U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of Nicotine Pouch PMTAs

New Products Subject to this Review[1]	
STNs	PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17, see Appendix A
Common Attributes	
Submission date	December 23, 2024
Receipt date	December 24, 2024
Applicant	Helix Innovations LLC
Product manufacturer	U.S. Smokeless Tobacco Company LLC
Application type	Standard
Product category	Other
Product subcategory	Other
Cross-Referenced Submissions	
All STNs	(b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
All STNs	Memorandum: Modernizing Approach to PMTA Review: Nicotine Pouch Pilot, September 6, 2025; Addendum to Modernizing Approach to PMTA Review: Nicotine Pouch Pilot, November 17, 2025
Recommendation	
Issue marketing granted orders for the new tobacco products subject to this review.	

Technical Project (TPL): /S/

Marzena Hiler (Spindle), Ph.D.
Health Scientist Technical Project Lead
Division of Individual Health Science

Signatory Decision: Concur with TPL recommendation and basis of recommendation

/S/

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 product application.

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1. EXECUTIVE SUMMARY

This Technical Project Lead (TPL) review relates to premarket tobacco product applications (PMTAs) 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 new products listed in Table 1 below ("new 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
PM0009121.PD10	on! PLUS nicotine pouches 6 mg Mint
PM0009121.PD11	on! PLUS nicotine pouches 9 mg Mint
PM0009121.PD13	on! PLUS nicotine pouches 6 mg Tobacco
PM0009121.PD14	on! PLUS nicotine pouches 9 mg Tobacco
PM0009121.PD16	on! PLUS nicotine pouches 6 mg Wintergreen
PM0009121.PD17	on! PLUS nicotine pouches 9 mg Wintergreen

1.1. APPH STANDARD

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). 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 the marketing of the new product 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 requires 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. 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 any new tobacco product would result in a net 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 to adults who use combusted cigarettes (CC) and then completely switch to a lower risk product).

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. 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. REVIEW FOR NICOTINE POUCHES

Whereas all the considerations described above comprise the APPH evaluation, their implementation in a review may differ across product categories and subcategories. Tobacco products from different categories and subcategories may differ in their general risk/benefit profiles, based on their inherent features, composition, function, and appeal. In making the APPH assessment specifically for a nicotine pouch product, FDA weighs, among other things, whether the product can be manufactured consistently, overall levels of harmful and potentially harmful constituents (HPHCs), nicotine pharmacokinetics (PK), and whether the applicant implemented sufficient mitigation measures to address accidental nicotine exposure among young children.

Current scientific literature (discussed below in this review) suggests that nicotine pouches generally belong toward the lowest end of the continuum of risk of tobacco products. However, whether this is true for any particular nicotine pouch product is considered on a case-by-case basis during the course of FDA's scientific review of a PMTA. FDA considers the potential that adults who smoke CCs or use traditional smokeless tobacco products may experience a reduction in health risks if they switch to the nicotine pouch product subject to that PMTA.

In terms of youth use, nicotine pouches have characteristics that may be appealing to youth, including concealability and the availability of flavors. To date, however, the available evidence does not demonstrate this category poses a significant risk to youth, as the current evidence does not show a significant uptake of the product category. While youth appeal and use are low, nicotine pouches present the risk of accidental nicotine poisoning, particularly for young children. For this reason, FDA examines an application to determine whether it contains sufficient mitigation measures to prevent accidental nicotine exposures in young children.

Given the current information regarding likely health risks and risk of youth use, the burden on the applicant for demonstrating adult benefit (in terms of the nature of the evidence and magnitude of

benefit) is comparatively low for this product category. In this case, this review will assess the benefit to adult tobacco product users through product-specific data on nicotine exposure and abuse liability. This evaluation will also consider information in the general scientific literature related to the population health impacts of the product category, as well as any longitudinal data evaluating switching to the new products included in the PMTAs.

1.3. SUBJECT APPLICATIONS

We have reviewed the subject applications to determine whether they contain sufficient evidence to demonstrate that marketing of the new products would be APPH. The new products are pouched oral tobacco products that do not contain cut, ground, powdered, or leaf tobacco.[2] The nicotine in the new products is made of or derived from tobacco. The on! PLUS new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17) come in three different characterizing flavors (Mint, Tobacco, and Wintergreen) and two nicotine levels (6 mg and 9 mg).

Product Science, made up of chemistry, engineering, and microbiology disciplines reviewed the applications for information on product consistency and stability. Based on information in the applications, the Product Science review determined that the new products can be manufactured in a way that does not introduce hazards and limits variability (e.g., in nicotine exposure).

The published literature, summarized in this review, suggests the overall risk to adults for this product category (i.e., nicotine pouches) is expected to be lower compared to both CC and smokeless tobacco products due to significantly lower levels of measured HPHCs. We reviewed these applications to confirm the HPHC profile for the new products was consistent with what is expected for the overall product category. The Product Science review found that the new products contain lower levels of most HPHCs when compared to General Snus and other oral and smokeless tobacco products (i.e., ZYN, pouched dry snuff, pouched moist snuff).

Of the 11[3] HPHCs analyzed in the new products, the majority of HPHCs were too low to be quantified in the new products. In fact, the new products do not contain measurable quantities of carcinogenic tobacco-specific nitrosamines (TSNAs), including NNN and NNK[4], or the carcinogenic polycyclic aromatic hydrocarbon, B[a]P[5]. Importantly, NNN, an HPHC, is the predominant driver of excess oral cancer risk among adult smokeless tobacco users, and therefore the absence of measurable levels of NNN in these products is expected to lower the associated cancer risk. These data support the conclusion that the new products likely pose lower health risks to users relative to traditional tobacco products, including CC and smokeless tobacco.

Moreover, the available scientific information regarding the very low or undetectable levels of HPHCs in nicotine pouch products relative to those found in other tobacco products is supported by data showing significantly lower biomarkers of exposure (BOE) among users of nicotine pouches, relative to CC and snus. In addition, published nonclinical studies demonstrate lower cytotoxicity of nicotine pouches relative to CC and no evidence of mutagenicity in tested nicotine pouch products. Although long-term

[2] In contrast to nicotine pouches, FDA defines smokeless tobacco as any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity. Section 900(18) of the FD&C Act.
[3] Acetaldehyde, Arsenic, B[a]P, Cadmium, Crotonaldehyde, Formaldehyde, Free Nicotine, Nicotine (total), NNK, NNN, NNK+NNN.
[4] See Table 3 Acronyms and Abbreviations
[5] See Table 3 Acronyms and Abbreviations

epidemiological evidence is not yet available to evaluate health risks of nicotine pouches, we can extrapolate from the available evidence on snus, based on similarities in manner of use and product characteristics, including that most HPHCs are lower in nicotine pouches relative to snus, as described above. The evidence on snus demonstrates that use of those products poses a significantly lower individual health risk compared to CC. Taken together, the new products, which are non-combusted, do not contain tobacco leaf, and show lower levels of HPHCs than General Snus, likely pose a lower overall individual health risk relative to adults who use CC and smokeless tobacco products.

To evaluate the risk that the new products will have an abuse liability that exceeds that of comparison products known to have a high abuse liability (e.g., CC, smokeless tobacco), behavioral and clinical pharmacology (BCP) reviewed one applicant-sponsored clinical study (b) (4) which evaluated the abuse liability of the on! PLUS 6 mg and 9 mg new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17). Based on the totality of evidence, all of the new products are expected to have a lower abuse liability than the high abuse liability comparison product because they produced statistically significantly lower nicotine C_{max} (i.e., maximum plasma nicotine concentration), alleviated craving and withdrawal symptoms to a lesser degree, and were associated with lower positive subjective effects ratings (e.g., liking, satisfaction) relative to the high abuse liability comparison product (usual brand moist smokeless tobacco). As such, the new products are not expected to exceed the abuse liability of smokeless tobacco and therefore do not raise concerns about posing an increased risk of dependence and addiction relative to high abuse liability tobacco products currently on the market (i.e., CC and smokeless tobacco).

Finally, we reviewed adverse experiences (AEs) from one applicant submitted clinical study. Overall, the reported AEs were mild to moderate in severity and no product-specific serious or unexpected AEs were reported.

Taken together, as TPL, I conclude that the new products have lower levels of HPHCs than CC and snus, the new products are expected to have lower abuse liability than CC and smokeless tobacco products and pose a lower overall individual health risk relative to CC and smokeless tobacco use.

In addition, the available literature suggests that nicotine pouches are predominantly used by adults who use other tobacco products, including CC and smokeless tobacco. Given these findings, as TPL, I evaluated available evidence regarding the potential for the new products to be used by current tobacco users and used in a way that would benefit them, such as a substitute for some or all of their traditional tobacco product use (i.e., CC, smokeless tobacco). To evaluate the potential for the new products to enable switching, BCP evaluated the abuse liability of the new products. As TPL, I find that based on the totality of evidence, the abuse liability of all the new products is expected to be lower than CC and smokeless tobacco. These findings suggest that the new products are likely to deliver sufficient nicotine to the user to reduce craving and withdrawal symptoms and therefore can support behavioral change (e.g., product substitution) among some users. Moreover, there are a small number of longitudinal studies conducted to date that provide some additional support for the potential for nicotine pouches, including the new products, to facilitate significant CC reduction or complete switching among some adults who smoke.

Although the new products may be a lower-risk alternative for adults who use other tobacco products, nicotine pouches are not without risk. The new products can still deliver harmful chemicals to users, including nicotine, a toxic and addictive chemical. For non-users, the new products pose a risk of addiction. Although not a main driver of tobacco-related disease, long-term nicotine exposure has been

associated with adverse cardiovascular effects, systemic inflammation, gastrointestinal effects, and effects on bone growth. In addition, there is some evidence that nicotine pouches may be associated with negative oral health outcomes (including parakeratosis, edema, and chronic inflammation).

In terms of the risks to nonusers, the potential impact of marketing a new tobacco product on youth is a critical piece of the APPH evaluation because the majority of tobacco use begins before adulthood. Nicotine pouches have features that may be appealing to youth—particularly the availability of a range of flavors as well as their ability to be used inconspicuously. To date, however, despite an upward trend in use (as discussed in Section 3.3.2), the observed prevalence of youth use of nicotine pouches as a product category remains low, suggesting relatively low appeal of the category. In addition, in terms of adults who do not use tobacco, the currently available data show that use of nicotine pouches was virtually non-existent for tobacco naïve adults. Therefore, based on the evidence available at this time, as TPL, I conclude that the potential risk to non-users, including youth, is currently low. However, trends in youth use can shift quickly, and historically we have witnessed how the emergence of a new product can drive the appeal of a category. Therefore, it is critical that FDA continue to monitor youth nicotine pouch use.

Targeted and responsible marketing are key factors to mitigating the potential risk to youth of marketing a new tobacco product. Accordingly, as TPL, I reviewed the labeling for the new products and, at this time, did not identify concerns regarding youth appeal or marketing that targets youth; I have not found that the proposed labeling raises those issues. In addition, the Office of Health Communication and Education (OHCE) reviewed the marketing plan and found that the applicant generally describes a reasonable approach to marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. As TPL, I recommend that the MGO include the marketing requirements and recommendations in Section V of the OHCE consult, as they will help mitigate the potential risk to youth posed by the marketing of the new tobacco products. In addition, the applicant proposed marketing plans that include restrictions beyond those required with PMTA authorization. OHCE has determined that these restrictions may help further (b) (4)

(b) (4)

(b) (4) As TPL, I recommend such measures, as they will further mitigate the potential risk to youth posed by the marketing of these tobacco products.

In addition to youth use, the new products also pose a risk to young children from accidental nicotine exposure. Indeed, there has been a significant rise in nicotine pouch ingestion among young children reported to U.S. poison control centers over the past few years. Nicotine pouch ingestion was associated with more serious adverse health outcomes for children despite accounting for fewer nicotine ingestions than other product formulations. Mitigation measures, such as child resistant packaging (CRP), are important for reducing the risk of accidental nicotine exposure. The new products contain CRP. CRP in the new products is intended to reduce the risk of poisoning in children by making it significantly difficult for children (under age 5) to open and obtain a toxic amount of the product within a reasonable time. As such, the new products' CRP serves to mitigate the risk of nicotine poisoning among children ages 5 and under.

In sum, FDA's evaluation determined that these PMTAs contain sufficient information to characterize the product design and demonstrate adequate process controls and quality assurance procedures for consistent manufacturing. Based on the product-specific information provided in the PMTAs and the available evidence on nicotine pouches, 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 adult tobacco users, including those who use CC and smokeless tobacco, who use nicotine pouches and significantly reduce their use of such products (or who switch completely) outweighs the risks to youth or nonusers, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to product marketing and product access.

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 PRODUCTS

The applicant submitted information for the new products listed in Appendix A, sold under the brand name on! PLUS. The new products are pouched oral tobacco products containing tobacco-derived nicotine, flavor ingredients, artificial sweeteners, stabilizers, fillers, and pH adjusters. The new products are packaged in cans and are available in three flavor variants (Mint, Tobacco, Wintergreen) with each flavor offered in two nicotine levels (6 mg and 9 mg). Each container contains 14 pouches. The new products are not smokeless tobacco products as they do not consist of cut, ground, powdered, or leaf tobacco[6].

2.2. REGULATORY ACTIVITY

On December 24, 2024, FDA received the subject PMTAs from Helix Innovations LLC. FDA completed an acceptance review on May 2, 2025, and issued an Acceptance letter to the applicant on May 2, 2025. FDA issued a Filing letter to the applicant on September 11, 2025.

Refer to Appendix B for a complete list of amendments and additional submissions received by FDA.

2.3. SCOPE OF REVIEW

This TPL review captures all compliance and scientific reviews completed for the new products. The applicant referenced two TPMFs in support of these applications (b) (4) . (b) (4) was reviewed by the chemistry and microbiology disciplines. (b) (4) was referenced for ingredient and manufacturing information and clinical studies of abuse liability; however, the information in (b) (4) is duplicative with what was provided in the PMTAs and therefore, reviewing this TPMF was not needed.

Table 2. Disciplines reviewed

Discipline	Reviewer(s)	Review Date
Product Science (Chemistry, Engineering, and Microbiology)	Pritesh Darji (Engineering)	12/12/2025
	Zeus De los Santos (Chemistry)	12/12/2025

[6] In contrast to nicotine pouches, FDA defines smokeless tobacco as any tobacco product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity. Section 900(18) of the FD&C Act.

Discipline	Reviewer(s)	Review Date
	La'Chia Harrison and Tasheka Pearcey (Microbiology)	12/12/2025
Behavioral and Clinical Pharmacology	Mollie Miller	12/11/2025
Medical	Edisa Padder	12/12/2025
Environmental science	John Teem	12/11/2025

Table 3. Consultations

Discipline or Office	Reviewer	Review Date
OCE – DPAL	Christopher Lee	12/10/2025
OHCE	Emily Talbert	12/16/2025
Epidemiology	Jacqueline Reuben	12/08/2025

3. SCIENTIFIC REVIEW

3.1. PRODUCT CHARACTERIZATION, CONSISTENCY, AND PACKAGING

3.1.1. Product Characterization

The applicant provided sufficient information about the product design and ingredients to characterize the new products from a product science perspective.

The new products are nicotine pouches containing tobacco-derived nicotine, flavor ingredients, artificial sweeteners, stabilizers, fillers, and pH adjusters.

The new products PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17 contain free-base nicotine and are available in three flavors (Mint, Tobacco, Wintergreen) with each flavor available in two nicotine levels (6 mg and 9 mg). They have a portion weight target of 0.714 g, and a portion length and width target of 27.5 mm and 10.5 mm, respectively.

The applicant did not provide target specifications and lower range limit for moisture content and particle size distribution for the new products and indicated that these are not routine design parameters for product characterization. Instead, the applicant provided test data or Certificate of Analysis (COA) for particle size distribution, including range limits for moisture for all new products. Additionally, the applicant provided test data for portion mass, pouch material basis weight, and pouch material porosity that are within acceptable range limits for all new products. Together, this information is adequate from an engineering perspective to characterize the moisture content and particle size distribution of the new products.

The applicant provided documentation for all single chemical substances and complex ingredients, including ingredient names, chemical abstract services number (CAS#), grade/purity specifications, functions, supplier information, and quantity ranges (minimum, maximum, and target quantities in mg/pouch) for each new product. This documentation demonstrates that all ingredients meet the stated grade (e.g., USP grade) and details how they are incorporated into the pouch filler to fully characterize

the new products. The ingredient information also confirms that the single and complex ingredients in all new products reflect the characterizing flavors of each product.

3.1.2. Product Consistency

The applicant provided sufficient information on the manufacturing of the new products to determine that they can be manufactured consistently without the introduction of hazards (e.g., metal shavings, microbial contamination). The applicant provided a manufacturing process flow for all the new products that includes six stages of operations: (b) (4) (b) (4) The provided description of the manufacturing process, quality controls, standard operating procedures, and work instructions indicates that the products can be manufactured to the specified design/range. Supplier qualification and monitoring information, and control procedures and acceptance criteria for incoming materials were submitted and assures the new products are made and received according to the specifications. Additionally, the applicant provided quality control records, which demonstrate that the manufacturing processes and quality controls used ensure the new products can be manufactured consistently to limit variability and introduction of unexpected hazards in the products.

Stability information is considered part of the "properties" of new tobacco products as defined under section 910(b) of the FD&C Act. FDA needs post-manufacturing product stability information from the applicant because bacterial communities and constituents in tobacco products change as a function of storage time (Chopyk et al., 2017; Djordjevic et al., 1993). Thus, information obtained through stability testing could be used to ensure that a product is microbiologically and chemically stable during the expected storage period and does not result in an increased risk to public health as the product sits in storage.

The applicant proposed a shelf life of (b) (4) for the new products and provided sufficient stability data for evaluation. The stability data provided included water activity (a_w), Total Aerobic Microbial Count (TAMC), Total Yeast and Mold Count (TYMC), and TSNAs, all of which met the applicant's specified acceptance criteria. However, the microbiology discipline found the applicant-provided validation information and test methods for the microbial counts, conducted by (b) (4) were insufficient because the methods were designed for use in foods, and not validated for tobacco products. In addition, the applicant provided TAMC and TYMC test data for on! Plus products not subject to this TPL review in the relevant CCS with method validation conducted by (b) (4) However, microbiology found the bridging approach inadequate because the applicant did not provide product composition information for the on! Plus products not subject to this TPL review and, moreover, there were differences in the test methods used by (b) (4) (e.g., incubation times, plating methods, volume of sample being tested). Without proper validation information and data on microbial stability, the microbiology discipline could not rely on the data generated from those methods and assess the products' stability over the proposed shelf life and additional information was needed to ensure that the finished new products are microbially stable over the shelf life in the relevant CCS. The microbiology discipline included a deficiency in the Product Science review. As discussed in further detail below (Section 3.1.5.), as TPL, I find the missing microbial count validation information does not preclude my APPH determination. From a chemistry perspective, the chemical stability information submitted by the applicant for PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17 demonstrates that the new products are stable during storage up to (b) (4) and can be manufactured consistently to control variability in the new products.

3.1.3. Packaging and Container Closure System

The new products PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17 are housed in a CCS that is composed of a can with a flat lid assembly (14 pouches per can)[7].

The new products contain CRP. Specifically, the packaging for the new products consists of a certified child-resistant polypropylene can and safety lid. Consumers open 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.

The applicant provided sufficient information to demonstrate that the risk of accidental exposure is adequately mitigated through the CRP. For all new products, the applicant provided CRP certification from an accredited laboratory meeting national or international standards and CRP test reports including testing protocols, raw data, and a summary of test results according to 16 CFR § 1700.20.

These CRP measures sufficiently mitigate the risk of accidental exposure to unintended users.

3.1.4. Product Issues Resulting in Adverse Experiences

No chemistry, microbiology, or engineering-related adverse experiences for the new products have been reported to FDA at this time.

3.1.5. Section Conclusion

As TPL, I agree with the review conclusions of the Product Science disciplines (i.e., engineering, chemistry, and microbiology) that these PMTAs contain sufficient information to characterize the product design and adequate processes and controls to help ensure that the new products meet the manufacturer's specifications.

The Product Science review of the manufacturing processes and controls confirms that the new products can be made in a reliable way that does not introduce hazards (e.g., metal shavings, microbial contamination). Moreover, the Product Science review confirms that the new products can be produced in a way that limits significant variability, including in nicotine content, throughout the shelf life of the new products.

As TPL, I find that the applicant provided sufficient chemical, and microbial stability data to demonstrate that all the new products are stable in their relevant CCS and can be manufactured consistently to control variability. The applicant proposed a (b) (4) shelf life for the new products in PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17.

The applicant provided stability testing data including a_w, microbial counts data (i.e., TAMC and TYMC) and TSNA data to support the proposed (b) (4) shelf life. However, the microbiology discipline found the applicant-provided validation reports and test methods for the microbial counts, conducted by (b) (4), were insufficient because the methods were designed and validated for use in foods, and not for tobacco products. In addition, the applicant provided TAMC and TYMC test data for on! Plus products not subject to this TPL review in the relevant CCS with method validation conducted by (b) (4) However, microbiology found the bridging approach inadequate because the

[7] The applicant refers to the CCS for PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17 as "C3".

applicant did not provide product composition information for the on! Plus products not subject to this TPL review and moreover, there were differences in the test methods used by (b) (4) (e.g., incubation times, plating methods, volume of sample being tested). However, as TPL, in this case, I find that the method validation concerns for microbial counts do not preclude my APPH determination as these are otherwise dry products with stable water activity (a_w). a_w, which is the measure of unbound (free) water in a product, informs the potential of a product to support microbial growth (Beuchat, 1983; Mutasa et al., 1990). It is generally recognized that microbial proliferation does not occur at a_w of <0.6 (Beuchat, 1983). The microbiology discipline concluded that the a_w method was adequately validated, indicating the results are reliable, and found the a_w for these products to be stable over time. In particular, the new products PM0009121.PD13 and PM0009121.PD14 had (b) (4) for the entire test period. PM0009121.PD10, PM0009121.PD11, PM0009121.PD16, and PM0009121.PD17 had a_w very slightly above 0.6 at baseline (b) (4) but decreased below (b) (4) by week 4 and remained below (b) (4) for the duration of testing. Further, since the water activity levels were below the level which can support microbial growth, we do not need TAMC or TYMC counts in this particular case. This is regardless of whether the applicant's TAMC or TYMC acceptance criteria exceed compendial standards. As TPL, I find that, in this case, the missing validation information for TAMC and TYMC testing does not preclude my APPH determination because these products are relatively dry with stable water activity below 0.6 and it is not expected that the water activity levels in these new products will support microbial proliferation over time.

Finally, engineering confirms the presence of a mitigation measure that is sufficient to address accidental nicotine poisonings in children in the new products. Specifically, the new products contain CRP with a certification. The CRP in the new products is intended to reduce the risk of poisoning in children by making it significantly difficult for children (under age 5) to open and obtain a toxic amount of nicotine within a reasonable time. As discussed below (Section 3.2.5), accidental exposure mitigation measures, such as CRP, are critical to addressing the risk of accidental nicotine poisonings among young children.

3.2. INDIVIDUAL HEALTH RISK

3.2.1. Relative Risks of Nicotine Pouches: Summary of Available Literature

Harmful and Potentially Harmful Constituents and Biomarkers of Exposure

Published studies demonstrate the relatively low toxicity of nicotine pouch products, in general, based on the very low to non-existent levels of HPHCs relative to those found in other tobacco products. In particular, one study demonstrated that TSNAs and PAHs present in loose and pouched moist snuff were undetectable in the tested nicotine pouches (i.e., dry and moist varieties of nicotine pouches) and were comparable to NRT (Back et al., 2023). Similarly, another study reported that the nicotine pouches tested contained lower levels of most toxicants including metals (e.g., nickel, cadmium, chromium) and TSNAs (i.e., NNN, NNK) compared to snus, and toxicant levels in nicotine pouches were lower than or comparable to NRT (Azzopardi et al., 2021). Finally, a third study analyzed TSNAs in 46 nicotine pouches from 20 different manufacturers. Although trace levels of NNN and NNK were detected in nicotine pouches, the levels were substantially lower than those commonly reported for CC and snus (Mallock, 2022). Given that the carcinogenicity of traditional smokeless tobacco is largely associated with exposures to TSNAs, which are formed during the curing and processing of tobacco leaves (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007), the absence of ground or cut tobacco in nicotine pouches is expected to significantly limit user exposure to TSNAs.

[8] See Table 3 Acronyms and Abbreviations

Consistent with this HPHC profile, two studies demonstrated significantly lower non-nicotine BOE data from nicotine pouch use relative to CC (Azzopardi et al., 2022; Rensch et al., 2023). In particular, data from a cross-sectional, 2-day inpatient study conducted in Sweden and Denmark reported statistically significantly lower levels of several BOEs among exclusive nicotine pouch users compared to current users of CC, and these BOE levels were generally comparable to those of former and never CC smokers (Azzopardi et al., 2022). In another controlled, in-clinic, parallel-cohort study, adult users of CC (n=144) were confined for seven days and randomized to either switch to mint-flavored 2, 4, or 8 mg nicotine pouches, continue smoking, or achieve complete tobacco abstinence. The study found that NNAL, a biomarker of exposure to the carcinogen NNK, and 18 of 19 other BOEs[9] were significantly lower in the nicotine pouch use groups compared to the CC smoking group; biomarker levels in the nicotine pouch group were comparable to the biomarker levels of those in the no-tobacco group (Rensch et al., 2023).

Non-Clinical Data

Non-clinical data regarding cytotoxicity, or the potential to damage or kill cells, and mutagenicity, or the potential to cause DNA mutations, can inform our understanding of potential health risks. Five *in vitro* toxicology studies reported that nicotine pouches are less cytotoxic compared to CC and snus (Bishop et al., 2020; East et al., 2021; Keyser et al., 2024; Yu et al., 2024; Yu et al., 2022). For example, tested nicotine pouches were shown to have lower cytotoxicity in human bronchial epithelial cells and human oral fibroblasts compared to the 1R6F reference cigarette and, to a lesser extent, a Swedish-style snus reference product (Bishop et al., 2020). Another *in vitro* study reported that nicotine pouch products (varying in flavor and nicotine strength) are less cytotoxic than a reference snus product (East et al., 2021). Consistent with these results, data from a third study found that nicotine pouches and snus are significantly less cytotoxic in human bronchial epithelial cells than CC, with a modest but measurable reduction in cytotoxicity in nicotine pouches compared to snus (Yu et al., 2022). A fourth study examined eight test products of up to 12 mg nicotine strength and found that, unlike CC and similar to snus, all eight test products were negative for mutagenicity and seven were negative for cytotoxicity (Keyser et al., 2024). In addition to lower in vitro toxicity, signaling pathways involved in cell proliferation and stress, as well as inflammatory markers, were minimally induced in cultured mouse embryonic stem cells treated with nicotine pouch extracts compared to those treated with snus extracts (Yu et al., 2024), offering potential mechanistic insights into the lower toxicity of nicotine pouches.

Short-Term Health Effects

There are limited data available on the short-term health effects of nicotine pouches. Oral health effects have been evaluated in a few studies. A small case series documented oral mucosal changes and associated histopathological findings including parakeratosis, edema, and chronic inflammation in nicotine pouch users (Miluna-Meldere et al., 2024). A 24-week randomized controlled trial (RCT) of established smokers compared the oral health outcomes between participants who continued to smoke and those who were instructed to switch to exclusive nicotine pouch use for the duration of the study (Liu et al., 2025). At both 12 weeks and 24 weeks, the nicotine pouch groups had statistically significant decreased gingival inflammation and bleeding index scores compared to baseline whereas the CC smoking group did not show any statistically significant changes in these endpoints (Liu et al., 2025). Use of smokeless tobacco has been associated with precancerous oral lesions (Chaffee et al., 2022; McKinney et al., 2025); further research is needed to compare the risk of oral lesions associated with nicotine pouches to that of smokeless tobacco products.

[9] The 19th biomarker, for nicotine equivalents, was not statistically different from continued use of CC.

Other studies have collected adverse experience reports from participants using nicotine pouches. Adverse experience data from industry-sponsored pharmacokinetic or BOE studies demonstrate that limited use of nicotine pouches in a study environment is generally well-tolerated. The reported adverse events were predominately mild and transient, and included headache, dizziness, nausea, vomiting, throat irritation, gingival bleeding, and hiccups (Azzopardi et al., 2022; Chapman et al., 2022; Kanobe et al., 2025; Liu et al., 2022; Lunell et al., 2020; McEwan et al., 2022; Renard et al., 2025; Rensch et al., 2023; Rensch et al., 2021).

In an eight-week RCT among adult smokers, the most commonly reported adverse events associated with nicotine pouch use were shortness of breath and coughing (Avila et al., 2024). In a cross-sectional survey with a convenience sample of 118 adults who reported current nicotine pouch use, the most frequent adverse events reported were mouth lesions (48%), upset stomach (39%), sore mouth (37%), sore throat (21%), and nausea (9%); severity of these self-reported AEs was not assessed (Dowd et al., 2024).

Long-Term Health Effects

Nicotine pouches are a novel class of products, which means that long-term health data are not yet available. However, given the understanding of product characterization in relation to Swedish snus and NRT (i.e., that HPHCs in nicotine pouches are generally lower than Swedish snus and similar to, or lower than, NRT), FDA is able to draw conclusions about likely health risks based on the epidemiological evidence that characterizes the relative health risks of Swedish snus.

FDA has authorized a Swedish snus product, General Snus, as a modified risk tobacco product, based on evidence demonstrating that this product is likely to pose a significantly lower individual health risk compared to cigarettes, as summarized in that TPL Review (US Food and Drug Administration Center for Tobacco Products, 2019). As described in the 2019 TPL review, the available evidence on Swedish snus demonstrates that exclusive snus use, when compared to CC, is associated with significantly lower risks of several smoking-related diseases, including oral cancer, lung cancer, myocardial infarction, chronic obstructive pulmonary disease (COPD), and stroke. Additional literature since that review continues to support these findings. For heart disease, a recent meta-analysis found no significant increase in the risk of ischemic heart disease or acute myocardial infarction among snus users (Lee et al., 2022). In general, the risk of stroke among cigarette smokers is likely higher than for snus users. A prospective cohort study observed that, while current snus use was associated with higher total stroke and ischemic stroke risk compared to never tobacco use (adjusted Hazard Ratio (aHR) 1.53, 95% CI: 1.02-2.32 and aHR 1.65, 95% CI: 1.06-2.57, respectively) (Titova et al., 2021), CC smoking has been found to increase risk of stroke by a factor of about 1.5- to 3-fold compared to never tobacco use (US Food and Drug Administration Center for Tobacco Products, 2019).

3.2.2. Ingredients and HPHCs in New Products

Chemistry's review of the applicant-submitted HPHC data for the new products demonstrates that, as expected for products in this category, the new products contain lower levels of most HPHCs compared to General Snus. In fact, the new products do not contain measurable quantities of most measured HPHCs including carcinogenic TSNAs (i.e., NNN, NNK), the carcinogenic polycyclic aromatic hydrocarbon, B[a]P, or metals.

The applicant provided the mean, minimum, and maximum ranges for HPHCs in all the new products and four General Snus comparison products (i.e., General Portion Original Large, General Mint Portion White Large, General Portion White Large, and General Wintergreen Portion White Large). The General

Snus products are appropriate comparison products because they are intended to be used in the same manner (i.e., orally) as the new products.

In addition to the HPHC test data that the applicant submitted for General Snus, the chemistry discipline used HPHC values from the published literature for ZYN, pouched dry snuff, and pouched moist snuff to compare HPHCs between the new products and other tobacco products available in the U.S. market. The results of the detectible HPHCs are summarized below:

PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17

- Higher free and total nicotine compared to General Snus comparison products
- Lower acetaldehyde compared to all comparison products[10]
- Lower formaldehyde compared to all comparison products

Altogether, the HPHC test data demonstrates that the new products contain lower levels of the majority of HPHCs, including NNN and NNK, when compared to General Snus. Regarding the free and total nicotine levels, that topic is addressed in the abuse liability evaluation in Section 3.2.3.

Chemistry's review of (b) (4) referenced for analytical methods and validation for the HPHCs tested in the new products, found the analytical methods to be sufficient to support this review. Although nicotine pouches can deliver harmful chemicals to users, in general, these products are expected to have relatively low levels of constituents CTP has identified as HPHCs and not contain other ingredients that could raise toxicological concerns (Back et al., 2023; US Food and Drug Administration Center for Tobacco Products, 2025). Chemistry evaluated the HPHCs present in the new products subject to this review and determined that the levels of those HPHCs were non-detectable or below all comparison products except for free and total nicotine in comparison to General Snus products. In addition to the HPHC evaluation, the chemist assessed the ingredients present, and the levels at which they are present; based on all of these findings, I, as TPL, in consultation with CTPs' Office of Science leadership, determined that the new products would not warrant a toxicology consult (e.g., the added ingredients did not include chemicals with known genotoxicity).

3.2.3. Abuse Liability of New Products

Abuse liability refers to the ability of a product to promote continued use, and the development of addiction and dependence. This can be relevant to determining the likelihood that people addicted to one nicotine product would switch to another. A new product with an abuse liability similar to that of a high abuse liability comparison product (like CC or smokeless tobacco) may increase the likelihood that individuals who use other tobacco products are able to switch to such a new product. However, high abuse liability also increases the likelihood that individuals who do not currently use tobacco who initiate use with a new product will become addicted to it. Moreover, a new product with high abuse liability may pose a risk to current users because continued use of a such a product may result in addiction severity that exceeds that associated with use of other tobacco products with lower abuse liability, making it more difficult for these users to stop using a high abuse liability new product despite any harmful consequences associated with continued use.

[10] The applicant provided HPHC test data for General Snus (i.e., Snus Mint Portion White Large, Snus Portion Original Large, Snus Portion White Large, and Snus Wintergreen Portion White Large) as comparison products for the new products. In addition, chemistry compared HPHC values of three oral and smokeless tobacco products from the literature (i.e., ZYN, pouched dry snuff, and pouched moist snuff) to compare the HPHC values of the new products.

The BCP review considered one applicant-sponsored clinical study (b) (4) with abuse liability outcomes. Study (b) (4) was a randomized crossover study designed to characterize nicotine PK, subjective effects, and product use behavior from 45-minutes of prescribed use of the tested new products (on! PLUS Wintergreen 6 mg [PM0009121.PD16] and 9 mg [PM0009121.PD17] and on! PLUS Tobacco 9 mg [PM0009121.PD14]) and usual brand moist smokeless tobacco among adults who use smokeless tobacco. This is an appropriate high abuse liability comparison product because adults who use smokeless tobacco are a likely and intended user population for the new products. The applicant-chosen prescribed use regimen is appropriate as it is the same for the new products and usual brand smokeless tobacco comparison product (45-minutes) and reflects naturalistic use of smokeless tobacco in literature (Hatsukami et al., 1988; Lemmonds et al., 2005; Nighbor et al., 2023).

This applicant-sponsored nicotine PK study did not test all of the new products but tested each nicotine level (6 and 9 mg) and characterizing flavor (Wintergreen, Mint, Tobacco). A previous generation of the on! PLUS Mint 9 mg new product (on! GEN 1 PLUS Mint 9 mg) was tested in (b) (4) Due to the similarities in total and free nicotine content, BCP bridged the data from on! Gen 1 PLUS Mint 9 mg used in the clinical study to the on! PLUS Mint 9 mg new products (PM0009121.PD11). BCP also found the applicant's bridging approach between the tested new products (on! GEN 1 Mint 9 mg, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17) and the untested new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13) to be acceptable because of similar measured total and free nicotine levels[11].

Based on the totality of evidence, the abuse liability of the on! PLUS 6 mg and 9 mg new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17) is likely lower than moist smokeless tobacco. Study results show that the nicotine C_{max} and $AUC_{0\text{-}180}$ for the tested on! PLUS 6 mg and 9 mg new products were statistically significantly lower than the high abuse liability comparison product. The tested new products alleviated craving and withdrawal symptoms to a lesser degree and were associated with lower positive subjective effects ratings (e.g., liking, satisfying) relative to the high abuse liability comparison product (moist smokeless tobacco).

Although the on! PLUS 6 mg and 9 mg new products likely have a lower abuse liability compared to moist smokeless tobacco, they still delivered sufficient nicotine to users and alleviated symptoms of craving and withdrawal from baseline. These findings suggest that the on! PLUS 6 mg and 9 mg new products can support behavioral change (e.g., product substitution) among some users while potentially reducing the risk of dependence and addiction relative to marketed smokeless tobacco products.

3.2.4. Adverse Experiences

The applicant submitted one clinical study (b) (4) that reported AEs associated with the new products. Overall, most of the AEs reported in the clinical study were mild to moderate in severity, and consistent with those reported in literature (Dowd et al., 2024). Because these AEs are consistent with what the literature reports for this product category (i.e., nicotine pouches) and are

[11] To bridge a tested product to an untested product, BCP requires that the products be sufficiently similar in the product characteristics that influence abuse liability. For nicotine pouches, BCP's primary bridging criteria include total and free nicotine content because nicotine content in tobacco products affects users' exposure to nicotine and pH moderates nicotine exposure by allowing free nicotine to more readily cross biological membranes, including oral mucosa (e.g., Chen et al., 1999; Nair et al., 1997; Nielsen et al., 2002; Wilhelm et al., 2022).

mostly mild or moderate in nature, the reported AEs are acceptable from medical's perspective. The manufacturer's post-market reporting will allow FDA to monitor and assess reported AEs associated with use of these new products in the market as actually used by consumers.

3.2.5. Accidental Exposure and Mitigation

The new products contain nicotine, which poses a risk for acute toxicity. In particular, accidental exposure of children to nicotine is a risk associated with a wide range of tobacco products, including nicotine pouches, and may result in nicotine poisoning (Kamboj et al., 2016; Olivas et al., 2025; Wang et al., 2017). Recent data from the National Poison Data System (NPDS) raises specific concerns about the rate and severity of accidental ingestions of nicotine pouches. Between 2020 and 2023, the rate of nicotine pouch ingestions among children under age 6 increased by 763.1%, to an annual rate of approximately four ingestions per 100,000 U.S. population. Ingestions of nicotine pouches were 1.5 times more likely to be associated with a serious medical outcome and twice as likely to be associated with a medical admission than other nicotine product formulations (e.g., gum/lozenge, liquid, powder/granules, tablet/capsule/caplet, other) combined (Olivas et al., 2025).

These new products include CRP. CRP has been used in the United States to reduce the risk of pediatric exposure to toxic substances. The use of CRP for a variety of toxic substances, including oral prescription medications, non-prescription medications, and household chemicals, has been highly effective in reducing pediatric exposure to toxic substances (Bakshi et al., 2023; Rodgers, 1996, 2002; Walton, 1982). A systematic review of the effects of CRP and their relevance to tobacco products concluded that CRP would likely reduce tobacco product poisonings among children under age 6 (Jo et al., 2017).

As discussed in Section 3.1.3, the engineering discipline found that the new products' primary packaging is child-resistant. The applicant provided CRP certification from an accredited laboratory meeting national or international standards and CRP test reports including testing protocols, raw data, and a summary of test results according to 16 CFR § 1700.20. The engineering discipline concludes that with CRP, the new products' primary packaging mitigates the risk of accidental ingestion and nicotine poisoning among children.

3.2.6. Section Conclusion

The available scientific information demonstrates that nicotine pouches generally fall toward the lowest end of the continuum of risk of tobacco products. As described above, the literature demonstrates the relatively low toxicity of nicotine pouches based on the very low or undetectable levels of most HPHCs relative to those found in other tobacco products; data showing significantly lower BOE among users of nicotine pouches, relative to CC and snus; nonclinical data demonstrating lower cytotoxicity of nicotine pouches relative to CC; and no evidence of mutagenicity in tested nicotine pouch products.

Product Science disciplines reviewed these applications to confirm the HPHC profile for these new products was consistent with what is expected for the overall product category. Their review found that as expected for products in this category, the new products contain lower levels of most HPHCs compared to General Snus. Of the 11[12] HPHCs analyzed in the new products, the majority of HPHCs were too low to be detected. In fact, the new products do not contain measurable quantities of most measured HPHCs including carcinogenic TSNAs (i.e., NNN, NNK), the carcinogenic polycyclic aromatic hydrocarbon, B[a]P, or metals. Importantly, NNN, an HPHC, is the predominant driver of excess oral

[12] Acetaldehyde, Arsenic, B[a]P, Cadmium, Crotonaldehyde, Formaldehyde, Free Nicotine, Nicotine (total), NNK, NNN, NNK+NNN.

cancer risk among adult smokeless tobacco users and therefore the absence of measurable levels of NNN in these products is expected to lower the associated cancer risk. These data support the conclusion that the new products likely pose lower health risks to users relative to traditional tobacco products, including CC and smokeless tobacco.

In addition, BCP evaluated outcomes related to abuse liability in the applicant-submitted clinical studies to confirm the new products would not pose an abuse liability risk greater than high abuse liability comparison products like CC or smokeless tobacco. The applicant provided one clinical study, which evaluated the abuse liability of the on! PLUS 6 mg and a previous generation of the 9 mg new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17). Overall, BCP concluded that the 6 and 9 mg on! PLUS new products likely have a lower abuse liability than moist smokeless tobacco because they produced statistically significantly lower nicotine C_{max}, alleviated craving and withdrawal symptoms to a lesser degree, and were associated with lower positive subjective effects ratings (e.g., liking, satisfaction) relative to this high abuse liability comparison product (usual brand moist smokeless tobacco). As TPL, I find that all new products are not expected to exceed the abuse liability of CC or smokeless tobacco and therefore do not raise concerns about posing an increased risk with respect to dependence and addiction relative to high abuse liability tobacco products currently on the market (i.e., CC and smokeless tobacco).

In terms of short-term health outcomes, the limited data in the literature suggest that the risks to users of nicotine pouches include the potential for AEs associated with nicotine exposure. There is also evidence that nicotine pouch use may be associated with negative outcomes for oral health, although the available evidence suggests the risk may not be higher relative to CC.

The medical review assessed reports of AEs from one applicant submitted clinical study. Overall, the reported AEs were mostly mild to moderate in severity, and consistent with those reported in the literature, and no product-specific serious or unexpected AEs were reported.

Although information on long-term health effects of nicotine pouches is not yet available, given the comparisons to Swedish snus, we can extrapolate from the long-term epidemiological data available regarding the health risks of Swedish snus. Moreover, given that most HPHCs in the new products are lower relative to General Snus, the new products are expected to fall towards the lower end of the continuum of risk.

Taken together, as TPL, I conclude that the new products, which are non-combusted and do not contain tobacco leaf, which significantly limits exposure to TSNAs, show lower levels of HPHCs than CC and snus and pose a lower overall individual health risk relative to CC and smokeless tobacco use.

Although the new products may be a lower-risk alternative for adults who use other tobacco products, the new products still deliver harmful chemicals to users, including nicotine, a toxic and addictive chemical, and thus are not without risk to users and non-users (Back et al., 2023; US Food and Drug Administration Center for Tobacco Products, 2025). For current tobacco users, the new products present a risk of continued nicotine dependence. For current non-users, the new products pose the risk of developing nicotine dependence. In addition, though data are limited, nicotine pouches have been associated with negative oral health outcomes, including parakeratosis, edema, and chronic inflammation. Although not a main driver of tobacco-related disease, long-term nicotine exposure has been associated with adverse cardiovascular effects such as hypertension, platelet aggregation and endothelial dysfunction; the acceleration of arteriosclerosis by increasing total and low-density

lipoprotein (LDL) cholesterol levels; and cardiovascular disease related inflammation (e.g., Benowitz et al., 2016; Brembach et al., 2023; Dorotheo et al., 2024). Chronic nicotine use has also been linked to systemic inflammation (Benowitz et al., 2016; Brembach et al., 2023), gastrointestinal effects (e.g., Chu et al., 2013), and effects on bone growth (e.g., Kallala et al., 2013). And for youth there are additional risks, as nicotine use during adolescence is associated with long-term impacts on brain development (Castro et al., 2023).

Moreover, the new products also pose a risk from accidental nicotine exposures, a risk that is particularly high for small children, who can be most affected by the nicotine poisoning. Accidental pediatric poisoning among children is a potentially severe risk associated with nicotine pouches as a product class as evidenced by reports received by FDA and the NPDS. During the two-year period of April 1, 2022, to September 30, 2024, NPDS data indicated that the number of reported nicotine exposure cases in the United States steadily increased. The majority of nicotine pouch exposure cases were among children, with 75.8% of exposure cases occurring in children under age 5. The new products contain CRP, which is a known mechanism to help mitigate this risk. The APPH standard requires an assessment of the risks and benefits to the population as a whole, including risks to children who may be exposed to tobacco products inadvertently. Given the risk of accidental exposure to, and child poisoning from, nicotine pouches, as TPL, I find that the inclusion of an accidental exposure mitigation measure with these new products is critical to finding them APPH. As TPL, I conclude that the new products' CRP serves to mitigate the risk of nicotine poisoning among children ages 5 and under.

3.3. POPULATION HEALTH IMPACT

3.3.1. Current Tobacco Users

Assessment of Behavioral Impact

In order to evaluate the benefit to adults, our assessment of a product's composition and likely health risks (discussed above) first establishes that the new product is expected to pose lower health risks to users of more harmful products. The evaluation of population health impact then considers (a) who is likely to use nicotine pouches, and (b) how they are likely to use them, in order to determine whether individuals who can benefit from nicotine pouches will use them in a way that can provide an individual benefit. As the known risks of a product increase or decrease, the burden of demonstrating a substantial enough benefit likewise increases or decreases. Given the relatively low risk posed by nicotine pouch products, the burden on an applicant in demonstrating benefit (in terms of the nature of the evidence and magnitude of benefit) is less compared to other tobacco products with greater risk. In this case, the evaluation of the behavioral impact of the new products relies on the evaluation of pharmacokinetic and subjective effects data, which can inform whether the new products, as formulated, have the potential to serve as an acceptable substitute for adults who use other more harmful tobacco products. Whereas the literature supports that nicotine pouches can effectively deliver nicotine and reduce cravings, because these products can also vary widely in terms of nicotine strength and delivery, the evaluation of abuse liability of the new products is critical to assess the extent and rate of nicotine delivery in current tobacco product users compared to other tobacco products, such as CC and smokeless tobacco products. In addition, these studies can also assess other aspects of using these tobacco products which relate to their abuse liability such as the subjective experience after use. We also consider existing evidence from the literature regarding the impact of nicotine pouches on switching behavior. Given the relative uniformity of these products in design and manner of use, we can extrapolate from this category-level evidence of use behavior to support conclusions about the new products. Finally, this evaluation considers the behavioral data provided by the applicant and discusses

any longitudinal data provided in the application regarding the impact of the new products on switching away from cigarettes or smokeless tobacco products.

Likely Users

Current (i.e., past 30-day) use of nicotine pouches among adults remains low, with use generally being more common among those who also use another tobacco product (Dai et al., 2024; Gaiha et al., 2023; Morean et al., 2023a, 2023b; Palmer et al., 2025). To date, two published nationally representative cross-sectional studies in adults have assessed current nicotine pouch use, with both studies finding that less than 1% of adults currently use nicotine pouches (Dai et al., 2024; Palmer et al., 2025). Current use appears more common among adults who are male, Hispanic or non-Hispanic White, young adults, and current or former CC smokers (Dai et al., 2024). For instance, in the May 2019 and September 2022 cycles of the Tobacco Use Supplement to the Current Population Survey (TUS-CPS), among current nicotine pouch users, the majority reported either current (25%) or formerly (33.8%) smoking CC (Reyes-Guzman et al., 2025).

Given the similarity in manner of use, nicotine pouches may be an appealing alternative to users of smokeless tobacco products. Although there are no nationally representative estimates available, several cross-sectional surveys suggest the likelihood of pouch use among smokeless tobacco users. For instance, in an analysis of data from CaCTUS (COVID-19 and Commercial Tobacco Use Study; collection: January-February 2021) of adults ages 21 and older, among current smokeless tobacco users, 12.8% reported current use of nicotine pouches and 41.0% reported ever use of nicotine pouches (Sparrock et al., 2023). Similarly, in the 2020 International Tobacco Control (ITC) Smoking and Vaping Survey, among those who had used smokeless tobacco in the past 30 days, 13.3% reported current nicotine pouch use and 21.0% reported ever use (Felicione et al., 2022).

Switching from more harmful tobacco products

Nicotine is the primary drug that promotes and sustains tobacco addiction (Benowitz et al., 2010; Stolerman et al., 1995) and therefore the delivery of nicotine plays a central role in facilitating switching among current tobacco users. The available data on nicotine pouch abuse liability indicate that nicotine pouches can deliver substantial amounts of nicotine, reduce nicotine craving and withdrawal after tobacco abstinence, and increase positive subjective effects (Kanobe et al., 2025; Keller-Hamilton et al., 2023; Lunell et al., 2020; Mallock-Ohnesorg et al., 2024; McEwan et al., 2022; Rensch et al., 2021; Staaf et al., 2022).

As discussed above (Section 3.2.3.), as TPL, I conclude that all new products are expected to have a lower abuse liability than smokeless tobacco and CC, and they are likely to deliver sufficient nicotine to the user to reduce craving and withdrawal symptoms and therefore may support behavioral change (e.g., product substitution) among some users.

As TPL, I find these data supportive that these new products have the capacity to support switching among current tobacco users.

Although limited, there is some literature observing the impact of nicotine pouch use on significant reduction of CC (or other tobacco products) or complete switching to nicotine pouches over time.[13] The

[13] In October 2025, Hartmann-Boyce et al. (2025) published a systemic review titled “Oral nicotine pouches for cessation or reduction of use of other tobacco or nicotine products” that assessed published studies as of January 2025. Based on limited

evidence indicates that while it is unlikely that a majority of users of inhaled products will take up the new products, those who do are expected to benefit. To date, several studies have been published, and while some of them are relatively small, taken together they provide some additional support for the potential for nicotine pouches to facilitate significant CC reduction among adults who smoke and may support complete switching from some of those users. In particular, three relatively small, randomized controlled trials (RCTs) (ranging from 4 to 8 weeks in duration) demonstrated that nicotine pouches can significantly lower cigarettes per day (CPD), compared to control (Avila et al., 2024) and can support significant reductions in CPD, compared to baseline, over the course of the study (Campbell et al., 2022; Fucito et al., 2025). Similarly, a 6-month actual use study of oral nicotine products, including nicotine pouches, found that across all products, more than one third of participants had reduced CPD by ≥50%; and 13% of participants reported quitting smoking (McDowell et al., 2024). Finally, one published study evaluated nicotine pouch use among both cigarette and smokeless users in a six week actual use study (Becker et al., 2023). At the week 6 follow-up, among those who reported smoking at baseline, 27% reported past 7-day smoking abstinence and 39% reported reducing their CPD by ≥50%. In addition, among smokeless tobacco users at baseline, 71% reported no use of smokeless tobacco products by week 6, while another 14% reported reducing their smokeless tobacco use by ≥50% (Becker et al., 2023).

The applicant submitted a total of four longitudinal studies, one of which evaluated the new products. In particular, the applicant submitted a six-week actual use study (b) (4) that evaluated use of new products PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, and PM0009121.PD17 among adult current users of smokeless tobacco (dip/snuff) and current dual users of smokeless tobacco and CC. The applicant reported that by the end of the study, 15% of smokeless users reported completely quitting use of dip/snuff. Among dual users, around 35% reported a 50-99% reduction in cigarette use each week, compared to baseline.

3.3.2. Non-Users of Tobacco

Evaluating the potential impact to non-users of tobacco, and particularly youth, is a critical part of the APPH assessment. Whereas the population benefit of a new product derives from adult users of more harmful tobacco products switching to a new product that provides a lower risk alternative, the potential harms are largely driven by the potential for the new products to cause additional tobacco use initiation among current non-users, particularly youth. Therefore, the PMTA assessment evaluates the likelihood that the new products will appeal to non-users, including youth.

To evaluate the risk to youth in PMTA review, CTP consistently relies on existing evidence regarding youth use of a product category. Surveillance data on overall product category use provide a strong indicator of the relative appeal of a tobacco product category and therefore can be a basis for estimating the potential risk of a new product. The observed use of nicotine pouches – such as what is gathered in national surveillance studies like National Youth Tobacco Survey (NYTS) – provide indicators of potential future behavior. However, these trends can shift quickly, and there is potential for any specific new product to exceed the use rates suggested by the overall category. Accordingly, as described in Sections 3.3.3 and 3.3.4, as TPL, I reviewed the labeling and the applicant's proposed

available evidence, the authors concluded that, at this time, they were uncertain if oral nicotine pouches help people quit smoking relative to conditions in which adults were assigned to continue smoking as usual or to quit using no support. While the review is highly limited, due to a lack of available studies, the authors note there are many additional studies underway, and the review will be updated as additional evidence becomes available. Additionally, the review did not make any conclusions around the use of nicotine pouches to reduce cigarette use.

(b) (4)

marketing plan to assess whether there may be concerns related to youth appeal or marketing that targets youth.

Youth Appeal

In terms of the risks to nonusers, the potential impact of marketing a new tobacco product on youth is a critical piece of the APPH evaluation because the majority of tobacco use begins before adulthood (US Department of Health and Human Services, 2012). Features of the nicotine pouch product category have the potential to make these products appealing to youth. First, nicotine pouches are available in a wide range of flavors (Marynak et al., 2021; Travis et al., 2025), with flavored products making up >95% of the market.[15] Given that flavor increases the appeal of tobacco products to youth (Camenga et al., 2018; Carpenter et al., 2005; Harrell et al., 2017; Pepper et al., 2016), the availability of nicotine pouches in multiple flavors may contribute to the attractiveness of the tobacco products among new and already established nicotine product users. In addition, research suggests that concealability, or the ability to use the product discreetly, is a youth-appealing feature of nicotine pouches (Han et al., 2025; Harlow et al., 2025; Vogel et al., 2023). Moreover, nicotine pouches can be packaged in ways making them hard to distinguish from gum or candy, which makes them easier to conceal from parents, teachers, or other authority figures (Harlow et al., 2025; Vogel et al., 2023).

While these features may increase youth appeal, observed rates of ever use of nicotine pouches among youth suggest relatively low levels of interest in the nicotine pouch product category to date. In the 2024 NYTS, 3.5% of middle and high school students reported ever using a nicotine pouch (high school: 4.7%, middle school: 1.8%). These rates increased from 2022, when 2.2% of middle and high school students reported ever nicotine pouch use (Feizy et al., 2025; Jamal et al., 2024), and Population Assessment of Tobacco and Health (PATH) Wave 7 data (2022/2023) showed that 0.6% of adolescents ages 12-17 reported ever using nicotine pouches (Palmer et al., 2025). Analyses of 2024 Monitoring the Future (MTF) data estimated that lifetime nicotine pouch use prevalence was 0.8%, 4.1%, and 6.8% among students in grades 8, 10, and 12, respectively (no CIs reported) (Miech et al., 2025).

Youth Use

Past 30-day nicotine pouch use among youth remains low, although it has increased over the years from when it was first assessed on NYTS in 2021 (0.8%). In 2024, weighted prevalence data from NYTS show that 1.8% of all U.S. youth reported current (past 30-day) use of nicotine pouches (2.4% and 1.0% among high school and middle school students, respectively) (Jamal et al., 2024). Other nationally representative surveys have assessed nicotine pouch use in youth and similarly indicate that current youth use is low. In data from Wave 7 of the PATH study (2022/2023), 0.2% of adolescents ages 12-17 reported past 30-day use (Palmer et al., 2025). Data from the 2024 MTF survey showed an overall significant increase in prevalence of current use among U.S. grade 12 students from 1.4% in 2023 to 3.5% in 2024 (Miech et al., 2025).

Among youth reporting nicotine pouch use, the majority report using flavored products. In the 2024 NYTS, most middle and high school users of nicotine pouches (85.6%) reported using a flavor other than tobacco-flavored or unflavored (Park-Lee et al., 2024). Among middle and high school current nicotine

[15] This estimate is based on NielsenIQ sales data from 09/08/2024-10/04/2025. This information is not a formal dissemination of information by FDA/CTP and does not represent Agency position or policy. These analyses, calculations, and conclusions, informed in part by the NielsenIQ Retail Measurement Service (RMS) data, are those of the author and do not reflect the views of NielsenIQ. See https://NielsenIQ.com/global/en/ for more information.

pouch users, mint was the most commonly reported flavor (53.5%), followed by fruit (22.4%) and menthol (19.3%) (Park-Lee et al., 2024).

About half of youth reporting current pouch use report infrequent use (53.7% reported using 1-5 days in the past 30 days) (Park-Lee et al., 2024). When considering differences between youth current ENDS users and nicotine pouch users, in the 2024 NYTS, 38.5% of ENDS users reported frequent use on 20 or more days in the past 30 days in contrast to 29.3% of nicotine pouch users (Park-Lee et al., 2024).

Adult Non-Users

Overall, the most recent wave of TUS-CPS (2022-2023) found that use of nicotine pouches was virtually non-existent for tobacco naïve adults (Delnevo et al., 2025). Based on limited data, former adult CC smokers report higher use of nicotine pouches than non-smokers, but a lower rate of use compared to current smokers (Dai et al., 2024; Li et al., 2021). However, it is unclear whether use of nicotine pouches among former adult smokers affects the likelihood of relapse or whether former users of other tobacco products (e.g., ENDS, smokeless tobacco) are similarly more likely to use nicotine pouches than never users of the respective products.

3.3.3. Labeling

OCE DPAL reviewed the new products' labeling and advertising and finalized a consult dated December 10, 2025. The applicant provided proposed labeling. Based on the information presented at this time, OCE-DPAL has not concluded that the proposed labeling is false or misleading in any particular.

As TPL, I reviewed the labels, labeling, and advertising and, at this time, did not identify concerns including content that appears designed to appeal to youth or statements that convey modified risk information.

3.3.4. Marketing of the New Tobacco Products

The Office of Health Communication and Education (OHCE) reviewed the marketing plan submitted by the applicant for the new products and finalized a consult dated December 16, 2025.

The OHCE consult concludes that 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 that the applicant provides limited information regarding how such measures would be implemented.

The applicant summarized several measures directed toward limiting youth exposure to the new products' marketing materials and activities for which OHCE is supportive:

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- (b) (4)
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OHCE recommends that any MGO letter for these new products note that these measures are likely to help further limit youth exposure and the potential for youth initiation, as well as encourage the applicant to implement its proposed approaches to limit youth exposure to the new products' labeling, advertising, marketing, and/or promotion.

3.3.5. Section Conclusion

Based on our review of the literature, summarized above, the available evidence supports the conclusion that current users of more harmful tobacco products, including CC and smokeless tobacco products, are the likely users of the new products.

Based on the information submitted, the new products have a lower abuse liability than smokeless tobacco and are expected to have lower abuse liability than CC, suggesting they are likely to deliver sufficient nicotine to the user to reduce craving and withdrawal symptoms and therefore may support behavioral change (e.g., product substitution) among some users. Thus, as TPL, I find that the abuse liability findings support the potential for the new products to appeal to current tobacco users and enable some adults to switch away from more harmful tobacco products.

The applicant provided evidence from an actual use study that evaluated switching in the new products. (b) (4) demonstrated that, by the end of the study, 15% of smokeless users reported completely quitting use of dip/snuff and among dual users, around 35% reported a 50-99% reduction in cigarette use each week, compared to baseline. Although limited, there is also some literature evaluating product switching, which suggests that nicotine pouches can facilitate significant reductions in CC or smokeless tobacco use and, in some cases, complete product switching.
The applicant-submitted data are consistent with the published studies and further support that the new products can enable adult users to switch away from cigarette/smokeless tobacco use.

Taken together, given the lower toxicity of nicotine pouch products, relative to CC and smokeless tobacco, the available evidence supports my conclusions that these new products will provide a benefit to adults who use CC and/or smokeless tobacco and either completely switch to the new products or significantly reduce CC use.

Whereas the new products are likely to provide a benefit to adult users, they may also pose a risk to non-users. In particular, although the new products can be a lower-risk alternative for adults who use other tobacco products, the new products may deliver harmful chemicals to users, including nicotine, a toxic and addictive chemical (Back et al., 2023; US Food and Drug Administration Center for Tobacco Products, 2025). Thus, nicotine pouches pose a risk of addiction to non-users, particularly youth. The population health impact is therefore affected by the extent to which the new products appeal to nonusers, including youth, and lead to increased tobacco use among nonusers and youth.

Nicotine pouches have features that may be appealing to youth, particularly the availability of a range of flavors as well as their ability to be used inconspicuously. To date, however, the observed prevalence of youth use of nicotine pouches remains low, suggesting relatively low youth appeal of the product category. While non-tobacco-flavored tobacco products, including menthol, are more appealing to youth than tobacco-flavored tobacco products, the concern about appeal of flavors to youth is partially alleviated by the current 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%. Therefore, based on the evidence available at this time, as TPL, I conclude that the new products' potential risk to youth is relatively low based on the currently available evidence. In addition, in terms of adults who do not use tobacco, the currently available data show that use of nicotine pouches was virtually non-existent for tobacco naïve adults.

In considering risk to youth, as TPL, I also reviewed the labeling and did not identify any concerns. Based on the information presented at this time, OCE-DPAL has not concluded that the proposed labeling is false or misleading in any particular. Because the applicant may change labeling and advertising after authorization, I recommend that the MGO letter include language that the new products subject to these MGOs comply with the FD&C Act, FDA's implementing regulations, and all other applicable laws and regulations.

Finally, as TPL, I considered the applicant's proposed marketing plan and its potential to target youth. OHCE reviewed the marketing plan and found that the applicant generally describes a reasonable approach to marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and promotion. 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 the marketing requirements and recommendations in Section V of the OHCE consult. The OHCE consult also identified additional measures that the applicant plans to take that could be helpful in mitigating youth exposure, such as:

(b) (4)

(b) (4) As TPL, I recommend such measures, as they will further mitigate the potential risk to youth posed by the marketing of these tobacco products.

Therefore, based on the evidence available at this time, as TPL, I conclude that the potential of the new products to benefit adult tobacco users, including CC smokers and smokeless tobacco users, who use nicotine pouches and significantly reduce their traditional tobacco product use or who switch completely outweighs risks to youth or nonusers, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to product marketing and product access. However, despite relatively low youth use of the product category, trends in youth use can shift quickly, and historically we have witnessed how the emergence of a new product can drive appeal of a product category. Therefore, it is critical that FDA continue to monitor youth nicotine pouch use of the new products subject to this review. If, once authorized, the marketing of these products leads to significant youth uptake, the benefits may no longer outweigh the risks, and these authorizations may be subject to withdrawal. Likewise, although the vast majority of nicotine pouch

users have prior tobacco experience, it is important to continue to monitor potential uptake of nicotine pouches among adult non-users, particularly young adults.

3.4. STATUTORY REQUIREMENTS

3.4.1. 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.

3.4.2. Tobacco Product Manufacturing Practices[16]

The 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 the new products do not fail to conform to the requirements in Section 906(e) of the FD&C Act.

3.4.3. 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.

3.4.4. Product Standards

There are no applicable product standards for these PMTAs.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

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 Hans Rosenfeldt, Ph.D. on December 16, 2025. The FONSI was supported by an Environmental Assessment (EA) prepared by FDA on December 16, 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)). The statute specifies that, in assessing whether 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 requires 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. In

[16] FDA has not promulgated a tobacco product manufacturing practices (TPMP) rule.

determining whether permitting the marketing of a new tobacco product would result in a net 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 for adult users who switch to lower risk products).

The published literature, summarized in this review, suggests the overall risk to adults for this product category (i.e., nicotine pouches) is expected to be lower compared to both CC and smokeless tobacco products due to significantly lower levels of measured HPHCs. We reviewed these applications to confirm the HPHC profile for the new products was consistent with what is expected for the overall product category. The Product Science review found that the new products contain lower levels of most HPHCs when compared to General Snus and other oral and smokeless tobacco products (i.e., ZYN, pouched dry snuff, pouched moist snuff).

Of the 11 HPHCs analyzed in the new products, the majority of HPHCs were too low to be quantified in the new products. In fact, the new products do not contain measurable quantities of carcinogenic TSNAs, including NNN and NNK, or the carcinogenic polycyclic aromatic hydrocarbon, B[a]P. Importantly, NNN, an HPHC, is the predominant driver of excess oral cancer risk among adult smokeless tobacco users, and therefore the absence of measurable levels of NNN in these products is expected to lower the associated cancer risk. These data support the conclusion that the new products likely pose lower health risks to users relative to traditional tobacco products, including CC and smokeless tobacco.

Moreover, the available scientific information regarding the very low or undetectable levels of HPHCs in nicotine pouch products relative to those found in other tobacco products is supported by data showing significantly lower BOE among users of nicotine pouches, relative to CC and snus. In addition, published nonclinical studies demonstrate lower cytotoxicity of nicotine pouches relative to CC and no evidence of mutagenicity in tested nicotine pouch products. Although long-term epidemiological evidence is not yet available to evaluate health risks of nicotine pouches, we can extrapolate from the available evidence on snus, based on similarities in manner of use and product characteristics, including that most HPHCs are lower in nicotine pouches relative to snus, as described above. The evidence on snus demonstrates that use of those products poses a significantly lower individual health risk compared to CC. Taken together, the new products, which are non-combusted, do not contain tobacco leaf, and show lower levels of HPHCs than General Snus, likely pose a lower overall individual health risk relative to adults who use CC and smokeless tobacco products.

To evaluate the risk that the new products will have an abuse liability that exceeds that of comparison products known to have a high abuse liability (e.g., CC, smokeless tobacco), BCP reviewed one applicant-sponsored clinical study (b) (4) which evaluated the abuse liability of the on! PLUS 6 mg and 9 mg new products (PM0009121.PD10, PM0009121.PD11, PM0009121.PD13, PM0009121.PD14, PM0009121.PD16, PM0009121.PD17). Based on the totality of evidence, all of the new products are expected to have a lower abuse liability than the high abuse liability comparison product because they produced statistically significantly lower nicotine C_{max} (i.e., peak plasma nicotine concentration), alleviated craving and withdrawal symptoms to a lesser degree, and were associated with lower positive subjective effects ratings (e.g., liking, satisfaction) relative to the high abuse liability comparison product (usual brand moist smokeless tobacco). As such, the new products are not expected to exceed the abuse liability of smokeless tobacco and therefore do not raise concerns about posing an increased risk of dependence and addiction relative to high abuse liability tobacco products currently on the market (i.e., CC and smokeless tobacco).

Finally, we reviewed AEs from one applicant submitted clinical study. Overall, the reported AEs were mild to moderate in severity and no product-specific serious or unexpected AEs were reported.

Taken together, as TPL, I conclude that the new products have lower levels of HPHCs than CC and snus, the new products are expected to have lower abuse liability than CC and smokeless tobacco products and pose a lower overall individual health risk relative to CC and smokeless tobacco use.

In addition, the available literature suggests that nicotine pouches are predominantly used by adults who use other tobacco products, including CC and smokeless tobacco. Given these findings, as TPL, I evaluated available evidence regarding the potential for the new products to be used by current tobacco users and used in a way that would benefit them, such as a substitute for some or all of their traditional tobacco product use (i.e., CC, smokeless tobacco). To evaluate the potential for the new products to enable switching, as discussed above in Section 1.2, BCP evaluated the abuse liability of the new products. As TPL, I find that based on the totality of evidence, the abuse liability of all the new products is expected to be lower than CC and smokeless tobacco. These findings suggest that the new products are likely to deliver sufficient nicotine to the user to reduce craving and withdrawal symptoms and therefore can support behavioral change (e.g., product substitution) among some users. Moreover, there are a small number of longitudinal studies conducted to date that provide some additional support for the potential for nicotine pouches, including the new products, to facilitate significant CC reduction or complete switching among some adults who smoke.

Although the new products may be a lower-risk alternative for adults who use other tobacco products, nicotine pouches are not without risk. The new products can still deliver harmful chemicals to users, including nicotine, a toxic and addictive chemical. For non-users, the new products pose a risk of addiction. Although not a main driver of tobacco-related disease, long-term nicotine exposure has been associated with adverse cardiovascular effects, systemic inflammation, gastrointestinal effects, and effects on bone growth. In addition, there is some evidence that nicotine pouches may be associated with negative oral health outcomes (including parakeratosis, edema, and chronic inflammation).

In terms of the risks to nonusers, the potential impact of marketing a new tobacco product on youth is a critical piece of the APPH evaluation because the majority of tobacco use begins before adulthood. Nicotine pouches have features that may be appealing to youth—particularly the availability of a range of flavors as well as their ability to be used inconspicuously. To date, however, despite an upward trend in use (as discussed in Section 3.3.2), the observed prevalence of youth use of nicotine pouches as a product category remains low, suggesting relatively low appeal of the category. In addition, in terms of adults who do not use tobacco, the currently available data show that use of nicotine pouches was virtually non-existent for tobacco naïve adults. Therefore, based on the evidence available at this time, as TPL, I conclude that the potential risk to non-users, including youth, is currently low. However, trends in youth use can shift quickly, and historically we have witnessed how the emergence of a new product can drive the appeal of a category. Therefore, it is critical that FDA continue to monitor youth nicotine pouch use.

Targeted and responsible marketing are key factors to mitigating the potential risk to youth of marketing a new tobacco product. Accordingly, as TPL, I reviewed the labeling for the new products and, at this time, did not identify concerns regarding youth appeal or marketing that targets youth; I have not found that the proposed labeling raises those issues. In addition, OHCE reviewed the marketing plan and found that the applicant generally describes a reasonable approach to marketing to its target audience and proposes measures to limit youth exposure to the products' labeling, advertising, marketing, and

promotion. As TPL, I recommend that the MGO include the marketing requirements and recommendations in Section V of the OHCE consult, as they will help mitigate the potential risk to youth posed by the marketing of the new tobacco products. In addition, the applicant proposed marketing plans that include restrictions beyond those required with PMTA authorization. OHCE has determined that these restrictions may help further limit youth exposure to the new products, the products' labeling, advertising, marketing, and/or promotion as well as the potential for youth initiation. For example, the applicant proposes to limit youth exposure to the new products by (b) (4)

(b) (4)

(b) (4) As TPL, I recommend such measures, as they will further mitigate the potential risk to youth posed by the marketing of these tobacco products.

In addition to youth use, the new products also pose a risk to young children from accidental nicotine exposure. Indeed, there has been a significant rise in nicotine pouch ingestion among young children reported to U.S. poison control centers over the past few years. Nicotine pouch ingestion was associated with more serious adverse health outcomes for children despite accounting for fewer nicotine ingestions than other product formulations. Mitigation measures, such as CRP, are important for reducing the risk of accidental nicotine exposure. The new products contain CRP. CRP in the new products is intended to reduce the risk of poisoning in children by making it significantly difficult for children (under age 5) to open and obtain a toxic amount of the product within a reasonable time. As such, the new products' CRP serves to mitigate the risk of nicotine poisoning among children ages 5 and under.

In sum, FDA's evaluation determined that these PMTAs contain sufficient information to characterize the product design and demonstrate adequate process controls and quality assurance procedures for consistent manufacturing. Based on the product-specific information provided in the PMTAs and the available evidence on nicotine pouches, 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 adult tobacco users, including those who use CC and smokeless tobacco, who use nicotine pouches and significantly reduce their use of such products (or who switch completely) outweighs the risks to youth or nonusers, provided that the applicant follows post-marketing requirements and implements marketing restrictions to reduce youth exposure to product marketing and product access.

Based on my review of the PMTAs, I find that permitting the marketing of the new products, as described in the applications and specified in Appendix Table 4, is appropriate for the protection of the public health. 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 the marketing of the new products. Under the provisions of Section 910, the applicant may introduce or deliver for introduction into interstate commerce the products, in accordance with the marketing order requirements outlined in the marketing granted orders.

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

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

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7. APPENDIX

Table 4. Acronyms and abbreviations

Acronym, abbreviation, term	Use
TSNA	tobacco specific nitrosamines
PAH	polycyclic aromatic hydrocarbons
NNN	N-nitrosonornicotine
NNK	nicotine-derived nitrosamine ketone
NRT	Nicotine replacement therapy
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PK	Pharmacokinetics
B[a]P	Benzo[a]pyrene
TAMC	Total Aerobic Microbial Count
TYMC	Total Yeast and Mold Count

APPENDIX A. NEW PRODUCTS

Table 5. New products subject to Marketing Granted Orders

Common Attributes[17,18,19,20]	
Submission date	December 23, 2024
Receipt date	December 24, 2024
Applicant	Helix Innovations LLC
Product manufacturer	U.S. Smokeless Tobacco Company LLC
Product category	Other
Product subcategory	Other

[17] We interpret package type to mean container closure system and Product Quantity to mean quantity within the container closure system, unless otherwise identified.
[18] Product name is brand/sub-brand or other commercial name used in commercial distribution.
[19] 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.
[20] Attributes in Appendix A may display converted values.

Attributes	New Tobacco Product
STN	**PM0009121.PD10**
Package name	on! PLUS nicotine pouches 6 mg Mint
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 grams (g)
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Mint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 milligrams/pouch (mg/pouch) Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 millimeters (mm) Portion Width: 10.5 mm
STN	**PM0009121.PD11**
Package name	on! PLUS nicotine pouches 9 mg Mint
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Mint
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 9 mg/pouch Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 mm Portion Width: 10.5 mm

STN	**PM0009121.PD13**
Package name	on! PLUS nicotine pouches 6 mg Tobacco
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 g
Characterizing flavor (CF)	Tobacco
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 mm Portion Width: 10.5 mm
STN	**PM0009121.PD14**
Package name	on! PLUS nicotine pouches 9 mg Tobacco
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 g
Characterizing flavor (CF)	Tobacco
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 9 mg/pouch Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 mm Portion Width: 10.5 mm
STN	**PM0009121.PD16**
Package name	on! PLUS nicotine pouches 6 mg Wintergreen
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Wintergreen
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 6 mg/pouch Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 mm Portion Width: 10.5 mm

STN	PM0009121.PD17
Package name	on! PLUS nicotine pouches 9 mg Wintergreen
Package type	white CR plastic can and flat lid assembly
Product Quantity	9 g
Characterizing flavor (CF)	Flavored
Flavored CF, as identified	Wintergreen
Nicotine source	Tobacco
Additional property	Nicotine Concentration: 9 mg/pouch Portion Count: 14 pouches Portion Mass: 0.714 g Portion Length: 27.5 mm Portion Width: 10.5 mm

Appendix B
Amendments and Additional Submissions Received for This Applicant

Amendments Received for These Applications

Submit Date	Receipt Date	Applications being amended	Reviewed	Brief Description
January 14, 2025	January 14, 2025	PM0009121	Yes	Updated labels and studies, and reference for (b) (4)
April 16, 2025	April 16, 2025	PM0009121	Yes	Updated HPHC and product characterization data and updated summaries for Modules 1.2 and 2.2-2.4
September 19, 2025	September 19, 2025	PM0009121	Yes	Contents of (b) (4)
October 9, 2025	October 9, 2025	PM0009121	Yes	Status and implementation plan for product packaging
October 17, 2025	October 17, 2025	PM0009121	Yes	Product characterization data requested in the October 9, 2025 teleconference with FDA
October 17, 2025	October 17, 2025	PM0009121	Yes	Testing and methodology data requested in the October 9, 2025, teleconference with FDA
October 22, 2025	October 22, 2025	PM0009121	Yes	Additional product characterization data requested in the October 9, 2025 teleconference with FDA
October 22, 2025	October 22, 2025	PM0009121	Yes	Additional method validation data requested in the October 9, 2025 teleconference with FDA

October 23, 2025	October 23, 2025	PM0009121	Yes	Supporting documentation for product packaging and EA
October 24, 2025	October 24, 2025	PM0009121	Yes	Unredacted EA
October 31, 2025	October 31, 2025	PM0009121	Yes	Additional product characterization data requested by FDA on October 27, 2025
November 7, 2025	November 7, 2025	(b) (4)	Yes	N/A- Withdrawal request for products not subject to this review
November 13, 2025	November 13, 2025	PM0009121	Yes	Additional product characterization and method validation data requested by FDA on October 17, 2025

Additional Submissions Received for This Applicant

Submit Date	Receipt Date	Reviewed	Brief Description
August 1, 2025	August 1, 2025	Yes	30 day notification containing marketing materials for PM0009121
August 14, 2025	August 14, 2025	Yes	30 day notification containing marketing materials for PM0009121
August 27, 2025	August 27, 2025	Yes	30 day notification containing marketing materials for PM0009121
September 11, 2025	September 11, 2025	Yes	30 day notification containing marketing materials for PM0009121
September 18, 2025	September 18, 2025	Yes	30 day notification containing marketing materials for PM0009121
September 26, 2025	September 26, 2025	Yes	30 day notification containing marketing materials for PM0009121
October 2, 2025	October 2, 2025	Yes	30 day notification containing marketing materials for PM0009121
October 16, 2025	October 16, 2025	Yes	30 day notification containing marketing materials for PM0009121