rationale for the 6 mg Menthol new product and noted that a new product with abuse liability higher than other 6 mg new products could increase the addictive potential of the new products, relative to moist snuff or other smokeless tobacco products, in individuals who use tobacco and nonusers, including youth.
- The BCP reviewer cited the following evidence as support for their conclusions:
    - The nicotine extraction and subjective effects ratings of the tested 3 mg Peppermint, Spearmint, Wintergreen, and Smooth new products (PM0000595.PD1, PM0000597.PD1, PM0000599.PD1, and PM0000607.PD1)

are similar and lower than that of the snus and moist snuff comparison products.
    - These data also suggest that the abuse liability for the 6 mg Peppermint, Spearmint, Wintergreen, and Smooth new products (PM0000596.PD1, PM0000598.PD1, PM0000600.PD1, and PM0000608.PD1) are expected to be lower than that of the snus and moist snuff comparison products.
  - Information reviewed in a cross-referenced TPMF ((b)(4)) does not indicate that the abuse liability of the 6 mg Citrus (PM0000602.PD1) and Chill (PM0000610.PD1) new products will differ from other 6 mg new products (e.g., the Smooth new product in PM0000608.PD1).
  - Product use frequency and duration of the 3 mg and 6 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, or Cinnamon products (PM0000593.PD1-PM0000600.PD1, PM0000603.PD1-PM0000606.PD1) did not differ from each other and were stable throughout the 10-week observational study discussed in Section 3.4.1.2, which suggests comparable abuse liability among these products.
  - Total nicotine exposure, peak plasma nicotine concentrations, and nicotine extraction associated with use of the tested 6 mg Smooth new product (PM0000608) are higher than that of the snus comparison product and comparable to that of the moist snuff comparison products.
  - Based on the bioequivalence analyses from SM18-01, which were performed using the nicotine PK profiles for the 6 mg Wintergreen and Smooth (PM0000600.PD1, PM0000608.PD1), acute nicotine exposure associated with directed product use is not expected to substantially differ across new products with the same nicotine content.
- The applicant did not provide clinical or observational data for the 6 mg Menthol new product and the BCP review concluded the abuse liability of the 6 mg Menthol new product cannot be bridged to other new products with a known abuse liability profile because the applicant did not provide sufficient data and bridging rationale.
- The BCP review did not determine that abuse liability of the 6 mg Menthol new product (PM0000612.PD1) is less than that of the moist snuff comparison product because the applicant did not provide sufficient data and bridging rationale for that new product.

3.3.2. Synthesis

Abuse liability refers to the potential of a substance to result in addiction and be used repeatedly or even sporadically, resulting in undesirable effects. High levels of abuse liability may result in compulsive and continued use of a product despite harm or risk of harm of the product. The abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the degree to which users of the tobacco product are likely to use and develop an addiction to the product.

The BCP review concluded that abuse liability of the 3 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, Cinnamon, Smooth, Citrus, Chill, and Menthol new products are not expected to be greater than that of General Snus or moist snuff comparison products (i.e., Longhorn Pouch Natural). The BCP review also concluded that abuse liability of the 6 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee,

Cinnamon, Chill, and Smooth are not expected to exceed that of these same comparison products. This conclusion was based on information submitted by the applicant indicating that the product use patterns, subjective effects, physiological responses, and nicotine exposure produced by the new products is comparable to the comparison products.

However, the BCP review did not determine that the abuse liability of the 6 mg Menthol new product (PM0000612.PD1) is less than that of the moist snuff comparison product. Based on nicotine extraction and exposure data submitted by the applicant, the BCP review concluded that nicotine exposure from the 6 mg Menthol new product may be similar to that of the moist snuff comparison product. The BCP review concluded that since factors other than nicotine content (e.g., the taste of the 6 mg Menthol new product) may impact nicotine exposure by influencing product use behavior (i.e., changing the frequency and duration of product use), actual use data is needed to determine if the 6 mg Menthol new product exposes users to as much or more nicotine than the moist snuff comparison product.

As TPL, I note that while the BCP review concluded that nicotine exposure and extraction from the 6 mg Smooth new product was similar to the moist snuff comparison product, the review also concluded that abuse liability of the 6 mg Smooth new product is expected to have comparable or lower abuse liability to moist snuff. The BCP review also concludes that the abuse liability of the the 6 mg Peppermint, Spearmint, and Wintergreen new products is comparable to the 6 mg Smooth new product and comparable or lower than the moist snuff comparison products. The BCP review states that that factors such as subjective effects and relative reinforcing properties also contribute to the abuse liability of a tobacco product. As TPL, I determine that BCP's finding that the abuse liability of the 6 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Coffee, and Cinnamon new products is similar to each other and comparable or lower than the moist snuff comparison products is compelling. As TPL, I also note that the bioequivalence analysis provided by the applicant demonstrated nicotine exposure was unlikely to differ across products with the same nicotine content but different characterizing flavors. Likewise, a nicotine PK study performed using the 6 mg Smooth and Wintergreen new products (SM 18-01), showed that nicotine exposure is unlikely to differ substantially between products with the same nicotine content but different characterizing flavors. As TPL, I do not expect that non-nicotine factors influencing abuse liability of the 6 mg Menthol products are different enough from the 6 mg Chill, Peppermint, Spearmint, and Wintergreen products to differentially affect abuse liability. All of these new products contain flavor ingredients that produce a cooling sensation or mint-like flavor.

As TPL, I also conclude that, while the applicant did not provide specific bridging data for the 6 mg Menthol new product, there is no evidence that the specific flavors in this new product significantly affect abuse liability. As TPL, I also note that this conclusion applies only to the new products subject to this review and cannot be extended to other tobacco products. The BCP review also concluded the abuse liability of the 6 mg Peppermint, Spearmint, Wintergreen, Cool Mint, Coffee, and Cinnamon new products is likely similar because of the frequency and duration with which these products were used over a 10-week period was stable (see Section 3.4.1.2 for additional discussion). The similarity of these patterns of use across new products with different characterizing flavors also supports my conclusion that the characterizing flavor of the new products subject to this review do not differentially

affect abuse liability. As TPL, I do not expect that non-nicotine factors influencing abuse liability of the 6 mg Menthol product are different enough from the other 6 mg new products to differentially affect abuse liability, and there was no evidence in the applications or that I am otherwise aware of that runs counter to this expectation.

In addition, even if the abuse liability of the 6 mg Menthol new product is similar to the abuse liability of moist snuff, as TPL, I determine that authorizing the 6 mg Menthol new product would still result in a reduction in overall health risks to current moist snuff users who switch completely to this new product. As discussed in Section 3.5.1, the new products subject to this review have significantly lower HPHC levels when compared to moist snuff. Unlike moist snuff, the new products do not contain measurable levels of TSNAs, a major driver of cancer risk. The chemistry review concluded that all testing methods to determine HPHC levels were validated and fit for purpose. As discussed in Section 3.6.1.5, the epidemiology review agreed with the applicant's assertion that the health effects of Swedish snus represent an upper limit on the likely long-term health effects of exclusive use of the new products. Finally, as discussed in Section 3.6.1.1, the severity of oral mucosal lesions declined and the number of subjects with oral mucosal lesions decreased from 90% to 70% when users switched from moist snuff to the new products subject to this review.

Given the totality of the evidence, as TPL, I conclude that the abuse liability of the 3 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Smooth, Chill, and Menthol new products are similar to each other and are not expected to exceed that of General Snus or the moist snuff comparator product. Likewise, as TPL, I conclude that the abuse liability of the 6 mg Cool Mint, Peppermint, Spearmint, Wintergreen, Citrus, Coffee, Cinnamon, Chill, and Smooth new products are similar to each other and are not expected to exceed that of General Snus or the moist snuff comparator product. As TPL, I also find that the abuse liability of the 6 mg Menthol new product is not expected to exceed that of the 6 mg Cool Mint, Peppermint, Spearmint, Wintergreen, and Chill new products. Given the similarities in nicotine content and multisensory subjective effects (i.e., cooling sensation, mint-like flavor) between these products, I do not expect that the non-nicotine factors influencing abuse liability of the 6 mg Menthol product are different enough from the other 6 mg new products to differentially affect abuse liability. In addition, even if the abuse liability of the 6 mg Menthol product is similar to the abuse liability of moist snuff, as previously discussed, as TPL, I determine that authorizing the 6 mg Menthol new product would still result in a reduction in overall health risks to current moist snuff users who switch completely to the new products.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

The following discussion is based on key findings regarding user populations provided in discipline reviews:

3.4.1.1. Intended user population

- The applicant states that the intended consumers of the new products are current tobacco users who are age 21 and older.

- In the applicant's retrospective patterns of use survey, more than 95% of 1,266 participants who used the new products were at least age 21.

- The ZYN Patterns of Use Study submitted by the applicant indicated that ZYN users in the study were adults, mostly white males, and residents of 11 states in the West and Pacific regions defined by the U.S. Census.

3.4.1.2. Current tobacco users

- Precursors of product use
  - Among users of the new products, the products were perceived as less harmful to health relative to cigarette smoking or smokeless tobacco use.
  - The BCP and social science reviews concluded that adults who currently use smokeless tobacco may be the population most likely to use the new products because of similarities in product design, manner of use, and nicotine exposure.
    - The BCP review determined that current smokeless tobacco product users are the population most likely to use the new products because of the high proportion of study participants (66.2%) who used smokeless tobacco products before they began using the new products.
  - However, as described in the section on product use below, the applicant's patterns of use study demonstrated considerable uptake among adults that smoke cigarettes and users of multiple tobacco products as well.
    - The epidemiology review concluded that more than 60% of participants in the prospective patterns of use study reported using the new products to help reduce or quit smoking.
    - Also, 19% of participants in the applicant's likelihood of use study who currently used any tobacco product (529/2,728) found the new products to be very or extremely appealing.
      - The new products were more appealing to adults that currently smoke with intentions to quit, with 25% (271/1,100) finding the new products very or extremely appealing.
  - The social science review concluded that current adults that smoke cigarettes had higher intentions to buy the new products compared to never and former users of tobacco or nicotine products as well as current users of one or more tobacco products other than cigarettes (e.g., ENDS, cigars, waterpipe, pipes, smokeless tobacco), although their mean intentions to buy were still low (2.47-2.97 on an 11-point scale).
  - The epidemiology review noted that a 2021 probability-based web panel of adults who smoke (n=1,018) designed to be representative of the U.S. found that 29.2% of participants had ever seen or heard of nicotine pouches, 16.8% reported interest in using pouches in the next 6 months, and 5.6% had ever tried nicotine pouches (Hrywna et al., 2022).
  - The fact that the new products come in a variety of characterizing flavors is appealing to current tobacco product users.

        - In the applicant's likelihood of use study, 48.0% of respondents who currently smoke with intentions to quit (528/1,100 respondents) found the variety of flavors for the new products to be very or extremely appealing.
            - In this same study, 38% (311/814 respondents) of respondents who currently smoke with no intentions to quit also found the variety of flavors either very or extremely appealing.
            - A much lower proportion of never users (17.3% or 280/1,620) and former users (16.2% or 132/817) found the new products' variety of flavors to be very or extremely appealing.
            - The social science review of these PMTAs concluded that the variety of flavors for the new products held appeal.

- Product use
    - The applicant conducted a study comparing users of the new products to users of other tobacco products to assess patterns of use (SMNA 17-12ZYN).
        - This study included both a retrospective survey and prospective study following users for 10 weeks.
            - In the retrospective survey, participants were asked to recall tobacco product use over the preceding 30-day period and respond to other questions including reasons for using the new products and intentions to quit using specific types of tobacco products.
            - Participants were also asked to recall their tobacco product use prior to when they began using the new products.
            - In the prospective study, participants were asked to report tobacco product use each day in a web-based diary for 10 weeks.
        - While the "nonuser" group in this study did not use the new products, all participants in both phases of the patterns of use study used at least one tobacco product.
    - In the retrospective survey, 1,266 users of the new products were compared to 733 participants who only used other tobacco products.
        - The vast majority of users of the new products (>98%) reported using other tobacco products during the weeks prior to using the new products.
            - This includes 42% reporting smoking cigarettes, 66.2% reporting using moist snuff, and 82.4% reporting using two or more tobacco or nicotine products prior to initiating use of the new products.
            - The epidemiology review noted that about half of the participants in the applicant's patterns of use study

reported using the new products because they came in flavors they liked.

- In the time period between initiating use of the new products and completing the survey (median time = 5-6 months; range = <1 month-24 months), the prevalence of moist snuff use among participants who used the new products decreased from 66.2% to 20.1% and the prevalence of cigarette use decreased from 42.0% to 15.1%, suggesting a reduction in moist snuff use and cigarette smoking while using the new products.
    - Among adults currently using cigarettes or moist snuff, use of the new products was associated with greater intentions to quit cigarettes/moist snuff:
        - In particular, among adults who smoke, those who also used the new products reported a greater intention to quit smoking compared to adults who smoke that did not use the new products (mean values of 4.98 and 3.18, respectively, on a 7-point scale).
        - Similarly, moist snuff users who also used the new products when the survey was taken reported a greater intention to quit moist snuff than moist snuff users who did not use the new products (mean value of 4.98 and 2.88, respectively, on a 7-point scale).
        - These differences in intentions to quit among adults who smoke and adults who use moist snuff are statistically significant.

- The 10-week-long prospective study evaluated patterns of use among users of the new products (n = 346) and tobacco users who did not use the new products (n = 196).
    - The proportion of participants who used the new products in addition to combusted cigarettes declined from 15.9% to 8.1% over the course of a 10-week longitudinal patterns of use study discussed later in this section.
    - The proportion of participants who used the new products with moist snuff (i.e., dual users) declined from 15.0% to 7.5%.
        - Among study participants who used the new products, the majority reported they had used new products to help reduce or quit cigarette consumption (84% and 60% by the end of the study, respectively).
    - Over the course of this longitudinal study, the proportion of those who exclusively used the new products increased from 50.3% to 65.6%.
    - Nearly one quarter (83 of 346 participants) of those who used the new products completely switched from other tobacco products and reported exclusive use of the new product by end of the 10-week prospective study period.

- (b)(4) [redacted]
- The epidemiology review noted that there was significant loss to follow up: a large portion of tobacco product users (49%) and nonusers (54%) left the study before it was completed and were not replaced.
    - The applicant reported switching data for participants who completed the 10-week prospective study (per protocol analysis) and these were likely the most committed product users.
- The epidemiology review concluded that complete switching among consumers using the new products with another tobacco product would likely be lower than 24%, noting that the proportion of switching observed in the prospective cohort study is likely overestimated. The review concludes that product uptake and switching from more harmful tobacco products is expected to be modest.
- Thus, based on data from this study and the scientific literature submitted by the applicant, the epidemiology review concluded that some adults who currently smoke may use the new products to reduce or quit cigarette consumption.

3.4.1.3. Non-tobacco users (including youth)

- Precursors of product use
    - The social science review states that current use of smokeless tobacco products declined from 2011 through 2020 and is generally lower than use of other tobacco products among youth.
        - This decline has been occurring at the same time the new products were on the market.
        - The social science review concludes that the applicant considers the expected users of the product to be similar to moist snuff tobacco users, a product type not commonly used by youth.
    - Based on the findings of the social science and epidemiology reviews, FDA expects that there would be relatively low use of the new products among this population.
        - Results from the likelihood of use study (5,165 participants) submitted by the applicant indicate that mean likelihood to purchase the new products among adults who have never-used tobacco products was low.
            - Mean likelihood to buy the new products among 807 never users ages 18-24 was 0.28 on a 0-10 scale, where 0 indicates “No chance” of purchasing the product.

        - Ninety percent (726/807) of these respondents reported a 1% or lower likelihood of buying the new products in the future.
        - It is not known whether intentions to buy for respondents ages 18-20 in this study differed from respondents ages 21-24; however, the 95% confidence interval for these data was 0.21-0.36, indicating little variation in responses from the total group.
    - Mean likelihood to buy the new products among 813 never users age 24 and older was 0.23 on the same scale.
        - Ninety-four percent (762/813) of these respondents reported a 1% or lower likelihood of buying the new products in the future.
    - The social science review also noted that the low overall interest in purchasing the new products was consistent with a study conducted in a consumer panel of U.S. adults that found low interest in buying the new products among never tobacco users (Plurphanswat et al., 2020).
  - Adults who formerly smoked also expressed low likelihood to purchase the product (0.15 on the same 0-10 scale).
- The study also evaluated overall appeal of the new products among these same groups on a 5-point scale (Not at all appealing – Extremely appealing).
  - 73.1% of never-users ages 18-24 (590/807 respondents) said the new products were “not at all appealing”, indicating low intentions to use these oral tobacco products among this population.
  - Never-users over age 24 (n=813) expressed similar ratings of overall appeal, except a smaller percentage found the new products to be “slightly appealing” (6.3% or 51/813 vs. 12.1% or 98/807).
- The new products’ variety of flavors were very or extremely appealing to 17.3% of never users and 16.2% of former users.
  - As noted in Section 3.4.1.2, appeal of the variety of flavors was much higher in adults who currently smoke with intentions to quit (48.0%).
  - In contrast, 42.9% of never users ages 18-24 (346/807) indicated that the new products’ variety of flavors were not at all appealing.
    - Less than 17% of adults who currently smoke found the new products’ variety of flavors not at all appealing.
- The study also evaluated perceptions of absolute risk of serious health problems from use of the new products.
  - Among those ages 18-24, never users were more likely than adults who smoke to believe that daily exclusive use of the new

products created a high or very high chance of serious health problems, regardless of whether they intended to quit (40% vs. 31%).
    - The same pattern was observed for never users over age 24 (41% vs 31%).

- Product use
    - Clinical or actual use studies
        - No clinical studies provided or reviewed by the applicant address use of the new products among current tobacco nonusers.
            - The BCP review concluded the likelihood of initiation of tobacco use with the new products is expected to be similar to smokeless tobacco products because of similarities in nicotine exposure and PK.
            - The BCP review also noted data from an observational study conducted by the applicant indicating that a small percentage (1.7%) of persons reported initiating tobacco product use with the new products.
    - Observational studies or surveys
        - The applicant did not provide information on any observational studies describing the patterns of initiation or experimentation with the new products by nontobacco users, including youth.
        - Based on published evidence, the epidemiology and social science reviews conclude that uptake of these products among nonusers, including youth, is expected to be relatively low.
            - The social science and epidemiology reviews cite estimates from the 2024 NYTS showing that 1.8% (480,000) middle and high school students used nicotine pouches in the past 30 days.
                - 1.0% (110,000) middle school and 2.4% (360,000) of high school students used nicotine pouches in the past 30 days.
                - Of the middle and high school students that reported past-30-day use of nicotine pouches in the 2024 NYTS, a majority (53.7%) reported using them fewer that five times in the last 30 days and 22.4% reported using them daily.
                - The social science and epidemiology reviews note small increases in current nicotine pouch use estimates between 2022 and 2024 (see Table 4 below) but conclude that, based on the currently available information, the prevalence of nicotine pouch use among middle and high school students remains relatively low.

Table 4. Trends in NYTS Current Nicotine Pouch Use Estimates

Group	2021*	2022	2023	2024
All Students	**0.8% (190,000)**	**1.1% (260,000)**	**1.5% (400,000)**	**1.8% (480,000)**
Middle School	0.3% (30,000)	0.5% (50,000)	NR	1.0% (110,000)
High School	1.1% (160,000)	1.4% (210,000)	1.7% (260,000)	2.4% (360,000)

*: Methodological changes were made due to COVID-19; comparing results from the 2021 NYTS with those of previous or future NYTS conducted primarily on school campus is not possible. **NR:** Not Reported

- Other studies have reported nicotine pouch use using convenience samples or unknown sampling methods, some of which found comparably low prevalence of use while others found higher prevalence compared to the national surveys and other studies discussed in this section. These are described below.
- A 2021 cross-sectional study of southern California 9th and 10th graders (n=3,516) found that 0.6% of participants reported ever use and 0.3% reported past 6-month use of any non-tobacco oral nicotine pouches (Harlow et al., 2022).
- In a study published using data from International Tobacco Control Policy Evaluation Project (ITC) Youth Tobacco and Vaping Survey, in 2019, 1.5% of U.S. adolescents aged 16-19 years (n=3,981) reported using nicotine pouches in the past 30 days (East et al., 2021). In comparison, 18.5% reported using ENDS and 7.9% reported using combusted cigarettes over the same interval.
- Conversely, in a 2021 convenience sample collected from a cross-sectional survey of U.S. participants ages 13-40 (n=6,131), 11.1% of respondents ages 13-20 reported ever use of nicotine pouches, while 6.4% and 5.1% of respondents in that same age group reported past 30-day use and past 7-day use, respectively (Gaiha et al., 2023).
    - Participants in this survey were recruited from online panels, using sampling quotas to recruit by age group and to match the proportion of sex and race/ethnicity with the latest U.S. census.
    - A separate study using the same sample reported past 30-day e-cigarette use of 36.9% overall and 29.8% among 13–20-year-olds, which is considerably higher than estimates reported elsewhere (McCauley, 2022).

        - As TPL, I concur with the authors of this study when they write "data were drawn from a convenience sample, limiting generalizability to the entire population of adolescent, young adult, and adult e-cigarette users in the United States."
    - The epidemiology and social science reviews note data from the Truth Initiative showing that 12% of people ages 15-24 surveyed between September 2021 and May 2022 reported using nicotine pouches in the past 30 days (Patel et al., 2023).
        - As TPL, I also note that 4.7% (108/2,282) of adolescents ages 15-17 in this survey reported current use of nicotine pouches, which is lower than for respondents ages 18 and older (14.4% or 800/5,550).
        - While the Truth Initiative data may be informative for assessing trends in use, as TPL, I concur with the authors statement that this convenience sample was "not sampled to be nationally representative."
    - In a 2021 online survey of about 600 young adults ages 18-25, 9.7% reported ever using any type of nicotine pouch (Morean et al., 2023).
    - However, due to several factors including target population, sampling technique, and sample size, the epidemiology and social science reviews concluded that these data are less robust and expressed greater confidence in prevalence estimates from the national survey discussed above.
- Of the middle and high school students that reported past 30-day use of nicotine pouches in the 2024 NYTS, approximately 85% reported using a non-tobacco flavored product, with mint being the most commonly used flavor (53.3%).
    - Middle and high school students reported similar preferences for non-tobacco flavored nicotine pouches in the 2023 NYTS (i.e., 86.6%).
    - The social science review concludes that, while non-tobacco flavored tobacco products are more appealing to youth than tobacco-flavored tobacco products, the concern about appeal of flavors to youth is currently partially alleviated by the low overall nicotine pouch use rates by youth.
    - As TPL, I also note that the majority of the new products include characterizing flavors that are common in smokeless tobacco products (e.g., Cool Mint,

Peppermint, Spearmint, and Wintergreen) and are not novel flavors likely to increase appeal to youth.

- The epidemiology review of these PMTAs concluded that the prospective patterns of use study provided by the applicant also indicates use of the new products by "nonusers" was low.
  - As discussed in Section 3.4.1.2, the "nonuser" group in the patterns of use study did not use the new products, but they did use at least one other tobacco product.
  - On average, about 2% (3.9/196) of nonusers (range = 1.0%-4.1%) reported using the new products during each week of the study and there was no increasing trend in those data.
    - The greatest use rates by nonusers came during the first two weeks of the study (2.6%) and the last week of the study (4.1%).
    - Between 1.0% and 2.0% of nonusers tried the new products each week during study weeks 3 through 9.

- Product Misuse by Children
  - As discussed in Section 3.6.1.2 below, the engineering review notes that the packaging for the new products consists of a certified child-resistant polypropylene can and safety lid.
    - The applicant states that the container is designed to be child-resistant, as the consumer opens the can by breaking the perforated label and twisting the lid to align the top and bottom arrows on the can to lift the lid.
  - Together, the child-resistant polypropylene can, safety lid, and perforated label mitigate the health hazards, especially to infants and children, by reducing risk that the products will be ingested by children.
  - The labeling for the new products includes directions to keep out of reach of children and that neither the pouch nor contents are to be consumed, which are expected to reduce risk of ingestion by children.
  - As discussed in Sections 3.6.1.6 below, the new products appear to have a low potential for adverse events associated with unintentional or intentional misuse from product design, including ingestion of pouch.
  - The toxicology review of the new products concluded that levels of nicotine in the new products are currently acceptable from a toxicology perspective and that the pouch material itself is unlikely to produce any adverse health effects in consumers.
  - The medical review of the new products notes that serious adverse events associated with severe poisoning (e.g., seizures, respiratory depression, confusion, lethargy, cardiac effects) were not reported in the applicant-sponsored studies and the Consumer Reported Complaints for the new products.
    - An Adverse Experience Database Search conducted by the medical reviewer on December 18, 2024 identifed a report of "nicotine poisoning" in a 20-month-old child exposed to a different nicotine pouch brand.

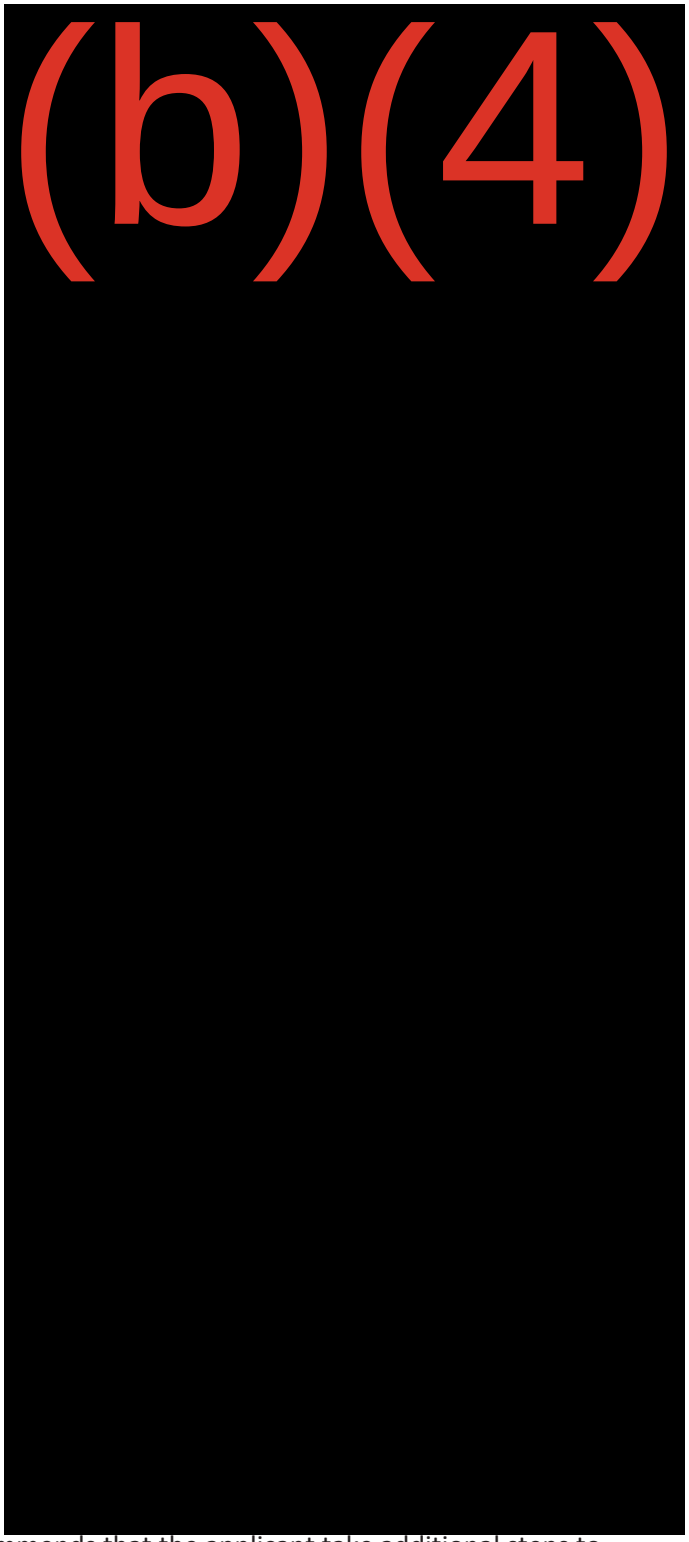
- As noted in the engineering review and discussed below in Section 3.6.1.2, the new products subject to this review are packaged in certified child-resistant polypropylene cans and safety lids, which reduce the risk of accidental exposure in children.
- No other engineering-related adverse experiences from product design were reported to FDA.

3.4.1.4. Vulnerable populations (other than youth)

- The applicant did not provide information from clinical studies that contain information on use of the new products among specific vulnerable populations (i.e., groups that are susceptible to tobacco product risk and harm due to disproportionate rates of tobacco product initiation, use, burden of tobacco-related diseases, or decreased cessation, other than youth).
- The applicant provided a review of published literature on Swedish snus use behavior, including limited information on Swedish snus use behavior in a rural population of Northern Sweden and a military population in Finland.
  - The literature showed that (1) Swedish snus use was similar between adults residing in town and adults residing in a rural area of Northern Sweden; and (2) prevalence of daily snus use among young male military recruits was higher (15.6%) than that observed in the general male population in Finland (2.1%).

3.4.1.5. Actions taken to mitigate risk to nonusers, including youth

- Per the OHCE consult and social science review:
  - The applicant submitted information on its proposed marketing plan for the new products on March 4, 2020, revised labeling and advertising materials in amendment PM0005200 on March 7, 2022, and an amendment (PM0007575) that included updated marketing plan information on December 21, 2023.
  - The OHCE consult concludes the applicant's proposed measures to restrict youth access, reduce youth appeal, and limit youth exposure to their labeling, advertising, marketing, and promotion are generally appropriate, but also noted the applicant provides only limited information regarding how such measures would be implemented.
    - Specifically, the updated OHCE consult supports the applicant's stated inten



- OHCE recommends that the applicant take additional steps to limit youth exposure to their point-of-sale advertising, including, for example, requiring advertising to be placed inside the store, and placing product displays near other age-restricted products and away from toys and candy.

- OHCE also notes the applicant's intention to use (b)(4) and reminds the applicant to ensure that such material does not include statements indicating that these products have been approved as smoking or tobacco cessation aids or any statements containing modified risk claims.
    - Should these new products be granted marketing authorization, OHCE recommends the applicant submit notifications of marketing materials 30 days in advance for a period for time and that FDA monitor the applicant's marketing activities and plans postmarket.
- However, the OHCE consult also states that, unless required as terms of an MGO, the applicant could alter its approach should the new products be authorized.
    - OHCE noted that should the new products be authorized, this concern may be addressed by incorporating the marketing restrictions and reporting requirements described in Section V of the OHCE consult.
    - For example, should marketing of the new products be authorized, OHCE recommended the applicant be required to establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to target delivery of such labeling, advertising, marketing, and/or promotion to individuals who are at or above the minimum age of sale.

3.4.1.6. Labeling and advertising

- As discussed in more detail in the OHCE review and OCE DPAL consult and elsewhere, the applicant initially submitted marketing plans and proposed (b)(4)
    - FDA issued a deficiency for (b)(4) for these products on July 24, 2020.
    - The applicant submitted amendment PM0005200 on March 7, 2022, (b)(4)
- The applicant also conducted a comprehension check to measure respondents' knowledge after viewing product labels and descriptions.
    - As discussed in the social science review, comprehension regarding the statements tested was high for most phrases among current tobacco product users, who are the likely users of the new products.
    - For example, 81.4% of respondents understood that "ZYN contains nicotine" and 76.3% correctly noted that "The package label includes a warning that nicotine is an addictive chemical".

- The statements evaluated in the comprehension check are consistent with labeling and marketing materials included in amendment PM0005200.

- The applicant provided proposed labeling as noted above. Based on the information presented at this time, as TPL, I have not concluded that the proposed labeling is false or misleading in any particular.

3.4.2. Synthesis

As TPL, I concur that current users of smokeless tobacco products are the most likely consumers of the new products because smokeless products are used in the same manner and in similar amounts, likely would have overlapping user populations, and have similar characterizing flavors as the new products. The applicant also describes general demographic and psychographic audience characteristics that were used to inform its labeling and advertising approaches based on insights obtained from consumer research and unsolicited product reviews and customer testimonials. The OHCE consult determines that the applicant proposes directing its marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion.

As discussed in Section 3.4.1.2, the applicant's patterns of use study provided information about product use among participants who used the new products as well as those who used other tobacco products. While the applicant referred to some participants as "nonusers" of the new products, it is important to note that all participants were current users of at least one tobacco product. The applicant used "nonuser" to denote participants who did not use the new products in addition to other tobacco products.

In the applicant's retrospective survey, participants that used the new products (n = 1,266) and participants who only used other tobacco products (n = 733) were asked to recall tobacco product use over the preceding 7- and 30-day periods. Participants were also asked to respond to other questions including reasons for using the new products and intentions to quit using specific types of tobacco products.

The data from the retrospective survey shows that prevalence of cigarette and moist snuff use declined after study participants began using the new products. Among users of the new products, 42% retrospectively reported smoking cigarettes before they began using the new products, but 15% of users reported using cigarettes in the 30-day period before the retrospective survey. Likewise, 66% retrospectively reported using moist snuff before they began using the new products, but 20% of users reported using moist snuff in the previous 30 days. Thus, as TPL, I conclude that some proportion of adults who smoke and use moist snuff find the new products to be suitable substitutes, a finding that contributes to my appraisal of the potential public health impact of the new products.

The applicant's 10-week-long prospective study observed actual use behavior among current adult users of the new products (n = 346) and tobacco users who did not use the new products (n = 196). Each participant in the prospective study was asked to report all tobacco product use each day in a web-based diary.

By the end of the 10-week prospective patterns of use study, 24% of all dual users (i.e., those who used the new products with cigarettes, smokeless tobacco, or other tobacco products) switched completely to the new products and nearly two-thirds of study participants who used the new products reported exclusive use of the new products. Likewise, the prevalence of cigarette or moist snuff use among those who also used the new products (i.e., dual use) declined during this study. The epidemiology review noted that complete switching observed in this study was likely elevated due to a number of methodological factors, and thus the true rate of switching would likely be lower than 24%. In particular, epidemiology cites loss to follow up as a potential source of bias leading to an overestimate of switching; however, their review did not examine data showing systematic differences between those lost to follow up and those who remained in the study, therefore, it is unclear the degree to which this limitation influenced the results.

The information provided by the applicant suggests that the new products appeal to adults who currently use cigarettes or smokeless tobacco, and particularly those with an intent to quit. A majority of participants in the 10-week prospective study report using the new product to quit or reduce their use of other tobacco products.

The epidemiology review concluded that the characterizing flavors of the new products did not affect patterns of use significantly, including the rate at which dual users switched to exclusive use of the new products.

The data also suggest that the variety of the new products' flavors is appealing to current tobacco product users. As discussed in Section 3.4.1.2, 48% of adults who currently smoke with intentions to quit (528/1,100) found the new products' variety of flavors to be very or extremely appealing. A much lower proportion of never users (17.3% or 280/1,620) and former users (16.2% or 132/817) found the new products' variety of flavors to be very or extremely appealing. Thus, as TPL, I conclude that new products' variety of flavors is less likely to contribute to tobacco product use among current nonusers when compared to adults who currently smoke with intentions to quit. Moreover, the new products include flavors that are common to the flavor varieties of smokeless tobacco products, as well as of nicotine gum products authorized as nicotine replacement therapy (NRT), supporting the evidence that this feature is important to consumer acceptability. As TPL, I consider the implication of these data to be that the availability of the new products with these characterizing flavors contributes to the overall likelihood that users of more harmful products like cigarettes and moist snuff may be interested in trying the products and continuing to use them in order to switch completely to the new products.

The lack of a statistically significant effect of characterizing flavor on complete switching is consistent with the data indicating that the characterizing flavor of these products does not affect abuse liability of the new products, which was discussed in Section 3.3.1.1. Indeed, as pointed out in the BCP review of these PMTAs, switching can be affected by factors that influence abuse liability (e.g., nicotine exposure, subjective and reinforcing effects). However, while abuse liability and patterns of use are likely related, they are distinct dimensions of tobacco product use. As discussed in the epidemiology review, the primary objectives of the prospective patterns of use study were to explore daily tobacco product use among users and nonusers of the new products and describe the tendency to use the new products exclusively or with other tobacco products. As noted above in Section 3.3.1.1.,

data from the applicant's patterns of use study, which indicate that patterns of use for the new products are not differentially affected by characterizing flavor, should be viewed as complementary to the abuse liability data about the new products.

In terms of the risks to nonusers, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. However, based on estimates from national surveys and other published findings, the epidemiology and social science reviews conclude that prevalence rates for youth use of nicotine pouches are relatively low. As TPL, I note that 1.0% (110,000) of U.S. middle school and 2.4% (360,000) of U.S. high school students reported currently using nicotine pouches in the 2024 NYTS. By comparison, 3.5% (410,000) of middle school students and 7.8% (1,210,000) of high school students reported current ENDS use in the same survey.

As TPL, I expect youth initiation with the new products to be relatively low based on the totality of the evidence related to appeal and intentions to use the new products. The epidemiology and social science reviews also note that higher prevalence estimates for youth use of nicotine pouches have been published but expresses greater confidence in prevalence estimates from the national surveys mentioned above. As TPL, I concur with the conclusion in the epidemiology and social science reviews that data from studies using convenience samples or unknown sampling methods are less robust when compared to representative samples, which often also have larger samples sizes to allow for more precise estimates. As TPL, therefore, I have greater confidence in nicotine pouch prevalence estimates from the NYTS, a study with a nationally representative sample which often also has larger sample sizes to allow for more precise estimates, when compared to prevalence estimates from studies using convenience samples or unknown sampling methods.

While non-tobacco-flavored tobacco products are more appealing to youth than tobacco-flavored tobacco products, the concern about appeal of flavors to youth is currently partially alleviated by the low overall nicotine pouch use rates by youth. For example, while 2024 NYTS results show that approximately 85% of middle and high school students who reported past 30-day use of nicotine pouches used non-tobacco flavored nicotine pouches, the overall prevalence of nicotine pouch use for those students was 1.8%. As TPL, I also note that the majority of the new products include characterizing flavors that are common in smokeless tobacco products (i.e., Cool Mint, Peppermint, Spearmint, and Wintergreen) and are not novel flavors.

The information provided in patterns of use study, combined with data from published literature, led the epidemiology review to conclude that some adults who currently smoke may use the new products to reduce or quit cigarette consumption. However, the epidemiology review noted that overall uptake of the new products by adults who currently use cigarettes is likely to be relatively low, and uptake may be more likely among current users of moist snuff. However, for both groups, the data support that use of the new products can facilitate complete switching. Importantly, as TPL, I expect that current tobacco product users who switch completely to the new products will experience a potential reduction in individual health risk, because of substantially lower HPHC content in the new products, relative to both cigarettes and smokeless tobacco products. Accordingly, these data support that the new products have the potential to substantially benefit current

adult users who switch to the new products. Since use of these products would benefit adults who smoke and adults who use smokeless tobacco that switched completely, I conclude that the benefit of the new products to adults who smoke and adults who use smokeless tobacco is sufficient to overcome the risk to nonusers, including youth. Finally, based on evidence suggesting the potential for reduction in lung cancer risk following significant reduction in CPD (Chang et al., 2021), the new products may also pose a benefit to adults who switch and significantly reduce their cigarette use.

Also, the applicant's data suggest that the new products do not appeal to adults who have never used tobacco or those who formerly used tobacco products: these groups reported low to no intention to purchase the products, and the majority found the products "not at all appealing". The applicant submitted a likelihood of use study indicating that mean likelihood to purchase the new products among respondents ages 18-24 who have never used tobacco products is low (0.28 on a 0-10 scale, where 0 indicates "No chance" of purchasing the product). The same study found that 73.1% of never users ages 18-24 said the new products were "Not at all appealing" and more 18-24 year-old never-users than people who smoke believed daily exclusive use of the new products created a high or very high chance of serious health problems, regardless of whether they intended to quit (40% vs. 31%). As is also discussed above in Section 3.4.1.3, the social science review concluded that appeal and likelihood to buy the new products was also low among former users and never-users, including those ages 18-24.

With regards to product misuse by children, including ingestion of the new products, I as TPL note that the applicant has taken steps to reduce risk of such misuse and the potential adverse effects do not appear to be severe. Specifically, the engineering review notes that the packaging for the new products consists of a certified child-resistant polypropylene can and safety lid. The consumer opens the can by breaking the perforated label and twisting the lid to align the top and bottom arrows on the can to lift the lid. Together, the child-resistant polypropylene can, safety lid, and peforated label mitigate the health hazards, especially to infants and children, by reducing risk that the products will be ingested by children. The labeling for the new products includes directions to keep out of reach of children and that neither the pouch nor contents are to be consumed, which are expected to reduce risk of ingestion by children. The medical review noted that serious adverse events associated with severe poisoning involving the new products subject to this review have not been reported in the applicant-sponsored studies and the Consumer Reported Complaints for the new products. FDA did receive report of "nicotine poisoning" in a 20-month-old child exposed to a different nicotine pouch brand. As discussed below in Section 3.6.1.2, the new products subject to this review are packaged in certified child-resistant polypropylene cans and safety lids, which reduce the risk of accidental exposure in children. This child-resistant primary packaging is expected to mitigate the health hazards of the new products, especially to infants and children, by reducing risk that the products will be ingested by children. The toxicology review concludes that levels of nicotine in the new products are currently acceptable from a toxicology perspective and that the pouch material itself is unlikely to produce any adverse health effects. As TPL, I also note that the levels of nicotine in the new products are similar to smokeless nicotine and snus products that are currently marketed. Thus, as TPL, I conclude that health risks of the new products to children do not exceed those of other tobacco products that are currently marketed.

Finally, though uptake among nonusers, including youth, is expected to be relatively low, as TPL, I agree with OHCE's evaluation of the applicant's marketing plans and all recommendations in the OHCE consult with respect to youth appeal and mitigation. Accordingly, I recommend that the MGO letter include additional marketing requirements and recommendations to reduce youth exposure to advertising, marketing, labeling, and promotion of the new products.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

The following discussion is based on key findings regarding toxicant exposure provided in discipline reviews:

3.5.1.1. Toxicity

- The new products are manufactured by Swedish Match North America LLC under a chemical quality control program based on the GOTHIATEK standard, which sets maximum levels of some HPHCs (Swedish Match, 2022).
- Levels of 36 of the 42 HPHCs evaluated in the new products are too low to be quantified.
    - The HPHCs that are quantifiable in at least one of the new products are acetaldehyde, coumarin, formaldehyde, naphthalene, nicotine, and nornicotine.
        - In contrast, 15 HPHCs are quantifiable in General Snus using the applicant's methods, indicating total HPHC exposure from the new products is lower compared to General Snus.
    - Acetaldehyde is present in the new products in all PMTAs, and levels are 78-93% lower when compared to mean levels in General Snus.
    - Formaldehyde is present in the new products in all PMTAs and levels are 24-52% higher in the new products when compared to General Snus.
    - Naphthalene is present in the 3 mg and 6 mg Citrus new products (PM0000601.PD1-PM0000602.PD1) and levels are 56%-94% higher in the Citrus new products when compared to General Snus.
    - Coumarin is present in the 3 mg and 6 mg Cinnamon new products (PM0000605.PD1-PM0000606.PD1) but not in General Snus.
    - As detailed in Section 3.5.1.2 below, the levels of acetaldehyde and formaldehyde in all the new products, levels of coumarin in the 3 mg and 6 mg Cinnamon new products, and levels of naphthalene in the 3 mg and 6 mg Citrus new products are relatively low and are acceptable from a toxicology perspective.
- The new products do not contain measurable quantities of carcinogenic TSNAs, including NNN and NNK, or the carcinogenic polycyclic aromatic hydrocarbon B[a]P.
    - In comparison, General Snus, which has both PMTA and MRTP authorizations from FDA, contains quantifiable levels of NNN and NNK (0.524 and 0.163 µg/g, respectively).

        - The levels of nitrite, a precursor for TSNAs (Law et al., 2016; Wang et al., 2017), in the new products are also lower compared to General Snus (≤ 1.8 and 3.0 µg/g, respectively).
        - Nornicotine, a precursor to NNN (Tricker et al., 1988), is quantifiable in the new products, but levels are 98-100% lower compared to General Snus.
    - The available scientific evidence indicates that NNN is the predominant driver of excess oral cancer risk among adults who use smokeless tobacco, so the lack of detectable levels of NNN in these products has significant clinical relevance.
- The new products also have lower levels of total nicotine and free nicotine (↓14-61% and ↓21-66%, respectively) compared to General Snus.
    - The chemistry review noted that the nicotine content of the new products is within the range of nicotine values typically seen in popular smokeless tobacco products that are commercially available in the U.S.
    - Also, nicotine PK data, subjective effects, and heart rate data mentioned in Section 3.3.1.1 above indicate that nicotine exposure from the new products is similar to smokeless tobacco products, including the General Snus comparison products.
- Like many snus and moist snuff products, the new products contain ingredients that can enhance HPHC uptake (e.g., (b)(4)), but levels of most HPHCs are lower in the new products compared to snus and moist snuff.

3.5.1.2. Exposure assessment

- The new products have ingredients (i.e., (b)(4)) that are not present in the smokeless products to which the applicant compared the new products.
    - The exposure assessment included in the toxicology review of these PMTAs shows that oral exposure to these ingredients from using the new products is not expected to exceed the reference values for toxicity established by Joint FAO/WHO Expert Committee on Food Additives (JECFA).
    - While the reference values cited in the applicant's exposure assessment are not developed for tobacco products, the underlying toxicity data used to derive the reference values may inform the toxicological evaluation of the ingredients in tobacco products consumed through the oral route.
- While formaldehyde levels in the new products are higher compared to General Snus, the applicant's exposure assessment indicates that oral exposure to formaldehyde levels in the new products is similar to moist snuff (Hoffmann et al., 1987) and below the tolerable daily intake (TDI) established by the World Health Organization (World Health Organization, 1996).
    - Thus, exposure to formaldehyde from the new products is not currently expected to pose increased toxicological concerns relative to General Snus.
- The applicant also provided an exposure assessment suggesting that oral exposure to coumarin levels in the new products is not expected to pose concerns from a toxicology perspective because levels are not expected to exceed the TDI established by the European Food Safety Authority (EFSA Panel on Food Contact Materials Enzymes Flavourings and Processing Aids, 2004).

    - Thus, coumarin in the new products is not currently expected to pose toxicological concerns.
- The Citrus new products (PM0000601.PD1-PM0000602.PD1) contain higher levels of naphthalene when compared to General Snus.
    - Estimated exposure to naphthalene from the Citrus new products is more than 14,000 times below the level, set by the US Environmental Protection Agency, to which humans can be exposed each day for a lifetime without appreciable risk of adverse health effects.
    - The toxicology review states that levels of naphthalene in the Citrus new products are below levels in ambient air.
    - Thus, naphthalene in the Citrus new products is not currently expected to pose toxicological concerns.
- Although (b)(4) , which is added to the new products, can act as permeation enhancer and increase HPHC exposure, levels of HPHCs are generally lower in the new products than in comparison products.
    - As mentioned in Section 3.5.1.1 above, levels of NNN, NNK, and B[a]P in the new products are too low to be quantified.
    - At the present time, the (b)(4) added to the new products do not create additional concerns about HPHC exposure from a toxicology perspective.

3.5.1.3. Biomarkers of exposure

- The applicant stated that it did not submit any data on biomarkers of HPHC exposure because there are so few HPHCs quantifiable in the new products and levels of those HPHCs are so low when compared to smokeless tobacco products.
- The applicant provided a literature review indicating that moist snuff users who switch to snus have lower NNAL levels, a biomarker for NNK exposure.
    - Unlike snus, the new products do not contain quantifiable levels of NNK, so moist snuff users who switch completely to the new products are expected to have lower levels of TSNA exposure than those who switch to snus.
    - The patterns of use study submitted by the applicant showed that 24% of dual users switched completely to the new products over a 10-week period.
        - The toxicology review determined that, based on the information provided, it is reasonable to expect that those who switch completely to the new products would be exposed to fewer harmful toxicants, including NNK.

3.5.2. Synthesis

As TPL, I agree that HPHC levels in the new products, in general, are considerably lower than those in smokeless tobacco products. FDA considers HPHCs to be chemicals that cause, or have the potential to cause, direct or indirect harm to users or nonusers of tobacco products (US Food and Drug Administration Center for Tobacco Products, 2012). The new products do not contain measurable quantities of the carcinogenic polycyclic aromatic hydrocarbon B[a]P or carcinogenic TSNAs, including NNN and NNK. The available scientific evidence

indicates that NNN is the predominant driver of excess oral cancer risk among adults who use smokeless tobacco. Levels of nearly all HPHCs reported in these PMTAs are lower in the new products than in the comparison products, including General Snus. In 2019, FDA found that, as actually used by consumers, these General Snus products 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.

For the three HPHCs that are higher in the new products (i.e., formaldehyde, naphthalene, and coumarin), the estimated exposure is below the amount that can be consumed orally by humans each day over a lifetime without appreciable health risk (Herrman et al., 1999) or background exposure or levels that are found in ambient air. As a result, they do not raise concerns regarding the conclusion that the toxicological risk profile of these products is likely to be considerably lower than other smokeless tobacco products.

Based on conclusions in the toxicology review, as well as the published Biomarker of Exposure (BOE) data and bridging information provided by the applicant, as TPL, I conclude that it is reasonable to expect that adults who use smokeless tobacco that switch completely to the new products would be exposed to fewer harmful toxicants, including NNN and NNK.

Based on the BCP and epidemiology reviews of these PMTAs, I conclude that dual use of the new products with smokeless tobacco products is likely to be common. It is noteworthy that 65% of participants reported exclusive use of the new products by the end of the 10-week prospective patterns of use study submitted by the applicant, but it is unclear if this shift in tobacco product use persisted beyond the study period. The applicant did not provide evidence indicating that dual use of the new product with another tobacco product reduces HPHC exposure. As TPL, however, I conclude that replacing even some smokeless tobacco products or combusted cigarettes with the new products is expected to reduce total HPHC exposure because of the much lower HPHC levels in the new products when compared to combusted cigarettes and smokeless tobacco products. As TPL, I note that this conclusion is limited to HPHC exposure and does not indicate that replacing even some combusted cigarettes or smokeless tobacco products will necessarily reduce risk of adverse health effects.

However, while dual use is likely to be common, as TPL, I conclude that a substantial portion of dual users may switch to exclusive use of the new products. As noted in Section 3.4.1.2 above, 24% of all dual users switched completely the new products during a 10-week prospective study. Among study participants who used the new products, 8.1% were also using combusted cigarettes. Over the study period, the prevalence of dual use of combusted cigarettes declined from 8.1% to 4.9%. Similarly, the number of participants who used the new products with smokeless tobacco products declined from 13.3% to 8.4% by the end of the study.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

The following discussion is based on key findings regarding health effects provided in discipline reviews:

3.6.1.1. Toxicology

- Nonclinical studies
  - Neither the new products nor the CRP2.1 comparison product appeared to be mutagenic or genotoxic in the nonclinical studies reported in the PMTAs.
    - In contrast, particulate matter (TPM) from 1R6F reference cigarette smoke was mutagenic and genotoxic in the nonclinical studies reported.
- Clinical data with toxicity endpoints
  - Among 57 current daily snus users participating in an open-label, observational study with the new products (SM 17-02), the severity of oral mucosal lesions declined across the six-week study period and the number of subjects with oral mucosal lesions decreased from 90% to 70%.
- Toxicant and study integration
  - The applicant provided supporting data from published literature on oral safety, cancer risk, cardiovascular effects, metabolic effects, gastrointestinal effects, and other health effects of snus products (e.g., respiratory, musculoskeletal, and psychiatric disorders).
    - The toxicology review of these PMTAs concluded that evidence from these published studies can be bridged to the new products based on similarities in manufacturing methods, structural materials, ingredients, flavors, HPHCs that are present, and methods of use.
    - No novel health or toxicological concerns associated with the new products were identified in the literature review conducted by the applicant.
    - The toxicology review concludes that cigarette users who switch completely to the new products are expected to experience reduced risk of cancer, respiratory toxicity, and cardiovascular toxicity.
  - As the new products expose users to similar levels of nicotine to those found in snus, but generally have reduced or non-measurable levels of HPHCs, the applicant claims published data on health effects and use behavior of Swedish snus may be considered as a measure of maximum health risks from use of the new products.
  - From a toxicology perspective, the applicant's statement that the new products are less harmful than Swedish snus is reasonable given that HPHC levels are generally lower than in Swedish snus products, and carcinogenic nitrosamines and polycyclic hydrocarbons are not detectable.
    - The toxicology review determined that the lower exposure to HPHCs from new products relative to most smokeless products

indicates that users who do switch will likely reduce their risk of cancer.
    - Moreover, cigarette users who switch to the new products will likely have an even greater reduction in both the risk of cancer and hazards such as respiratory and cardiovascular toxicity.

3.6.1.2. Engineering

- The applicant provided consumer use studies and complaint reports that indicate that broken pouches and nicotine residue in the container and on pouches creates a concern for product misuse (i.e., being used in ways other than intended based on product labeling) or manipulation.
- While the applicant did not perform risk analysis or specify what measures were taken to mitigate manufacturing defects, the applicant stated that the potential risk of any health effects on skin contact is low because the new products do not contain any ingredients in concentrations together with the calculated exposure that would lead to any unacceptable risk in acute toxicity or irritation and sensitization.
    - The applicant also stated that quality control measures have improved over time, resulting in fewer complaints for broken or torn pouches, but does not specify what measures were taken to mitigate manufacturing defects.
        - During a recent 12-month period, an average of 32.4 (range = 9-51) complaints were received each month for every 1 million pouches of the new product sold.
    - As such, the engineering review concluded that the applicant had adequately addressed concerns about product misuse or manipulation.
    - Also, the medical review concluded that the new products appear to have a low potential for serious adverse effects associated with unintentional or intentional misuse.
        - An Adverse Experience Database Search conducted by the medical reviewer on December 18, 2024 identifed a report of “nicotine poisoning” in a 20-month-old child exposed to a different nicotine pouch brand.
        - As discussed below in this section, the new products subject to this review are packaged in certified child-resistant polypropylene cans and safety lids, which reduce the risk of accidental exposure in children.
        - No other engineering-related adverse experiences from product design were reported to FDA.
    - While broken pouches increase the likelihood of unintentional exposure to nicotine from the new products or product misuse, the toxicology review concluded that levels of nicotine in the new products are currently acceptable from a toxicology perspective and that the pouch material itself is unlikely to produce any adverse health effects.
- The engineering review states that the new products’ primary packaging consists of a 21 Code of Federal Regulations (CFR) 177.1520(c)-compliant and certified child-resistant polypropylene can and safety lid.

- The engineering review also states that the primary packaging was certified to be child-resistant by testing that complies with 16 CFR 1700.20 (Test procedure for special packaging)
- The engineering review concludes that the new products' primary packaging mitigate the health hazards of the new products, especially to infants and children, by reducing risk that the products will be ingested by children.

3.6.1.3. BIMO inspection findings

- Bioresearch monitoring (BIMO) inspections were not recommended by CTP's Office of Compliance and Enforcement (OCE) for any sites included in these PMTAs.
- The applicant described four bioresearch studies in these PMTAs, none of which were deemed to be pivotal for the medical or toxicology reviews or reported an unacceptable number of adverse events.

3.6.1.4. Addiction as a health endpoint

- Based on submitted nicotine exposure and PK data, the addiction potential of the new products is likely comparable to that of currently marketed smokeless tobacco products in the U.S.
  - Adults who currently use smokeless tobacco that completely or partially switch to the new products use are likely to maintain their nicotine addiction.
- Tobacco nonusers who initiate use of the new products may be as likely to progress to nicotine addiction as those who initiate tobacco use with smokeless tobacco products.
- Current users of inhaled tobacco products are unlikely to completely switch to the new products.
  - In those who do initiate use of the new products, dual use of inhaled tobacco products is likely.
    - As discussed in Section 3.4.1.2, however, the prevalence of cigarette use among dual users decreased from 8.1% to 4.9% in a 10-week prospective patterns of use study, suggesting that some users of inhaled products did switch completely to the new products.
  - However, given that nicotine PK of the new products is associated with reduced magnitude of reinforcement (i.e., a longer T_{max} and lower C_{max}) when compared to combusted cigarettes or ENDS, users who replace (not supplement) inhaled tobacco products with the new products may experience reductions in the severity of their nicotine addiction, though not complete elimination of nicotine addiction.

3.6.1.5. Short and long-term health effects (clinical and observational)

- The epidemiology review of these PMTAs focused on the applicant's bridging of long-term epidemiological studies on health effects of Swedish snus to the new products.
  - The applicant did not provide any documents containing information on observational studies on long-term health effects of the new products.
  - The applicant justified bridging the literature on long-term health risks of Swedish snus to the new products based on similarities in user topography.

        - The epidemiology review concluded that the applicant's justification was reasonable.
    - The applicant provided the Health Effects and Meta-Analysis Update Report and 2013 Environ Report describing studies assessing a range of health risks of Swedish snus among snus or snuff users compared to adults who smoke, non-snus users, and never tobacco users.
    - The epidemiology review also noted that studies assessing health effects of Swedish snus on lung cancer and COPD suggest there is no evidence that Swedish snus causes lung cancer and COPD, which together account for over 50% of the smoking-attributable mortality burden.
    - The applicant reasoned that since the new products have similar user topography, but lower HPHCs levels, compared to Swedish snus, the health effects of Swedish snus represent an upper limit on the likely long-term health effects of exclusive use of the new products.
        - The epidemiology review of these PMTAs found the applicant's rationale reasonable.
- As discussed in Section 3.6.1.1, one of the clinical studies, SM 17-02, provides a limited evaluation of the oral health effects associated with using the new products and concluded that there were no adverse effects to dental plaque acidogenicity and mucosal lesions.
    - Dental plaque acidogenicity, an index of oral health, was not adversely affected in current adult snus users who also used the new products for six weeks.
    - The severity of oral mucosal lesions declined across the six-week study period and the number of subjects with oral mucosal lesions decreased from 90% to 70%.
    - As with any observational study evaluating a multifactorial disease process, especially a small study (57 participants) with a short study duration (6 weeks), there are limitations to the generalizability of the data and predictive value of the findings.
        - However, the findings of this study suggest that dual use of snus and the new products does not increase severity of dental plaque acidogenicity and data are consistent with a reduced risk for oral mucosal lesions when compared to snus.
- Based on the similarities between Swedish snus and the new products as informed by the chemistry and toxicology reviews, the medical review of these PMTAs supports the applicant's conclusion that the expected health risks for the new products are no greater than those of snus that are summarized in the literature review.
    - As discussed in Section 3.5.1.1, however, the available scientific evidence indicates that NNN is the predominant driver of excess oral cancer risk among adults who use smokeless tobacco, so the lack of detectable levels of NNN in the new products has significant clinical relevance.
- The applicant concludes that dual users of snus and cigarettes appear to have a similar disease risk as adults who exclusively smoke.
    - The applicant also concludes that those who switched from cigarettes to snus had increased health risks compared to never tobacco users, lower

health risks than those who continued to smoke, and similar risks to those who quit using tobacco.
    - Since there are limited clinical data on the health effects of the new products compared to snus, the assessment of whether the health risks of the new products are comparable to those of snus was informed and substantiated by the chemistry and toxicology evaluations of similarities between the two product types.
- For former and never tobacco users who initiate use of the new products compared to users who no longer or have never used any tobacco product, there is an expected increased risk of health effects associated with both short- and long-term exposure to nicotine including, poor reproductive outcomes (e.g., preterm delivery, stillbirth, adverse effects on fetal development).

3.6.1.6. Likelihood and effects of product misuse

- Warning labels on packaging state that the products' pouch and contents are not intended to be consumed to mitigate the risk of misuse but does not include the potential for poisoning.
    - However, serious adverse events associated with severe poisoning (e.g., seizures, respiratory depression, confusion, lethargy, cardiac effects) were not reported in the applicant-sponsored studies and the Consumer Reported Complaints for the new products.
- Based on the labeling, the packaging that encloses the pouches provides evidence of tampering.
    - The applicant states that instructions to break the side label perforation when opening adequately explains how consumers should check for product tampering.
    - The engineering review concluded that the applicant provided an adequate rationale for how the perforated side labels provide tamper-resistance.
- The products appear to have a low potential for adverse events associated with unintentional or intentional misuse from product design (e.g., ingestion of pouch).
    - However, manufacturing defects such as broken pouches may increase the potential for misuse and risk of adverse health effects.
- Misuse of the new products (i.e., being used in ways other than intended based on product labeling) was common among current U.S. users, including longer durations of use (80.7% reporting using the product >60 minutes always or sometimes), using more than one pouch (29.2% reporting using one pouch at a time only sometimes or never), and inappropriate placement in the mouth (44% reporting placement between the gum and upper lip only sometimes or never).
    - The BCP review noted that, although these patterns of misuse may result in increased nicotine exposure relative to when used as intended, the incidence of product misuse does not raise concerns about increased abuse liability or addiction potential of the new products relative to smokeless tobacco products currently on the market.
- Thus, the prevalence of product misuse identified in these PMTAs does not raise concerns about increased nicotine exposure, abuse liability, or addiction potential of the new products relative to smokeless tobacco products currently on the market.

3.6.1.7. Adverse experiences

- Subjects in the clinical studies experienced a relatively low level of adverse experiences (AEs) associated with the new products. These AEs were either mild or moderate in severity, with the majority being mild, and typically resolved within three to seven weeks.
    - The medical review of these PMTAs noted there were no reported deaths or other severe adverse events (SAEs) in the evaluated clinical studies.
    - No participants discontinued enrollment in the clinical study because of AEs.
    - The medical review concluded that the most commonly reported AEs observed in the clinical studies (i.e., mild oral disorders like dry mouth and gingival blisters) are expected in users of smokeless tobacco products.
        - The AEs reported in these PMTAs cannot necessarily be extrapolated to the general population because of methodological limitations that are common in many clinical studies (e.g., the number of study participants was small, the duration of the studies was short, and not all characterizing flavors and nicotine concentrations were used by study participants).
- In the literature review submitted by the applicant that bridges health effects of snus to the new products (see Section 3.6.1.5.), two clinical studies reported serious AEs (i.e., confusion, dizziness, nausea, tremor, sensation of emptiness, tiredness) after snus administration.
- The applicant's Consumer Reported Complaints did not result in any serious adverse outcomes but included most common experiences as gum irritation, being "buzzed" from nicotine contents, burning sensation, and throat irritation or burning.
    - The most common issue related to improper use of the product was swallowing or ingestion of the pouch.
- While some of the AEs observed in the clinical trials could lead to further health complications (e.g., dry mouth or xerostomia increases the risk of caries, periodontal disease, and oral mucosal lesions) or exacerbate underlying conditions in subpopulations of users (e.g., medically compromised patients on medications known to cause xerostomia), the sample sizes in these studies are too small to extrapolate these AEs to a larger population.
    - The oral-related AEs reported by the applicant do not raise concerns from a medical perspective because the majority were considered mild and resolved by the end of the studies, which were 3-7 weeks in duration.

3.6.2. Synthesis

From a toxicology perspective, these products are likely to pose lower risks to users than most smokeless tobacco products, including Swedish snus, given the overall reduction in HPHC levels. For example, General Snus, a brand of Swedish snus that has both PMTA and MRTP authorizations from FDA, contains 15 HPHCs that are quantifiable by the applicant's methods, while the new products contain five. Also, levels of three of the HPHCs that are quantifiable in the new products are lower compared to General Snus. As discussed in Section 3.5.1.2, levels of the two HPHCs that are higher in the new products are still so low they are currently not expected to be a concern from a toxicology perspective. Unlike General Snus, the new products do not contain quantifiable levels of NNN or NNK. The available scientific evidence indicates that NNN is the predominant driver of excess oral

cancer risk among adults who use smokeless tobacco, so the lack of detectable levels of NNN in these products has significant clinical relevance. The new products also do not contain quantifiable levels of carcinogenic polycyclic hydrocarbons, including B[a]P.

As noted in Section 3.1.1, the toxicology review of these PMTAs concluded that the new products and General Snus have similar manufacturing methods, structural materials, ingredients, flavors, HPHCs that are present, and methods of use. Based on the toxicology review of these PMTAs, as TPL, I conclude that exposure to the ingredients of the pouch material is unlikely to have significant adverse health effects. As also noted in Section 3.1.1, the chemistry review concluded that user topography, nicotine content, pH, and units of use are similar in General Snus and the new products. Based on these conclusions, the medical review concludes that the expected health risks for the new products are no greater than those of Swedish snus that are summarized in the applicant's literature review.

Also, the new products did not produce genotoxic effects in the applicant's nonclinical toxicology studies (i.e., Ames test, in vitro micronucleus assay), while combusted cigarettes did. The toxicology review concludes that cigarette users who switch completely to the new products are expected to experience reduced risk of cancer, respiratory toxicity, and cardiovascular toxicity.

The epidemiology review concluded that the applicant's justification for bridging the published literature on the long-term health effects of Swedish snus to the new products based on similarities in user topography was reasonable. The literature cited by the applicant included published data assessing a range of health risks of Swedish snus among snus or snuff users compared to adults who smoke, non-snus users, and never tobacco users. These data do not indicate that Swedish snus causes lung cancer or COPD, which together account for over 50% of the smoking-attributable mortality burden. This reduction in mortality alone suggests lower overall health risks for exclusive Swedish snus use compared to cigarettes. The applicant reasoned that since the new products have similar user topography but lower HPHCs levels compared to Swedish snus, the health effects of Swedish snus represent an upper limit on the likely long-term health effects of the new products. The medical, epidemiology, and toxicology reviews of these PMTAs found the applicant's rationale reasonable and, as TPL, I concur.

The BCP review concludes that the addictive potential of the new products is similar to smokeless tobacco products. As such, adults who currently use smokeless tobacco that completely or partially switch to the new products are likely to maintain their nicotine addiction. Also, current nonusers who initiate use of the new products may be as likely to progress to nicotine addiction as nonusers who initiate tobacco use with smokeless tobacco products. However, as discussed in Section 3.4.1.3, the social science review concluded that appeal and likelihood to buy for the new products were low among former tobacco users and never-users, regardless of age.

As discussed in Section 3.4.1.2, it is unlikely that most current users of inhaled tobacco products will completely switch to exclusive use of the new products. However, given that the nicotine PK of the new products is associated with reduced magnitude of reinforcement when compared to combusted cigarettes, users who replace some of the combusted cigarettes they normally consume with the new products may experience reductions in their

nicotine exposure, which may lead to reduced severity, but not elimination, of their nicotine addiction. Even if only a small percentage of adults who currently smoke take up the products and switch completely or significantly reduce their cigarette consumption, this would result in public health benefits.

Despite the low likelihood that users of inhaled tobacco products will switch completely to the new products, the likelihood of use study discussed in Section 3.4.1.3. above shows that nearly half of adults who currently smoke with intentions to quit found the variety of flavors for the new products to be either very or extremely appealing. Similarly, the prospective patterns of use study also discussed in Section 3.4.1.3 above shows that about half of the users of the new products who also used cigarettes stopped smoking by the end of the 10-week study.

There were no reported deaths or severe AEs in the evaluated clinical studies included in these PMTAs. Subjects in the clinical studies experienced a relatively low level of AEs associated with the new products, with the majority of AEs being mild. The engineering review did not identify any AEs related to product design and stated that the new products appear to have a low potential for AEs resulting from product design-related misuse and manipulation.

While these PMTAs included evidence that the new products are misused (e.g., pouches used for a longer duration than instructed by the applicant) with some regularity, the types of misuse noted for the new products (i.e., product use duration longer than instructed, placing the product in other areas of the mouth than where instructed, and simultaneous consumption of more than one pouch) are also common with smokeless tobacco products. As such, the influence of product misuse on nicotine exposure, abuse liability, and addiction potential is expected to be similar for the new products and smokeless tobacco products. As discussed in Section 3.6.1.7, the medical review of these PMTAs concluded that the new products appear to have a low potential for AEs associated with unintentional or intentional misuse and that there were no AEs reported due to product misuse in the clinical studies sponsored by the applicant, but noted these risks could be affected by manufacturing defects. Based on information in the toxicology, engineering, and medical reviews of these PMTAs, as TPL, I also conclude that since the new products have lower HPHC levels when compared to General Snus, the potential AEs from product misuse are unlikely to be greater than those produced by smokeless tobacco products. Based on the engineering review, I, as TPL, also conclude that unintentional nicotine exposure or misuse from broken pouches is not common and does not currently create an unacceptable increase in risk of adverse health effects for the new products.

While the AEs observed in the clinical trials were mild, common in adults who use smokeless tobacco, and observed in participants who used either the new products or Swedish snus, some (i.e., gingival blisters, dry mouth) could lead to further health complications or exacerbate underlying conditions in certain user populations. Some of the AEs are likely attributable to nicotine exposure (i.e., nausea, dizziness) and not the new products per se. The majority of AEs associated with use of the new products resolved by the end of the studies, which were three to seven weeks long. The medical and toxicology reviews also noted a statistically significant reduction in the number and severity of lesions in the oral mucosa in a clinical trial with the new products. However, the medical review of these

PMTAs concluded the sample sizes in these studies are too small to extrapolate these AEs to a larger population. As TPL, I conclude that the adverse effects produced by the new products are unlikely to be unique when compared to smokeless tobacco products, and the oral lesions produced by the new products may be less severe.

Based on the totality of the evidence, including lower overall HPHC levels, as TPL, I conclude that the potential health effects of the new products are expected to be less severe than that of combusted cigarettes, moist snuff products, and Swedish snus. Based on the toxicology review of these PMTAs, as TPL, I conclude that exposure to the ingredients of the pouch material is unlikely to have significant adverse health effects. While users of inhaled products are unlikely to take up the new products in substantial numbers, I conclude that the new products' variety of flavors are very or extremely appealing to nearly half of adults who currently smoke with intentions to quit surveyed by the applicant and a significant portion of adults who currently smoke that also use the new products may completely switch to the new products.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

The following discussion is based on key findings regarding population health that were provided in the discipline reviews:

3.7.1.1. Toxicology

- The toxicology and medical reviews conclude that it is reasonable to expect the health risks of Swedish snus to represent an upper limit on the health risks of the new products for exclusive users because the new products expose consumers to similar levels of nicotine but generally lower levels of HPHCs, including levels of carcinogenic nitrosamines and polycyclic hydrocarbons that are too low to be quantified.
    - The health risks of snus addressed in the published literature focus on oral safety, cancer risk, cardiovascular effects, metabolic effects, and gastrointestinal effects, as well as respiratory, musculoskeletal, and psychiatric disorders.
    - As discussed in Section 3.6.1.1., the toxicology review concluded that evidence from the published literature on snus can be bridged to the new products.

3.7.1.2. Population health impact (PHI) model

- The epidemiology review of these PMTAs noted that the applicant did not provide information on population health modeling regarding marketing the new products.
    - The applicant stated that research findings indicate the new products are "…likely associated with substantially lower health risks among individual consumers than most, or even all, of the tobacco products that currently dominate the U.S. tobacco market (cigarettes and moist snuff)."
    - The epidemiology review also noted that such modeling does not appear to have been published previously.

- However, as discussed in Sections 3.5 and 3.6 above, the epidemiology, toxicology, and medical reviews concluded that the health risks from exclusive use of the new products are likely lower when compared to Swedish snus.
- As discussed in Section 3.4.1.3, FDA expects the risk of initiation with the new products, including initiation among youth, to be low.
- As discussed in Section 3.4.2, the switching rate observed in the prospective study, when combined with lower HPHC exposure, suggests a reduction in individual health risk for current tobacco users, including current users of smokeless tobacco products.

3.7.2. Synthesis

Since HPHC levels in the new products are generally lower than in Swedish snus, and carcinogenic tobacco-specific nitrosamines and polyaromatic hydrocarbons for which data was submitted are not detectable in the new products, the health risks of Swedish snus likely represent an upper limit on the health risks of the new products for exclusive users. The health risks identified in the published literature on snus submitted by the applicant include oral safety, cancer risk, cardiovascular effects, metabolic effects, gastrointestinal effects, as well as respiratory, musculoskeletal, and psychiatric disorders. As noted in Section 3.6.1.4, the addiction potential of the new products is likely comparable to that of currently marketed smokeless tobacco products in the U.S. As noted above in Section 3.6.2, potential health effects of the new products are expected to be less severe than combusted cigarettes or moist snuff products.

Also, these PMTAs demonstrate that at least some dual users are likely to become exclusive users. By the end of a 10-week patterns of use study conducted by the applicant, 24% of dual users had switched completely to the new products. Since substantial uptake of use among current users of inhaled tobacco products is unlikely, the majority of current users who begin using the new products are likely to be adults who use smokeless tobacco. Based on lower HPHC exposure, current users of smokeless tobacco products are expected to reduce the severity of their health risks if they switch completely to the new products.

However, there is evidence from the applicant's patterns of use study that a small number of adults who smoke may begin dual use with the new products. For example, in the time period between initiating use of the new products and completing the retrospective survey, the prevalence of cigarette use decreased from 42.0% to 15.1%, suggesting a reduction in cigarette smoking while using the new products. Also, the majority of participants in the retrospective survey who used the new products reported doing so to help reduce or quit cigarette consumption (84% and 60%, respectively, by the end of the study). It is unclear how frequently users of the new products eventually stop using all tobacco products because all participants in the patterns of use study used at least one tobacco product when the study began. As TPL, I conclude that while the number of adults who currently smoke that switch completely to the new products may potentially be small, the reduced HPHC exposure will produce substantial reduction in risk of adverse health effects for adults who currently smoke that do switch completely.

Finally, the new products' potential health benefits to adult tobacco product users are not outweighed by risks to nonusers, including youth. As discussed in Section 3.1.4, evidence,

including prevalence estimates from NYTS, suggests low uptake of these products among nonusers, including youth. Similarly, as discussed in Section 3.4.1.3, the prospective patterns of use study provided by the applicant indicate that the appeal and intentions to use among participants ages 18-24 were low. Thus, FDA expects that there would be low intentions to use these oral tobacco products among youth. Also, uptake of the new products by nonusers was low. For example, about 2% (range=1.0%-4.1%) of participants using a tobacco product other than the new products subject to this review (which the applicant referred to as "nonusers") began using the new products during each week of the 10-week study and there was no increasing trend in those data. Since the majority of "nonusers" participating in this study used cigarettes or moist snuff, using the new products instead of their normal product is unlikely to increase health risk because overall HPHC exposure would be reduced. As TPL, I therefore conclude that risk of initiation with the new products is expected to be relatively low and exclusive use of the new products is likely associated with substantially lower health risks when compared to cigarettes or smokeless tobacco. In terms of benefit, HPHC levels in the new products are generally lower than General Snus, a product for which FDA has issued marketing orders. The consensus of the medical, toxicology, epidemiology reviews is that health risks from Swedish snus represent an upper limit on the likely long-term health effects of exclusive use of the new products. The literature cited by the applicant does not indicate that Swedish snus causes lung cancer or COPD, which together account for over 50% of the smoking-attributable mortality burden. This reduction in mortality alone suggests lower overall health risks for exclusive Swedish snus use when compared to cigarettes. Thus, as TPL, I similarly expect that the new products will have lower overall health risks compared to cigarettes or smokeless tobacco products and therefore permitting marketing of these new products, with all required restrictions in place, will promote the public health.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

Based on the findings and evaluations discussed in Sections 3.1-3.7, and further described in Section 5 below, I find that permitting the marketing of the new products in accordance with the requirements in the marketing granted orders is APPH.

3.8.2. Tobacco product manufacturing practices

These PMTAs contain sufficient information to characterize the tobacco product design and adequate processes and controls to help ensure that the new products meet the manufacturer's specifications. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in Section 906(e) of the FD&C Act.

3.8.3. Labeling

For all PMTAs, the applicant provided proposed labeling. Based on the information presented at this time, we have not concluded that the proposed labeling is false or misleading in any particular.

3.8.4. Product standards

There are no applicable product standards for the new products.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

The following key findings were provided in the environmental science review.

Environmental science concluded that the environmental assessments for all PMTAs contain sufficient information to determine whether the proposed actions may significantly affect the quality of the human environment. As TPL, I agree with this conclusion.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Christy Leppanen on January 2, 2025. The FONSI was supported by an environmental assessment prepared by the applicant on January 2, 2025.

5. CONCLUSION AND RECOMMENDATION

Section 910 of the FD&C Act requires that, for a product to receive a PMTA marketing authorization, FDA must conclude, among other things, that permitting the product to be marketed would be APPH. Section 910(c)(2)(A). In making a determination about whether permitting the marketing of a product is APPH, Section 910(c)(4) directs FDA to consider the risks and benefits to the population as a whole, including users and nonusers of tobacco products, taking into account, among other things, the likelihood that those who do not use tobacco products will start using them. FDA's scientific review is not limited to considering only information in a PMTA, but also extends to any other information before the Agency, including the relevant existing scientific literature (see Section 910(c)(2)).

FDA interprets the APPH standard to require a showing that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole, which includes youth, young adults, and other vulnerable populations. In determining whether permitting the marketing of a new tobacco product would result in a new benefit to public health, FDA weighs the potential negative public health impacts (e.g., harm from initiation and use among nonusers, particularly youth) against the potential positive public health impacts (e.g., benefit from adult users of more harmful tobacco products completely switching or significantly reducing combustible cigarette use).

Before determining that permitting the marketing of a tobacco product would be APPH, FDA also takes into account whether the applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls including process controls and quality assurance procedures, toxicology, abuse liability, and other factors that can impact the product's risks and benefits to individual users, including relative to those of other tobacco products on the market.

Based on the evaluation of these PMTAs and the available evidence, as TPL, I determine that these PMTAs contain sufficient information to characterize the product design and that there are adequate process controls and quality assurance procedures to help ensure the new products are manufactured consistently. Based on the information provided in the PMTAs, the abuse liability of the new products is lower than combusted cigarettes and is similar to smokeless tobacco products. The overall toxicological risk to the users of the new products is lower compared to cigarettes due to

significantly lower HPHC levels. Risk is also reduced compared to smokeless tobacco products including General Snus and as evidenced by low levels of HPHC exposure and results of nonclinical studies. In addition, current adults who smoke cigarettes had higher intentions to buy the new products when compared to current users of other tobacco products. While substantial uptake of use among adults who currently smoke is unlikely, the applicant's retrospective survey indicates that a substantial portion of adults who currently smoke who also use the new products may switch completely, though long-term switching was not evaluated. Similarly, the longitudinal prospective patterns of use study submitted by the applicant indicates that a significant proportion of dual users may switch completely to the new products. Therefore, the applicant has demonstrated the potential for these new products to benefit current adults who use smokeless tobacco product and adults who smoke that switch completely to the new products. In addition, based on evidence suggesting the potential for reduction in lung cancer risk following significant reduction in CPD, the new products may also pose a benefit to adults who switch and significantly reduce their cigarette use.

In terms of the risks to nonusers, youth are considered a vulnerable population for various reasons, including that the majority of tobacco use begins before adulthood and thus youth are at particular risk of tobacco initiation. In connection with evaluating risk to youth, FDA also examined the marketing plans and restrictions described in the applications. Given the strong evidence regarding the impact of youth marketing exposure on youth appeal and initiation of tobacco use, a marketing authorization should include post-market requirements to help ensure that youth exposure to tobacco marketing is limited. In addition, the applicant's study findings demonstrated low intention to purchase the new products among adult never and former established tobacco users, including those ages 18-24. As discussed in Section 3.4.1.3, more than 90% of never users ages 18-24 reported that their likelihood of buying the new products in the future was less than 1%, nearly 75% said the new products were not at all appealing, and 62% said the new products' variety of flavors were not at all or slightly appealing. If, once authorized, the marketing of these products leads to significant youth uptake, the benefits may no longer outweigh the risks, and this authorization may be subject to withdrawal. Together, based on the information provided in the PMTAs and the available evidence, the potential to benefit adults who use smokeless tobacco and adults who smoke who switch completely to the new products would outweigh the risk to youth, provided the applicant follows post-marketing requirements aimed at reducing youth exposure and access to the products.

Regarding product stability, the applicant stated that the shelf life of the new products is (b)(4) . The applicant provided chemistry and microbial data to support that the new products are stable over at least (b)(4) . As such, the information reported in these PMTAs is sufficient to support the applicant-proposed shelf life.

Based on my review of these PMTAs and the available evidence, I find that permitting the marketing of the new products, as described in these applications and specified in Table 5 of Appendix A, is appropriate for the protection of the public health. The potential of the new products to benefit current adults who use smokeless tobacco and adults who smoke outweighs the risks to youth, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to marketing of the new products and youth access to the new products. If, once authorized, the marketing of these products leads to significant youth uptake, the benefits may no longer outweigh the risks, and this authorization may be subject to withdrawal.

The issuance of these marketing granted orders confirms that the applicant has met the requirements of section 910(c) of the FD&C Act and authorizes marketing of the new products. Under the provisions of section 910, the applicant may introduce or deliver for introduction into interstate commerce the tobacco products, in accordance with the marketing order requirements outlined in the marketing granted orders, including all appendices.

FDA has examined the environmental effects of finding the new products APPH and made a Finding of No Significant Impact (FONSI).

Marketing granted orders should be issued for the new products subject of this review, as identified on the cover page of this review.

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7. APPENDIX

Appendix A. New products

Table 5. New tobacco products subject to Granted Orders

Common Attributes [14,15,16,17]	
Submit date	March 4, 2020
Receipt date	March 4, 2020
Applicant	Swedish Match USA Inc.
Product manufacturer	Swedish Match USA Inc.
Product category	Other
Product subcategory	Other
Attributes	**New Tobacco Product**
STN.PD	**PM0000593.PD1**
Product name	ZYN Cool Mint 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 Gram (g)
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Cool Mint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 milligrams (mg)/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 millimeters (mm) Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000594.PD1**
Product name	ZYN Cool Mint 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Cool Mint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

[14]We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[15]Product name is brand/sub-brand or other commercial name used in commercial distribution.
[16]In addition to portion mass, the applicant submitted two of the three dimensions (i.e., portion length, portion width, portion thickness) which allowed for calculation of the third dimension.
[17]Effective April 14, 2022, FDA's authority to regulate tobacco products was extended to include tobacco products containing nicotine from any source. Therefore, nicotine source should be included in future submissions.

STN.PD	PM0000595.PD1
Product name	ZYN Peppermint 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Peppermint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000596.PD1**
Product name	ZYN Peppermint 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Peppermint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000597.PD1**
Product name	ZYN Spearmint 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Spearmint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

STN.PD	PM0000598.PD1
Product name	ZYN Spearmint 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Spearmint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000599.PD1**
Product name	ZYN Wintergreen 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Wintergreen
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000600.PD1**
Product name	ZYN Wintergreen 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Wintergreen
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

STN.PD	PM0000601.PD1
Product name	ZYN Citrus 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Citrus
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000602.PD1**
Product name	ZYN Citrus 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Citrus
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000603.PD1**
Product name	ZYN Coffee 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Coffee
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

STN.PD	PM0000604.PD1
Product name	ZYN Coffee 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Coffee
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000605.PD1**
Product name	ZYN Cinnamon 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Cinnamon
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000606.PD1**
Product name	ZYN Cinnamon 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Cinnamon
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

STN.PD	PM0000607.PD1[18]
Product name	ZYN Smooth 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Smooth
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000608.PD1[18]**
Product name	ZYN Smooth 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Smooth
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000609.PD1[18]**
Product name	ZYN Chill 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Chill
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

[18]For PM0000607.PD1 - PM0000608.PD1 and PM0000609.PD1 – PM0000610.PD1, due to added ingredients such as sweeteners and cooling agents, FDA has determined that all new products have a non-tobacco characterizing flavor for the purposes of this review.

STN.PD	PM0000610.PD1[18]
Product name	ZYN Chill 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Chill
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000611.PD1**
Product name	ZYN Menthol 3 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Menthol
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 3 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm
STN.PD	**PM0000612.PD1**
Product name	ZYN Menthol 6 mg
Package type	Polypropylene Can and Polypropylene Lid
Product quantity	6 g
Characterizing flavor (CF)	Menthol
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 15 pouches Portion Mass: 0.40 g Portion Length: 28 mm Portion Width: 14 mm Portion Thickness: 4.5 mm

Appendix B. Amendments and additional submissions received

Table 6. Amendments and Additional Submissions received

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
August 3, 2020	August 3, 2020	All[19]	Yes	Notify FDA of intended Deficiency letter response date
September 24, 2020	September 24, 2020	All[19]	Yes	Response to July 24, 2020 Deficiency Letter
March 7, 2022	March 7, 2022	All[19]	Yes	Amended labeling and advertising materials
October 12, 2023	October 12, 2023	All[19]	Yes	Revised study reports, literature search results, organized references, and health risk investigations and summary
December 21, 2023	December 21, 2023	All[19]	Yes	Updated labeling materials and marketing plans

Additional Submissions Received for This Applicant

Submit Date	Receipt Date	Reviewed	Brief Description
February 12, 2021	February 16, 2021	Yes	OS Meeting Request
August 2, 2023	August 2, 2023	Yes	Request to update POC
October 12, 2023	October 12, 2023	Yes	Request to keep same RHPM for PMI/Swedish Match USA Inc.

[19] This amendment applies to all STNs.PDs subject of this review.